

# SLEEP

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**Scientific Highlights/Abstracts of Original Investigations**



## Oral Presentation Sleep Apnea: Consequences

### 001.J

#### DISCORDANCE IN SUBJECTIVE AND OBJECTIVE MEASURES OF DAYTIME SLEEPINESS

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**Introduction:** Recently, the criteria for the diagnosis of OSA were recommended as the presence of physiological impairment as well as the manifestation of excessive daytime sleepiness (EDS).<sup>1</sup> However, the extent that sleepiness is characteristic of this population and the primary method of measuring daytime sleepiness remains unresolved. It is also unclear how many of those with more severe disease fail to manifest either objective or subjective sleepiness and therefore may not be candidates for treatment.<sup>1</sup> The purpose of this study was to describe the profile of sleepiness in subjects with moderate/severe OSA and to examine the consistency and proportion of subjects that manifest sleepiness based on three conceptually distinct measures: a measure of subjective sleepiness (Epworth Sleepiness scale [ESS]),<sup>2</sup> objective sleepiness (Multiple Sleep Latency Test [MSLT]), and of sustained attention (Psychomotor Vigilance Task [PVT]).<sup>3</sup>

**Methods:** Subjects participated in a multisite study where inclusion criteria were ages 20-60, clinical judgment of EDS, RDI  $\geq 20$ , and a candidate for CPAP. Exclusion criteria included any co-existing sleep disorder or co-morbidity that would affect daily functioning. Subjects completed a battery of outcome measures that included the ESS, MSLT, and PVT at baseline and again following 3 mo. of CPAP use. Subjects with complete data for the ESS, MSLT, and PVT were included in these analyses ( $N = 107$ ). Sleepy subjects were differentiated from non-sleepy subjects for each of these measures based on the following cut-points: ESS  $\geq 11$ ; MSLT  $< 10$ ; and presence of  $\geq 2$  performance lapses/10 min. on the PVT.

**Results:** The sample (92% male, 87% white, mean  $\pm$  SD age = 45.9,  $\pm$  8.9, mean BMI 38.7  $\pm$  8.6, mean RDI = 66  $\pm$  31) had a mean ESS = 14.1  $\pm$  4.8, mean MSLT sleep latency = 7.3  $\pm$  5.2, and a mean PVT total lapses = 4.5  $\pm$  8.4. As shown in the table, approximately half of the subjects manifested sleepiness both subjectively and objectively when the MSLT was used to measure objective sleepiness, with approximately a third of the patients manifesting subjective and objective sleepiness when the PVT measured objective sleepiness. Only 29% exhibited sleepiness on all three measures. Thirteen percent of the sample failed to manifest any sleepiness measured either subjectively or objectively. There was a low correlation between the ESS and either the MSLT ( $r = 0.26$ ,  $p = 0.0009$ ) or the PVT ( $r = 0.19$ ,  $p = 0.04$ ); there was no significant correlation between PVT and the MSLT ( $r = 0.06$ ).

**Table 1—Percentage of Subjects with Subjective or Objective Daytime Sleepiness (N = 107)**

Test	MSLT $\geq 10$	MSLT $< 10$	PVT $< 2$	PVT $\geq 2$	MSLT $\geq 10$ / PVT $< 2$	MSLT $< 10$ / PVT $\geq 2$
ESS $< 11$	14%	11%	21%	4%	13%	3%
ESS $\geq 11$	18%	57%	36%	39%	7%	29%

ESS  $< 11$  = Subjectively not sleepy;  $\geq 11$  = Subjectively sleepy  
MSLT  $\geq 10$  = Objectively not sleepy;  $< 10$  = Objectively sleepy  
PVT  $< 2$  = Objectively not sleepy;  $\geq 2$  = Objectively sleepy

**Conclusions:** In this sample of subjects with moderate/severe OSA there is considerable discordance between the manifestation of sleepiness as assessed by these often used assessments. The lack of substantial linear association among these sleepiness probes reflects an unknown combination of true between patient differences in the nature of sleepiness consequences resulting from sleep apnea; true variance due to non-apnea related factors; and measurement error. Moreover, as approximately 1 out of 10 patients did not manifest sleepiness raises issues regarding the utility of sleepiness assessment for use in treatment decisions and who should be prescribed CPAP therapy.

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### 002.J

#### PREDICTORS OF DAYTIME SLEEPINESS IN SLEEP DISORDERED BREATHING

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**Introduction:** Daytime sleepiness is a common complaint in patients with sleep-disordered breathing (SDB). The multiple sleep latency test (MSLT) is a standardized and objective

method for assessing daytime sleepiness. Previous studies have shown minimal, if any, associations between the severity of SDB and the level of objective sleepiness during the MSLT. The objective of this study was to examine whether patient factors such as age, gender, race, body mass index (BMI), and the apnea-hypopnea index (AHI) were associated with differences in the MSLT in patients with SDB.

**Methods:** The study sample consisted of all patients that have had an overnight sleep study and an MSLT in the Johns Hopkins Sleep Disorders Center over the last two decades. SDB was defined as an AHI of at least 10 events/hr on the overnight sleep study. Since the results of the MSLT represent time to an event (sleep onset), survival analysis techniques were used to examine the predictors of daytime sleepiness. Each of the four naps during the MSLT was separately modeled using Kaplan-Meier product-limit analysis and Cox proportional hazards regression to determine the predictive value for the following variables: age, gender, race, BMI, and AHI. Multivariable models were constructed to assess the independent effects of these variables on daytime sleepiness. To determine the population-averaged associations, the technique of Wei, Lin, and Weissfeld (1) was used to obtain the pooled estimates and the associated standard errors for the above variables. Although analyses were conducted with continuous and categorical variables, results from the categorical analyses are presented for ease in interpretation. Continuous variables were categorized using tertiles from the distribution in the patient sample.

**Table 1—Relative Risks for Daytime Sleepiness (MSLT <10 min) in SDB (Result from Multivariable Cox Regression Analyses, \*p < 0.05)**

Predictor	Nap 1	Nap 2	Nap 3	Nap 4	Pooled Estimates
<b>Age, years</b>					
< 44	1.00	1.00	1.00	1.00	1.00
44 - 54	0.96	0.95	0.94	0.98	0.96
≥ 55	0.87*	0.87*	0.85*	0.88*	0.87*
<b>Gender</b>					
Female	1.00	1.00	1.00	1.00	1.00
Male	1.15*	1.17*	1.20*	1.18*	1.17*
<b>Race</b>					
White	1.00	1.00	1.00	1.00	1.00
Non-White	1.23*	1.31*	1.15*	1.14*	1.21*
<b>BMI, kg/m<sup>2</sup></b>					
< 31.1	1.00	1.00	1.00	1.00	1.00
31.1 - 38.0	1.04	1.11*	1.09	1.05	1.07
≥ 38.1	1.10*	1.12*	1.11*	1.12*	1.11*
<b>AHI, events/hr</b>					
< 32.8	1.00	1.00	1.00	1.00	1.00
32.8 - 65.1	1.27*	1.32*	1.26*	1.30*	1.29*
≥ 65.2	1.59*	1.75*	1.82*	1.84*	1.72*

**Results:** The study sample consisted of 3,548 patients (76.3% men) with a mean AHI of 53.5 events/hr (SD: 31.9), mean BMI of 35.9 kg/m<sup>2</sup> (SD: 8.8) and mean age of 49.8 years (SD: 12.5). Cox proportional hazard modeling (see table) revealed that patient factors including younger age, male gender, non-white race, and increasing BMI were independently predictive of increased daytime sleepiness. No significant differences were observed in the relative risks for these variables across the four naps. Severity of SDB, as assessed by the apnea-

hypopnea index, was also independently associated with daytime sleepiness. Compared to the first AHI tertile (reference group), the relative risks for an MSLT of less than 10 minutes for the second and third AHI tertiles were 1.29 (95% CI: 1.20-1.37) and 1.72 (95% CI: 1.60-1.85), respectively. Tests of interactions between severity of SDB and demographic variables were not significant.

**Conclusions:** (1) Survival analysis is an appropriate and efficient method for analyzing the results of the MSLT. Sleep latency data from all four naps should be used to model the results of the MSLT to determine population-averaged effects. (2) In patients with SDB, younger age, male gender, non-white race, increasing BMI, and increasing AHI are independently associated with daytime sleepiness.

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### 003.J

#### REGIONAL BRAIN INFLAMMATION: A PUTATIVE MECHANISM UNDERLYING THE NEUROBEHAVIORAL DEFICITS OF OBSTRUCTIVE SLEEP APNEA

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**Introduction:** In an animal model of obstructive sleep apnea, intermittent hypoxia (IH) elicits early increases in neuronal apoptosis within vulnerable brain sites such as the cortex and CA1 region of the hippocampus (1). This early process is followed by astrocytic and neuronal proliferation, leading to partial functional recovery. Although the mechanisms underlying the temporal characteristics of the injury and repair processes that mediate the functional neurocognitive alterations are still being elucidated, recent findings from our laboratory unequivocally indicate that the expression and activity of inducible nitric oxide synthase (iNOS) are enhanced during the early phase of IH-induced brain injury (2). We hypothesized that chronic IH will lead to up-regulation of pro-inflammatory cytokine pathways and other enzymes critically involved in inflammation such as COX2 or platelet-activating factor receptor (PAFR).

**Methods:** Adult Sprague-Dawley rats were exposed to either intermittent (10% O<sub>2</sub> alternating with room air every 90 sec during daylight; IH) or sustained hypoxia (10% O<sub>2</sub> during daylight; SH) for up to 14 days using computer-driven environmental chambers. Cortical tissue lysates were prepared at 0, 1, 3, 7, and 14 days exposure, and RNA extraction was performed. RT-PCR reaction was used with specific primers to examine changes in gene expression of the pro-inflammatory cytokines IL1  $\beta$ , IL6, TNF  $\alpha$ , TGF  $\beta$ , GM-CSF, as well as changes occurring COX2 and PAFR expression. To control for loading, RT-PCR was simultaneously conducted for the housekeeping gene GAPDH.

**Results:** IH, but not SH, induced prominent and sustained increases in IL1  $\beta$  and TNF  $\alpha$  gene expression, with small but significant increases in GM-CSF gene expression. No changes in IL6 and TGF  $\beta$  occurred. Similarly, increased gene expression of COX2 and PAFR occurred in IH, but such changes were absent in SH.

**Conclusions:** The intermittent hypoxia that characterizes obstructive sleep apnea elicits marked up-regulation of pro-inflammatory gene expression. Some of these genes (e.g., IL1  $\beta$  and TNF  $\alpha$ ) may play a dual role leading to early onset of neuronal apoptosis while inducing neuronal protection at later stages. On the other hand, increased COX2 and PAFR gene expression may contribute to slowly evolving neuronal excitotoxicity and astrocyte proliferation.

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#### 004.J

##### THE CONTRIBUTION OF OXYGEN DESATURATION TO THE DEVELOPMENT OF WHITE MATTER HYPERINTENSITIES IN ELDERLY MALE TWINS

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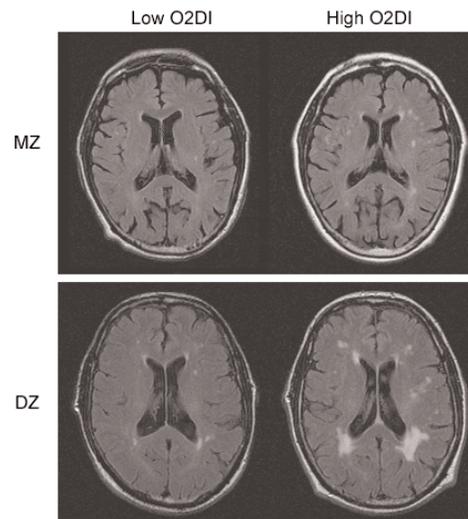
**Introduction:** Repetitive intermittent hypoxia produces sustained elevations in blood pressure in animal models(1). Several mechanisms can explain this effect, including structural changes to the endothelium caused by altered monocyte and adhesion molecule expression (2). These mechanisms also predict a relationship where repetitive intermittent hypoxia associated with sleep disordered breathing could lead to altered endothelial function and increased incidence of white matter hyperintensities (WMHIs) in the brain. Due to the increased incidence of WMHIs as a function of aging, the cotwin control model is well suited to testing this hypothesis.

**Methods:** Forty-one pairs of twin brothers were studied (19 MZ, and 22 DZ; mean age at MRI = 72 years) drawn from the NHLBI twin study. MRI data consist of dual spin-echo axial images collected on a GE Signa 1.5T scanner. WMHIs were quantified using an automated volumetric technique. O2DI indices (SaO2 drops below 90% per hour of sleep) were calculated for each subject from a single night in-home Edentrace

II study. Sleep studies were conducted four years after acquisition of MRI brain scans.

**Results:** Twin pair differences in O2DI were significantly correlated with twin pair differences in total WMHI brain volume ( $r = 0.31, p < .05$ ). The correlation within DZ pairs was  $r = .32$ , and within MZ pairs was  $r = .19$ . Two representative twin pairs discordant for O2DI are presented in Figure 1. The MZ twins have O2DI values of 13.2 and 37.2 and corresponding WMHI volumes of 0.10 and 1.21 cc. The DZ twins have O2DI values of 10.6 and 25.7 and WMHI volume of 3.3 and 7.6 cc.

**Figure 1**— Axial MRI images displaying WMHIs (white), ventricles and sulci (black) and brain tissue (gray). Data are axial images at the level of the lateral ventricles from one MZ twin pair (aged 76) and one DZ twin pair (aged 78).



**Conclusions:** The data support the hypothesis that repetitive intermittent hypoxia is a factor in the development of brain WMHIs, although does not rule out other causes associated with sleep disordered breathing. This is strong effect given the major impacts of aging and the genetic susceptibility for the development of WMHIs (3). The lower correlation in MZ compared to DZ pairs suggest common genetic influences for WMHIs and nocturnal hypoxic load. It should be noted that the effect was present even when using relatively unsophisticated measurement of nocturnal hypoxic load, and total WMHI brain volume. Selective measurement of WMHIs in the vascular hypoperfusion areas of the centrum semiovale and basal ganglia where WMHIs due to endothelial damage are most evident may lead to even stronger relationships being revealed.

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elderly male twins. *Stroke* 177-1181; 1998.

### 005.J

#### THE RELATIONSHIP BETWEEN POLYSOMNOGRAPHY MARKERS OF DISEASE SEVERITY TO HEMODYNAMIC AND RESPIRATORY FUNCTION DURING GRADED EXERCISE IN OBSTRUCTIVE SLEEP APNEA PATIENTS

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**Introduction:** Markers of disease severity in those with obstructive sleep apnea (OSA) have not been clearly defined in the literature. While physical exam characteristics have been shown to accurately predict the presence of OSA, controversy exists as to how these variables may aid in the understanding of OSA disease severity (1). In addition, the primary mechanisms underlying the association between hypertension and obesity to that of OSA are still not well understood, such that cardiopulmonary responses obtained during standard exercise testing in conjunction with physical exam findings may be a useful means of evaluating daytime measures of physiological function in OSA patients (2, 3). The purpose of this investigation was to describe the extent to which graded exercise testing may reveal abnormalities of hemodynamic response in obstructive sleep apnea (OSA) patients, particularly with respect to cardiac output (Qc), blood pressure (SBP, DBP, MAP), and total peripheral resistance (TPR) and how such responses may relate to polysomnographic (PSG) markers of OSA severity.

**Methods:** Fifteen, newly diagnosed OSA patients (6 male and 9 female) completed maximal graded exercise tests (GXT) on an electronically braked stationary cycle ergometer. Qc and calculated TPR were taken during sitting rest and at one submaximal exercise intensity ( $55.1 \pm 10.7$  % pk Watts). Heart rate (HR), SBP, DBP, and calculated rate pressure product were also taken at peak exercise. These hemodynamic variables were correlated to PSG markers of OSA severity (respiratory disturbance index (RDI), lowest SaO<sub>s,2</sub>s during sleep (lowSaO<sub>s,2</sub>s), and percent time that SaO<sub>s,2</sub>s was less than 90 percent. Multiple linear regression models were generated to estimate contributions of measured anthropometry and exercise variables to the PSG markers of disease status.

**Results:** Peak oxygen consumption for the group was  $21.4 \pm 5.0$  ml·kg<sup>-1</sup>·min<sup>-1</sup> (range  $\approx$  13.6 - 32.1). Peak exercise heart rates achieved in exercise testing represented 87 percent of age-adjusted predicted maximal values for this sample of middle-aged ( $44.5 \pm 11.6$ ) borderline obese (Body Mass Index (BMI):  $36.0 \pm 5.9$ ) subjects. Regression analysis revealed that the combination of neck circumference, submaximal, exercise stroke volume (SV), and TPR explained 74 percent of the variance in lowSaO<sub>s,2</sub>s ( $P \approx$  0.019) observed in PSG testing. Similarly, neck circumference, submaximal

mean arterial pressure, and SV, explained 79 percent of the variance relative to low SaO<sub>s,2</sub>s ( $P \approx$  0.010).

**Conclusions:** Exercise hemodynamic markers in combination with neck circumference may be helpful in preliminary evaluation of patients under consideration for more expensive PSG testing for diagnosis of Obstructive Sleep Apnea. These preliminary results suggest the value of a clinical trial to assess the performance of hemodynamic exercise testing for the prediction of OSA.

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### 006.J

#### CIRCADIAN ALTERATIONS IN ATRIAL NATRIURETIC PEPTIDE, VASOPRESSIN, & URINE PRODUCTION IN OSA

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**Introduction:** There is growing evidence of a relationship between OSA and disorders of hydration such as nocturia (Umlauf et al 1999) and leg edema (Blankfield et al 2000). However, little work has been conducted to examine circadian hydration in persons with OSA. Two purposes of this study were: 1) to examine circadian patterns of urine production along with the excretion of atrial natriuretic peptide (ANP) and arginine vasopressin (AVP) and 2) to conduct a feasibility test of monitoring ANP and AVP over extended periods of time using urine specimens.

**Methods:** A sample of community-dwelling elders (n=30) was recruited based on self-reported sleep apnea symptoms and nocturia ( $\geq 2$ /night) as part of a federally funded study. Subjects were observed for 24 hours in a clinical research setting at a university hospital and polysomnography was conducted overnight. Strict intake and output procedures were followed to create five observation intervals (2pm-6pm, 6pm-10pm, 10pm-6am, 6am-10am, 10am-2pm). Subjects voided at 2pm the first day, then ad-lib, and at the end of each observation interval. Voided volumes were pooled for each observation interval and specimens for assay were taken from these five volumes, which provide an automatic averaging of metabolite excretion per urine collection interval and permits interpolation into rate of production.

**Results:** Both men and women (f=17; m=13) and minority subjects (African-Americans, n=18; Caucasian, n=11) participated and the mean age was 65.5 (SD 8.38; range 51-91). Two-thirds of the sample (n=19) was found to have clinically diagnosable OSA (AHI $\geq 5$ ), although none of the subjects were apnea free. Distinct circadian patterns in percentage of daily

urine output were evident when comparing subjects with  $AHI \geq 15$  ( $n=21$ , AHI range 18.7-77.4) to those with lower AHIs ( $n=9$ , AHI range 0.66-14.7) and normal urine output (Figure 1). Although AVP is normally expected to become elevated when the individual is recumbent (during sleep), no statistical differences were noted over the 24 hour observation period in the sample nor when comparing by individual time intervals and by levels of AHI. Significant elevations in ANP excretion were found in the sample in when comparing between levels of AHI. ANP levels were higher overnight and in early morning intervals (10p-6a; 6a-10a) among the group with  $AHI \geq 15$  (Figure 2). Contrary to supposition, neither ANP nor AVP were related to age of subject.

Figure 1

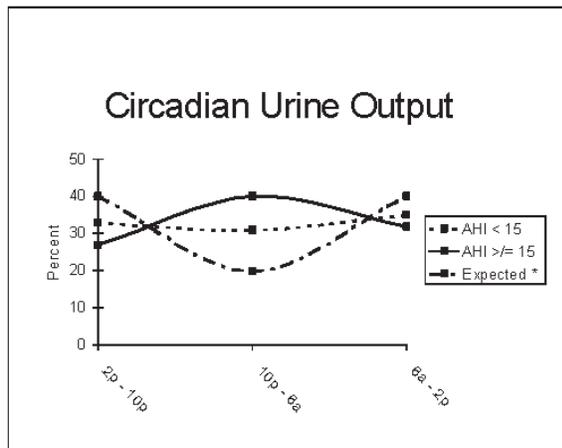
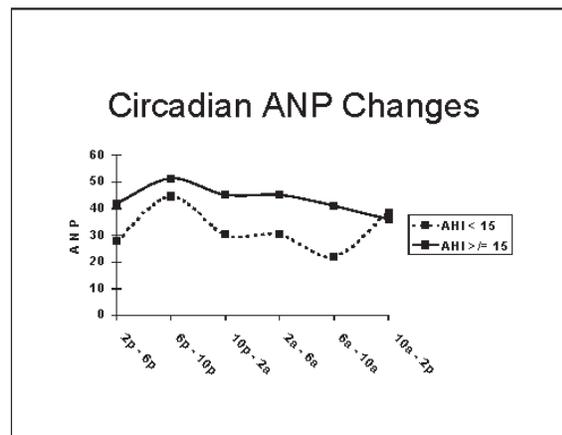


Figure 2



**Conclusions:** These findings suggest that persons with OSA may have a circadian disturbance in water homeostasis, not just excessive urine output at night. This is consistent with the recent report of lower extremity edema as a potential clinical marker of OSA (Blankfield et al 2000). Further, using urine specimens to track ANP and AVP will significantly aid in the design of future studies of the effect of OSA and/or its treatment on urine production, edema, and hydration.

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#### 007.J

#### OBSTRUCTIVE APNEIC EVENTS INDUCE ALPHA-RECEPTOR MEDIATED VASCULAR CONSTRICTION

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**Introduction:** Obstructive sleep apnea (OSA) is characterized by recurrent autonomic activation associated with alteration of heart rate, systemic arterial pressure and peripheral vascular tone. Muscle sympathetic activity peaks during the late phase of apnea while peripheral vasoconstriction, assessed in the digit vascular bed, appears to coincide with arousal and recovery from apnea. The current study investigated the vasoconstriction response to apnea by the peripheral arterial tone (PAT) signal(1).

**Methods:** Three patients with severe OSA (AHI 71.1, 88.9 and 72.8) free of peripheral vascular disease underwent a standard polysomnography together with a continuous overnight recording of the PAT signal (Itamar, Cesarea, Israel). The protocol included administration of oxygen (2 L/min, 4 L/min) and intraarterial infusion of the alpha-receptor antagonist phentolamine (0.66 mcg/min, 2.0 mcg/min and 20 mcg/min) during nREM sleep (stage 1 and 2). Each provocation or infusion step lasted for at least 30 minutes. A total of 499 apneas or hypopneas with clear EEG arousal during different experimental conditions were scored. The ratio between the largest pulse amplitude during apnea and the smallest amplitude post apnea (PAT ratio) was calculated using computerized software.

**Results:** The baseline untreated PAT ratio based on 223 events was 0.305 (0.104) suggesting an almost 70% post apnea vasoconstriction. There was no apparent correlation between apnea type, length or desaturation and the degree of constrictive response in this small material. The PAT ratio was only marginally affected by oxygen administration (2 L/min (38 events) and 4 L/min (31 events)) to 0.351 (0.105), and 0.321 (0.079), respectively. In contrast, infusion of phentolamine (0.66 mcg/min (52 events), 2.0 mcg/min (81 events) and 20 mcg/min (74 events)) induced a gradual inhibition of the post apnea constriction response to 0.412 (0.104), 0.393 (0.131) and 0.472 (0.161), respectively.

**Conclusions:** Post apnea vasoconstriction monitored in the digit vascular bed by the peripheral arterial tone is to a large extent mediated via vascular sympathoadrenergic alpha-receptor activation. Apnea related alteration of PAT therefore

reflects changes in the digital arterial volume that follow arousal-induced sympathoadrenergic activation.

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### 008.J

#### SNORING AND COGNITIVE IMPAIRMENT IN A MEMORY CLINIC POPULATION

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**Introduction:** Although many studies have documented cognitive impairment and sleepiness as neurobehavioral manifestations of sleep apnea in middle-aged populations, whether sleep apnea has similar correlates in old age remains unclear. Data from healthy elderly populations suggests minimal associations; studies of dementia show conflicting results, perhaps reflecting in part both vascular and non-vascular (Alzheimer's) contributions to altered brain function. In this study we examined snoring as a proxy for sleep disordered breathing in a large, unselected population of aged patients presenting at a tertiary care medical center Memory Assessment Clinic.

**Methods:** Subjects were 596 individuals (X age = 75.3, SD = 8.8) presenting to a Memory Assessment Clinic for evaluation of mental function. All patients underwent testing with the Folstein Mini-Mental State Exam (MMSE) (range 0 to 30, lower score signifying greater impairment). For logistic models, MMSE scores of  $\leq 18$  were considered indicative of moderately severe dementia. Snoring and medical history was typically provided by spouse or family member accompanying the patient. Snoring was defined by a positive response to a question reflecting snoring frequency, which could be answered "never," "just a few times," "sometimes," "often," or "always." Positive snoring history was defined as an estimated frequency of "sometimes" or higher (n = 289). "Don't know" responses were eliminated for these analyses, leaving 405 individuals with complete data on all variables. We defined cardiovascular disease (CVD) as history of hypertension, MI, CVA, or cardiac surgery and a treated or untreated blood pressure in excess of 140 mmHg systolic or 90 mmHg diastolic taken during the clinic visit. For logistic regression analyses, positive snoring history and presence of CVD were combined into a single variable (snore/CVD).

**Results:** Univariate and multivariate odds ratios for moderately severe dementia (MMSE  $\leq 18$ ) are shown below; n's refer to named categories.

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Education (non HS grad)(n=91)	3.82 (2.35-6.21)	3.35 (2.03- 5.53)
Race (non-White) (n=55)	2.73 (1.53-4.86)	2.12 (1.15-3.90)
Age (> 74) (n=205)	1.45 (0.95-2.20)	1.01 (0.99-1.04)
Gender (Male) (n=149)	0.60 (0.39-0.94)	0.69 (0.43-1.10)
Snore/CVD (n= 90)	1.91 (1.18-3.08)	1.77 (1.07- 2.94)

**Conclusions:** These findings suggest that snoring in the presence of cardiovascular disease was associated with profound cognitive impairment in a memory clinic population. These results were independent from factors known to impact upon mental status, including age, race, education level, and, in this case, gender. Given new data suggesting an association between sleep apnea and the APO-E 4/4 genotype, an allele with firmly established linkage for both systemic vascular disease and AD, these results are compatible with a role for sleep apnea in the evolution of vascular dementia.

Research supported by AG-10643, AG-06066; NS-35345

### Oral Presentation

#### The Hypocretin/Orexin System & Narcolepsy

### 009.A

#### OREXIN-A CONTAINING LATERAL HYPOTHALAMIC NEURONS EXPRESS ADENOSINE A1 RECEPTOR IMMUNOREACTIVITY

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**Introduction:** We have shown that local perfusion of antisense oligonucleotides against orexin-II receptor into the sub-coeruleus increased REM sleep and induced cataplexy-like episodes in rats whereas, microdialysis perfusion of orexin-A in the cholinergic basal forebrain increased wakefulness. Extracellular levels of orexin-A are highest, during the active period, in the basal forebrain. These studies suggest that increased orexinergic tone induces wakefulness, whereas reduced orexinergic tone increases REM sleep. What controls orexinergic neurons? We have suggested that extracellular adenosine increases during wakefulness and inhibits the wakefulness-promoting neurons of the basal forebrain via A1 receptor to induce sleep (A1R). As a first step toward identifying whether adenosine is involved in the control of orexinergic neurons, we examined the expression of A1R on orexinergic neurons. To our knowledge, A1R expression has not been examined in the orexinergic zone of the LH

**Methods:** Adult male Sprague-Dawley rats (n=5), (300-400 g) were housed in cages with 12:12 h light-dark cycle, (food / water ad libitum). The animals were sacrificed and their brain were removed, and serially sectioned into (30 um) coronal sections. The A1R (Chemicon International Inc) and orexin-A antibody (Peninsula Laboratories) were purchased commercially. The goat anti-rabbit F(ab') fragment conjugated with Alexa Fluor 594 was used to convert the adenosine A1 receptor antibody to a different species (goat). This allowed the secondary antibody (conjugated to FITC) to bind selectively to rabbit anti-orexin-A antibody. Fluorescence microscopy was carried out using the Axioplan 2 microscope and Slidebook 3 software. Orexinergic neurons and A1R were identified with excitation:emission at 495:519 and 590:617nm. In each animal, 2 in 3 sections were used for immunohistochemistry and the section with highest number of orexinergic neurons was selected for counting the number of orexinergic neurons with and without A1R immunoreactivity. Doubled labeled neurons

were considered to be orexinergic neurons with A1R.

**Results:** We counted a total of 1581 (approximately 10% of the total) orexinergic neurons in five animals with an average of 316 (SEM =  $\pm$  22) orexinergic neurons in each animal. Of these 486 or approximately 30% showed A1R immunoreactivity (Mean ( $\pm$  SEM) number/animal =  $97 \pm 6$ ).

**Conclusions:** Our data suggest that A1R are expressed on orexinergic neurons and is, to our knowledge, the first study implicating adenosine in the control of orexinergic tone.

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**Research supported by Department of Veterans Affairs, the NIMH Grants R37MH39683 (RWM) and KO1MH01798 (MMT) and by the Sleep Medicine Education and Research Foundation (MMT).**

## 010.A

### PROJECTIONS FROM THE MEDIAN PREOPTIC NUCLEUS TO HYPOCRETIN AND FOREBRAIN CHOLINERGIC AROUSAL SYSTEMS IN RATS

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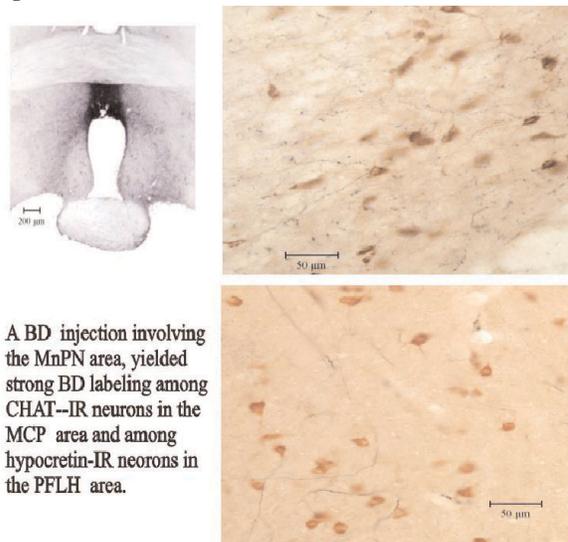
**Introduction:** The rostral and caudal parts of the median preoptic nucleus (MnPN) as well as the ventrolateral preoptic area exhibit c-fos protein immunoreactivity (IR) following sustained sleep. We have shown that sleep-related fos-IR colocalizes with the inhibitory neurotransmitter, gamma-aminobutyric acid, in MnPN neurons. We hypothesize that MnPN neurons are a source of inhibitory modulation of hypocretin and forebrain cholinergic arousal systems. In present study we examined the projections of the MnPN in adult Sprague-Dawley rats, by placing deposits of the anterograde tracer, biotinylated dextran amine (BD), into the MnPN and adjacent regions. We mapped the distribution of anterograde labeled axons in cholinergic regions of the magnocellular preoptic area (MCP) and among hypocretin IR-neurons in the perifornical lateral hypothalamic area (PFLH).

**Methods:** Twenty two male Sprague-Dawley rats (280-320g) received injections of biotinylated dextran (BD) targeting various subregions of the preoptic area and anterior hypothalamus. Rats were anesthetized with Ketamine/Xylazine (80/10 mg/kg, IP) for tracer injections. BD in a 10% solution was delivered iontophoretically (5mA, 7 sec duty cycle; 30-45 min) via glass micropipettes (tip diameter 10-15m). survival

period is 10 days post BD injection. Sections through the injection site, the MCP and PFLH area were cut at 40 $\mu$ m and Nickel-diamino benzidine hydrochloride was used to visualize the BD. Sections in the MCP area were incubated in rat (mouse) anti-CHAT (1:1000, Boehringer Mannheim biochemical) 48 hours and biotinylated goat-anti-rat (mouse) IgG (1:200, vector elite kit) 2 hours, followed with ABC complex kit (1:100, vector) 2 hours then developed with DAB. Sections in PFLH area were incubated in mouse-anti-Orexin A (1:5000, Oncogene) for 48 hours, following incubation in Biotinylated secondary antibody rabbit IgG (1:200, vector) for two hours. Then incubated in ABC kit for two hours and developed with DAB. The computer-aided plotting system (Microbrightfield) Neurolucida was used to analyze injection sites and terminal fields. Sections of six rostral-caudal levels of the MCP and PFLH were selected for analysis, Section outlines are mapped under 20x magnification and the locations of swellings on BD-labeled axons were plotted at 400x magnification.

**Results:** 1. BD injections involving in the caudal MnPN area yielded moderate to strong BD labeling among Chat-IR neurons in the MCP area and among hypocretin-IR neurons in the PFLH area. 2. A BD injection confined to the lateral to the MnPN resulted in minimal labeling in the MCP area and the PFLH area.

**Figure 1**



A BD injection involving the MnPN area, yielded strong BD labeling among CHAT-IR neurons in the MCP area and among hypocretin-IR neurons in the PFLH area.

**Conclusions:** These results support the hypothesis that MnPN neurons are a potential source of sleep-related inhibitory modulation of hypocretin and forebrain cholinergic arousal systems.

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**Research supported by VA Medical Research Service and HL60296.**

**011.A****DIURNAL VARIATION IN EXTRACELLULAR OREXIN-A LEVELS IN THE RAT BASAL FOREBRAIN.**

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**Introduction:** Daily variations in sleepiness are influenced by the duration of prior wakefulness (W) and the circadian time of day. Our previous work indicates that the sleepiness associated with prior W may be due to an accumulation of an inhibitory neuromodulator, adenosine, in the basal forebrain (BF) region that contains neurons that promote EEG activation and W. The current study examined the possibility that orexin-A, an excitatory neuropeptide, may mediate circadian variations in W via an excitatory action on the W-promoting neurons in the same BF region. Support for this hypothesis includes the following: perfusion of exogenous orexin-A in the BF of rats increases W and decreases sleep; orexin neurons project to the BF; orexin neurons receive input from the suprachiasmatic nucleus. Based on human studies of sleepiness, we predicted that an excitatory messenger of the circadian W drive will exhibit elevated extracellular levels during the second half of the active (waking) period.

**Methods:** Guides were stereotaxically implanted in anesthetized male rats (lights on from 0700h. to 1900h). Probes (CMA)microdialysis; 2 mm length x 0.5 mm diameter, 100kD membrane cutoff; perfusion flow rate of 1.0 ul/min) were later placed at the coordinates: AP -0.4, ML +2.5, DV-8.8. Four, 6h samples per 24h period were collected (1900 - 0100h, 0100 - 0700h, 0700 - 1300h, 1300 - 1900h), and also during a 6h afternoon period of forced W. Samples were frozen, lyophilized, re-constituted in 180ul, and orexin-A detected by an enzyme immunoassay. Typically, standard curves were linear from concentrations of 0.08 ng/ml to 2.0 ng/ml of orexin-A.

**Results:** Probes placed in a 500 ng/ml standard solution of orexin-A recovered  $4.8 \pm 1.5$  % of the orexin-A in the solution (N = 4), indicating that orexin-A (MW =3,562) passed through the dialysis membrane. Orexin-A levels in BF samples (N=5) were much lower than previously observed in the hypothalamus, requiring the 6h sample times used herein. The dialysate concentration of orexin-A in the evening samples was  $0.14 \pm 0.03$  ng/ml (1900 - 0100h). Orexin-A levels peaked in the second half of the dark/active period (0100 - 0700h = night;  $0.27 \pm 0.04$  ng/ml), a level that was almost 2-fold higher than the evening time period ( $p < 0.05$ ; note that the amount of time in spontaneous W in these two time periods is very similar). The levels in morning samples (0700 - 1300h;  $0.19 \pm 0.06$  ng/ml) were somewhat lower than the peak observed in the night samples (N.S.), and levels declined further in the afternoon samples (1300 - 1900h;  $0.17 \pm 0.02$  ng/ml,  $p < 0.05$ ). Preliminary data indicate that a 6h period of forced W (100% W produced by gentle handling) slightly elevated orexin-A levels (to 137 % of the afternoon control period) an increase that was not significant (N=3) and was smaller than the maximal diurnal variation observed (189 % of baseline).

**Conclusions:** Orexin-A can be measured in BF microdialysis samples. The lower level of orexin-A in BF samples required longer sample times, compared to brain areas with dense orexin-A innervation (hypothalamus). Diurnal variation in BF orexin-A levels was observed, with peak daily levels occurring in the second half of the active period. The data indicate that diurnal variations produce greater changes in orexin-A than do behavioral state changes, and support the hypothesis that endogenous orexin mediates the circadian influence on sleep and wakefulness.

**Research supported by NIMH 39683 & 01798; Dept Vet. Aff.**

**012.A****HYPOCRETIN/OREXIN CONTENT IN THE MOUSE BRAIN: THE EFFECT OF CIRCADIAN TIME, AGE AND GENETIC BACKGROUND**

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**Introduction:** Canine narcolepsy is caused by mutations in the Hypocretin receptor-2 gene. Prepro-hypocretin gene knockout mice have a phenotype that is similar to human and canine narcolepsy. Therefore, hypocretin neurotransmission plays a key role in the regulation of sleep and arousal. Although mutations of hypocretin genes are rare in humans, there is a remarkable reduction in the number of hypocretin neurons and hypocretins are absent in CSF from most cases. To further understand the physiology of the hypocretin system, we developed an enzyme immunoassay (EIA) to measure hypocretin levels in the whole mouse brain. We investigated possible circadian variation in these peptides and alterations in their levels with age, strain and genetic background.

**Methods:** Brains were collected from C57BL/6J mice at 9 time points during light/dark 12:12, light/light and dark/dark cycles. C57BL/6J mice (8 weeks to 122 weeks) brains were collected during the light period for the ageing study. C57BL/6J, CAST/Ei, SJL/J, DBA/2J were used for the strain variation study. Mutant mice studied included: clock mice (WT, n=6; HZ n=5; KO n=5), dopamine transporter mice (WT n=10; HZ n=8; KO n=8), vesicular monoamine transporter mice (WT, n=10; HZ, n=10), histamine receptor H1-KO mice (WT, n=11; KO, n=9), histamine receptor H2-KO mice (WT, n=8; KO, n=13), histamine receptor H3-KO mice (WT, n=11; KO, n=12), leptin pathway deficient ob/ob and db/db mice. The whole mouse brain was removed and kept at -80°C. Peptides were extracted from frozen brains by boiling in extraction solution. An enzyme Immunoassay (EIA) method was developed and used for this study.

**Results:** The EIA method has good correlation with the commercially available RIA:  $r=0.746$  for hypocretin-1 and  $0.778$  for hypocretin-2. Hypocretin levels in the whole mouse brain did not vary significantly with circadian time or age. The strain CAST/Ei had the highest hypocretin-1 and -2 levels

while SJL/J mice had high hypocretin-1 levels but the lowest hypocretin-2 levels compared to C57BL/6J. DBA/2J mice had the second high level of hypocretin-2 contents. C57BL/6J has the lowest level of hypocretin-1 compared to other strains. Significantly lower hypocretin-2 levels (44%) occurred in H1 receptor knockouts compared to controls, but no differences were found in other mutant mice.

**Conclusions:** The EIA technique provides accurate measurement for hypocretin levels. No circadian difference in hypocretin levels was observed; however measurement in the whole brain may not reflect changes in discrete brain regions. Also, hypocretin levels are not altered with age. There is strain variation in brain levels that may reflect variations in sleep/activity behaviors between strains. Interestingly, H1 receptor knockouts have lower brain hypocretin-2 levels. This preliminary finding may suggest a loss of H1 excitatory input on hypocretin neurons as histaminergic neurons project heavily through the hypothalamus. These inputs may form part of a not previously studied positive feedback loop between hypocretin and histaminergic neurons. Other more indirect mechanisms may also be involved.

### 013.H

#### AGE-RELATED DECLINE IN THE LEVEL OF HYPOCRETIN (OREXIN)-2 RECEPTOR MRNA IN MOUSE BRAIN.

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**Introduction:** Sleep in the elderly is generally recognized as being of poor quality relative to younger adults. Nocturnal sleep in seniors is characterized by frequent awakenings, decreases in the quantity of deep slow wave sleep (Stages 3 and 4), and a concomitant decrease in delta frequencies in the EEG. Many of these changes in sleep architecture also occur in aged laboratory rodents. The hypocretin/orexin (H/O) system has recently been identified as being important in arousal state regulation. Degeneration of the H/O neurons has been found in human narcolepsy, a sleep disorder characterized by excessive daytime sleepiness (EDS) and cataplexy. In this study, we measured mRNA levels of three components of the H/O system, prepro-H/O, H/O receptor 1 (HcrtR1), H/O receptor 2 (HcrtR2), in eight brain regions from young (3 mo), middle-aged (12 and 18 mo) and old (24 mo) male C57BL/6 mice. Since dynorphin has recently been shown to colocalize with H/O, we also measured dynorphin mRNA levels.

**Methods:** A total of 24 mice (six animals/group) were sacrificed between 1100-1400h and eight brain regions were dissected: cortex, thalamus, hypothalamus, basal forebrain, hippocampus, cerebellum, pons, and medulla. Levels of the two peptide mRNAs were measured in the hypothalamus whereas the H/O receptor mRNAs were measured in all eight brain areas. mRNA levels were quantified using a real-time fluorescence detection method. After total RNA was isolated, genomic DNA contamination was removed by treatment with RNase-free DNase I in the presence of anti-RNase and first-strand cDNA was prepared from each sample. The "target" cDNAs (preproH/O, dynorphin, HcrtR1, HcrtR2) and a reference

cDNA (glyceraldehyde-3-phosphate dehydrogenase, G3PDH) were PCR-amplified simultaneously using an oligonucleotide probe with a 5' fluorescent reporter dye (6FAM for the target genes and VIC for G3PDH) and a 3' quencher dye (TAMRA). Target cDNA and G3PDH amounts were determined by fluorescence, normalized and the resultant ratios subjected to MANOVA followed by ANOVA and, where indicated, the Tukey/Kramer post-hoc test.

**Results:** Expression of the prepro-H/O and dynorphin genes did not change with age in the hypothalamus. An age-related change in the expression of HcrtR1 mRNA was observed only in the hippocampus ( $p=0.017$ ). In contrast, HcrtR2 mRNA levels showed an age-related variation in the hypothalamus ( $p=0.034$ ), thalamus ( $p=0.001$ ), hippocampus ( $p=0.007$ ), pons ( $p=0.025$ ), and medulla ( $p=0.0001$ ). Post hoc tests revealed significant differences between the 3- and 24-month old groups in HcrtR2 mRNA in these brain regions, except for the pons.

**Conclusions:** An age-related change in expression of HcrtR2 mRNA was observed 5 out of 8 brain areas tested. Although the mice used for this study were not characterized with respect to sleep, narcoleptic dogs have a non-functional HcrtR2 gene and exhibit excessive sleepiness. The HcrtR2 knockout mouse also exhibits disrupted sleep. Taken together, these data suggest that an age-related deterioration occurs in the H/O system that may underlie age-related sleep disorders.

**Research supported by 1R01MH61755 and 1R03AG18118.**

### 014.A

#### EXCITATORY EFFECTS OF HYPOCRETIN IN THE TRIGEMINAL MOTOR NUCLEUS ARE REVERSED BY GLUTAMATE ANTAGONISTS

*Peever Jh,<sup>1</sup> Lai YY,<sup>1</sup> Siegel JM<sup>1</sup>*

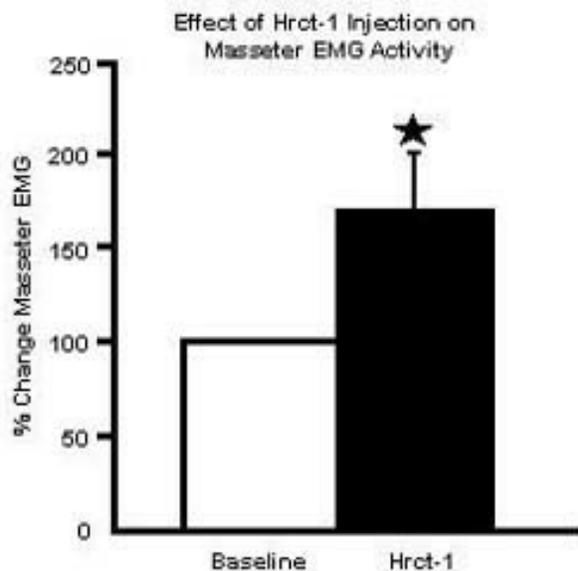
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**Introduction:** Hypocretin-1 and 2 (Hcrt, also called orexin-A and B) are excitatory neuropeptides that are involved in a wide-range of physiological processes, including sleep-wake homeostasis, and regulation of motor control. A deficiency in Hcrt neurons is implicated in narcolepsy (1). It has been reported that systemic administration of Hcrt increases motor activation and reverses the symptoms of narcolepsy (1). We found that microinjection of Hcrt into the trigeminal motor nucleus (5M) increases masseter muscle tone, and concluded that Hcrt microinjection excites 5M motoneurons. However, recent evidence demonstrates that administration of Hcrt increases glutamate release both in-vivo and in-vitro (2, 3). Based on these observations, we postulate that Hcrt may not only act postsynaptically, but may also regulate the presynaptic release of glutamate, which in turn would excite 5M motoneurons. To test this postulate we pretreated the 5M with glutamate antagonists prior to the application of Hcrt-1 in order to determine whether glutamate release is involved in the response of masseter muscle tone to Hcrt microinjections in 5M.

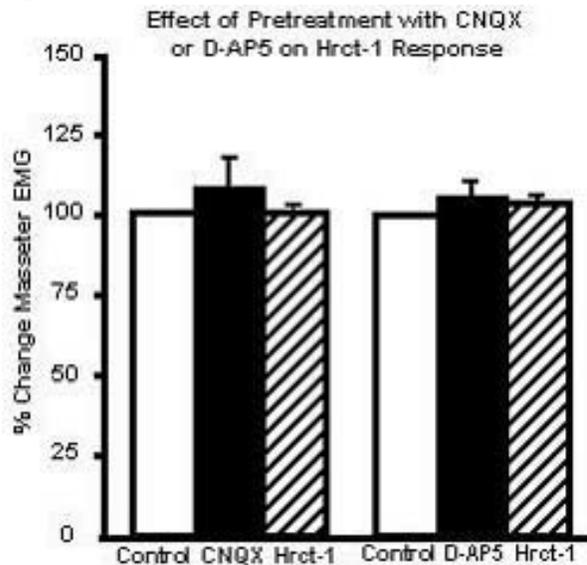
**Methods:** Eight decerebrate, unanaesthetized cats were used in these experiments. Mean arterial blood pressure and bilateral masseter muscle activity were monitored while microinjections of artificial cerebral spinal fluid (aCSF), Hrcr-1 or glutamate antagonists [6-cyano-7-nitroquinoxaline-2,3(1H,4H)-dione (CNQX) or D-(-)-2-amino-5-phosphonovaleric acid (D-AP5)] were made into the 5M. To verify that microinjection had no effect on basal masseter muscle activity aCSF was injected into 5M. To demonstrate the excitatory effects of Hrcr-1 on putative 5M motoneurons, we unilaterally microinjected 0.5 ml of 0.1 mM Hrcr-1 into 5M while monitoring masseter EMG activity. To determine whether muscle tone changes are mediated by Hrcr-dependent glutamate release, we unilaterally microinjected either 0.5 ml of 1 mM CNQX or 50 mM D-AP5 into 5M immediately prior to microinjection of 0.5 ml of 0.1 mM Hrcr-1.

**Results:** Unilateral microinjection of 0.5 ml of aCSF into 5M had no effect on ipsilateral masseter EMG activity (paired t-test:  $df = 5$ ;  $t = 0.727$ ;  $p = 0.816$ ). However, unilateral microinjection of Hrcr-1 increased ipsilateral masseter muscle tone (integrated EMG activity) by  $169.2 \pm 30\%$  (range: 4.1 – 351.9%) compared with baseline control (paired t-test:  $df = 13$ ;  $t = 2.68$ ;  $p = 0.02$ ) (see Fig.1). The latency and duration of the response were:  $8.2 \pm 2.1$  s (range: 1 – 24 s) and  $23.4 \pm 5.7$  min (range: 1.5 – 56.0 min), respectively. Unilateral microinjection of CNQX had no significant effect on ipsilateral masseter EMG activity (paired t-test:  $df = 7$ ;  $t = 0.896$ ;  $p = 0.40$ ). Unlike Hrcr-1 application alone, Hrcr-1 microinjection did not alter ipsilateral masseter EMG activity after application of CNQX (paired t-test:  $df = 7$ ;  $t = 0.896$ ;  $p = 0.43$ ) (see Fig.2). Unilateral microinjection of D-AP5 had no effect on ipsilateral masseter EMG activity (paired t-test:  $df = 3$ ;  $t = 0.765$ ;  $p = 0.50$ ); nor did the subsequent application of Hrcr-1 (paired t-test:  $df = 3$ ;  $t = 1.64$ ;  $p = 0.25$ ) (see Fig.2).

**Figure 1**



**Figure 2**



**Conclusions:** Microinjection of Hrcr-1 into the 5M increases masseter muscle tone, however, pretreatment with the glutamate antagonists, CNQX and D-AP5 abolishes this response. We hypothesize that Hrcr-1 does not postsynaptically excite 5M motoneurons, rather it acts to cause presynaptic release of glutamate, which in turn excites 5M motoneurons.

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**015.A**

**EFFECT OF LATERAL HYPOTHALAMIC LESIONS WITH THE NEUROTOXIN HYPOCRETIN2-SAPORIN ON SLEEP-WAKEFULNESS IN LONG EVANS RATS**

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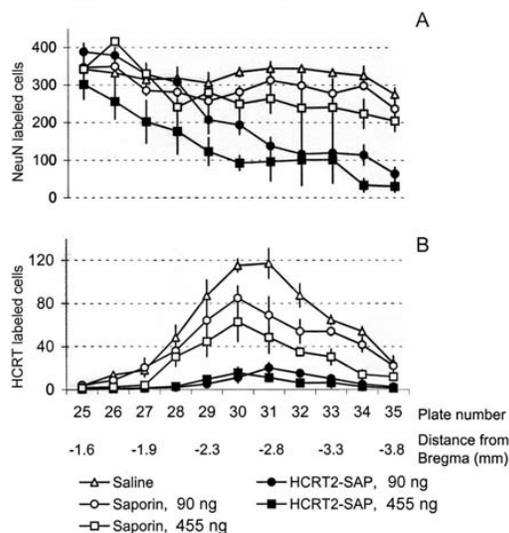
**Introduction:** Hypocretin has been linked to narcolepsy because humans with narcolepsy have a profound loss of HCRT neurons and HCRT-null mice have narcoleptic symptoms. To facilitate research on this peptide system we created a neurotoxin that kills cells expressing the hypocretin receptor (1) by conjugating the ligand, hypocretin-2 (HCRT2), to the

toxin saporin (SAP). Hypocretin2-saporin (HCRT2-SAP) applied to the lateral hypothalamus (LH) kills HCRT receptor bearing neurons, including the HCRT neurons and produces symptoms of narcolepsy (1). In this study we assess whether narcolepsy is due solely to HCRT neuronal loss or whether loss of other non-HCRT neurons in the LH is also likely to occur. We also monitor entrained and free-running rhythms after LH HCRT lesions to address the question whether HCRT neurons are necessary to awaken the animal at specific times of the day.

**Methods:** Twenty-three male Long-Evans rats (400-550 g) were implanted under anesthesia with a temperature transmitter and sleep recording electrodes. The temperature in the sleep recording room was 25°C, and a 12:12h light-dark cycle (7AM-7PM lights on; 100 lux) was maintained. Twenty-one days after lesion the lights were turned off and temperature rhythms were monitored under free-run conditions for one month. The HCRT2-SAP (90 ng or 455 ng/0.5 µl; Advanced Targeting Systems, San Diego, CA), saporin (90 ng or 455 ng/0.5 µl; Sigma), or pyrogen free saline were delivered (Picospritzer; 0.5 µl) bilaterally using a glass micropipette (tip diameter=20 µm).

**Figure 1**

Anterior-posterior distribution of NeuN- (A) and HCRT-neurons (B) in rats with lateral hypothalamic lesion



**Results:** Analysis of sleep and rhythms The two doses of HCRT2-SAP increased REM sleep, NREM sleep, and sleep-onset REM sleep periods at night 6 days post-injection. Nighttime amounts of NREM sleep returned to control levels 21 days post-injection in rats injected with 90 ng of HCRT2-SAP but remained increased in rats injected with 455 ng of HCRT2-SAP, although both doses of HCRT2-SAP effectively destroyed HCRT neurons (88 and 91% loss of HCRT cells respectively). SAP alone produced only transient increases in sleep. The 455 ng HCRT2-SAP rats were hypothermic at night (perhaps because of increased night time sleep) but temperature peak and nadir occurred at the same time as saline rats indicating that a profound loss of LH neurons, including

HCRT neurons does not alter the entrained temperature rhythm. In free-run conditions HCRT2-SAP lesioned rats also demonstrated an intact temperature rhythm. Analysis of neuronal loss Compared to saline rats (Fig. 1), HCRT2-SAP significantly reduced the numbers of NeuN-positive cells (NeuN marks a protein specific to neurons) in the perifornical area (34% neuronal loss for the dose of 90 ng and 55% for the dose of 455 ng,  $P < 0.01$ ). Number of NeuN positive cells in the dorsomedial (DMH) and ventromedial (VMH) nucleus of the hypothalamus was reduced by the 455 ng of HCRT2-SAP, but did not change in the rats treated with 90 ng of HCRT2-SAP. Number of NeuN-positive cells after SAP injection did not change in the DMH and VMH, and slightly decreased in the perifornical area.

**Conclusions:** The results indicate that narcoleptic-like sleep seen in the HCRT2-SAP treated rats is associated with the loss of HCRT neurons, but the increase in NREM sleep during the night is probably produced by the loss of other neurons besides HCRT-containing neurons. Moreover, LH and HCRT neurons are not responsible for awakening the animal but once awake the LH and HCRT neurons keep the animals awake at night. These results suggest that there is a loss of additional non-HCRT neurons in human narcolepsy.

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#### 016.A

##### IMMUNOSUPPRESSANT TREATMENT DELAYS ONSET OF GENETIC CANINE NARCOLEPSY AND PREVENTS DEVELOPMENT OF SEVERE SYMPTOMS.

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**Introduction:** Degenerative changes (1) and increased display of major histocompatibility complex class II (MHC-II) antigens (2) have been linked to symptom onset in genetically narcoleptic Doberman pinschers. This suggests that the degenerative changes and the development of narcoleptic symptomatology that result from a mutation of the hypocretin (orexin) receptor-2 gene in these dogs (3) may involve the immune system. We thus attempted to alter the course of genetic canine narcolepsy by administering immunosuppressive and anti-inflammatory drugs.

**Methods:** Experimental dogs were treated with methylprednisolone, methotrexate and azathioprine starting at postnatal day 3, and all dogs were raised in an environment that minimized pathogen exposure. To examine the possibility that the

drug regimen directly affected symptoms, transient treatment at the same dosages was carried out in 6 narcoleptic dogs. Symptoms in treated (n=7), untreated (n=7) and transiently treated (n=6) animals were quantified using the food elicited cataplexy test (FECT), modified FECT (mFECT), and actigraphy.

**Results:** With treatment, time to symptom onset was increased by a mean of 109% ( $F=29.6$ ,  $df=6, 1$ ,  $p<.002$ ), time spent in cataplexy during tests was reduced by more than 85% ( $F=32.5$ ,  $df=5, 223$ ,  $p<.0001$ ), and sleep and waking periods were greatly consolidated. Short-term drug administration did not reduce symptoms. Treatment was stopped at 6 months, after which experimental animals remained less symptomatic than controls for at least 1 year.

**Conclusions:** Oral administration of immunosuppressive and anti-inflammatory drugs delays disease onset and prevents the development of severe symptoms in these animals. Since approximately 95% of all human narcoleptics share an MHC-II haplotype (HLA-DQB1\*0602) and there is gliosis at the site of hypocretin cell loss, immune related factors may play a role in causing human narcolepsy as well. Our treatment is the first shown to affect symptom development in animal or human narcolepsy.

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### Oral Presentation Impact of Psychiatric Conditions on Sleep

#### 017.Q

#### DIURNAL VARIATION OF CSF HYPOCRETIN-1 (OREXIN A) LEVELS IN CONTROL AND DEPRESSED SUBJECTS

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**Introduction:** CSF hypocretin-1 levels have not been studied in mood disorders. Patients with narcolepsy, a condition frequently associated with depression, have low CSF hypocretin-1 levels. Hypocretins have excitatory effects on monoaminergic transmission. Major depression, a condition associated with short REM latency and HPA axis abnormalities, is typically treated with monoaminergic reuptake blockers. Hypocretin release is higher during the active phase in rats and may consolidate wakefulness and reduce sleep at specific circadian

times. The hypocretin system is also activated with sleep deprivation, an effect that could mediate the antidepressant effects of sleep deprivation. Finally, hypocretins have been suggested to activate the HPA axis. To study the role of hypocretins in depression, we examined CSF hypocretin-1 in control and depressed subjects (before and after treatment) over the 24hr period.

**Methods:** Fourteen controls (6 males,  $41\pm 4$  y) and 15 depressed subjects (5 males,  $39\pm 3$  y, baseline Hamilton Depression Scale= $19.5\pm 1.1$ ; 3 bipolar type 1, 4 bipolar type 2, others with unipolar or first depressive episode) were included. CSF was drawn continuously in supine subjects for 24hr using an indwelling intrathecal catheter under entrained light-dark conditions. Depressed subjects were studied before and after 5 weeks of sertraline (n=10, 3 non responders) or bupropion (n=5, 3 non responders). CSF hypocretin-1 was measured using a direct radioimmunoassay in 10 minute samples across the 24hr. Repeated ANOVA and sinusoid curve fitting were used to assess diurnal variation and estimate phase and amplitude, respectively. Other analyses involved t-tests across groups.

**Results:** Hypocretin levels did not vary with age and sex. Levels varied slightly but significantly across the diurnal cycle, with lower levels at midday ( $p<.0001$ ). Sinusoid curve fitting results are indicated in Table 1 and Figure 1. Interestingly, amplitude was reduced in depression (before and to a lesser extent after treatment) (Table 1 and Fig. 1). Baseline levels did not differ between depression and controls. Hypocretin-1 decreased after sertraline (-14%,  $p<.01$ ) but not bupropion (-4%, NS). Neither treatment-induced decreases nor changes in day/night differences (e.g. circadian amplitude) correlated with antidepressant response. Interestingly, however, day/night differences correlated before and after treatment, suggesting a stable trait in depressed subjects.

**Table 1**—Sinusoidal curve fitting in control and depressed patients

	Control	Depressed patients	
		Baseline	After Treatment
Phase†	13:58 ± 0:22	12:54 ± 1:45	13:09 ± 1:26
Amplitude*	5.72% ± 0.55	1.77% ± 0.81	2.83% ± 1.06

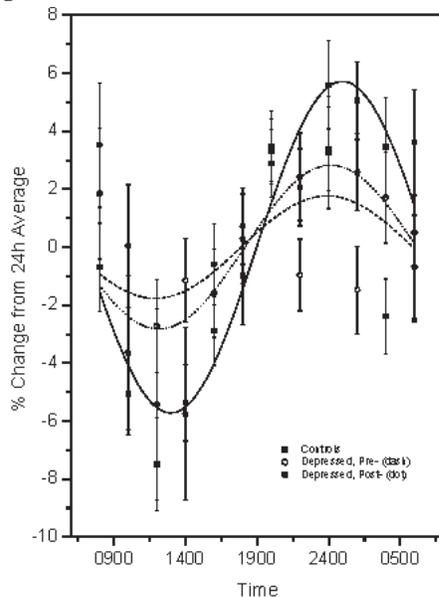
Data are mean ±SD. †=phase of hypocretin minimum (time).

\*= half peak to trough (% of baseline hypocretin values).

**Conclusions:** CSF hypocretin-1 levels fluctuates moderately but significantly across the 24hr (<15%) under bedrest condition. Lumbar sampling at anytime is thus adequate to diagnose narcolepsy. Slightly lower values are observed around 2 pm, possibly reflecting decreased release in the late part of the dark period and a delayed and dampened oscillation. Less likely, spinal levels may be truly reflecting brain levels and would be opposite with what was observed in nocturnal rodents. We also found that sertraline but not bupropion slightly decreased levels, suggesting serotonergic influences on hypocretin tone. Our results are consistent with previous findings in depression indicating that multiple diurnal physiological measures are dampened. Interestingly, relief of depression in many subjects was not correlated with restored rhythmicity but a slight improvement was noted after treatment. These results suggest that depressive mood and hypocretin diurnal variation are

independent, with the caveat that longer term treatment studies may lead to more significant changes in hypocretin diurnal variation.

**Figure 1**



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Research supported by NIH NS23724 to EM.

**018.Q**

**SLEEP EEG TOPOGRAPHY IN PATIENTS SUFFERING FROM MODERATE DEPRESSION**

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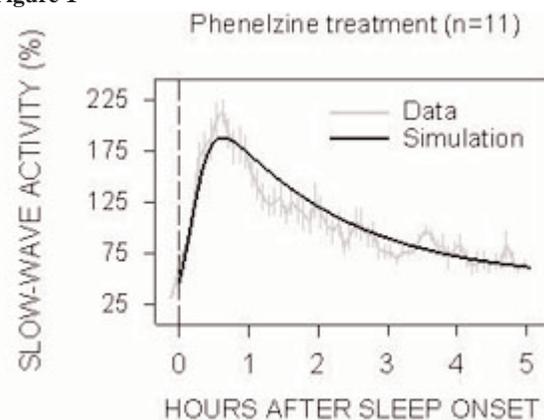
**Introduction:** After virtually complete elimination of REM sleep in depressed patients with the MAO inhibitor, phenelzine, EEG slow-wave activity (SWA, power within 0.75-4.5 Hz) reached a maximum within the first hour of sleep and then declined exponentially (1). This time course is consistent with Process S in the Two-Process model of sleep regulation, and has been successfully simulated without major adjustments by leaving-off the REM sleep trigger (2) (Figure). These data challenge the notion that SWA is abnormally distributed in patients with depression. To investigate possible alterations in homeostatic sleep regulation, we compared sleep and sleep EEG spectra between depressed patients and healthy controls. Given the possibility of local aspects of sleep regulation (3), regional EEG analyses were included.

**Methods:** Polysomnographic recordings were conducted in 16 drug-free outpatients with major depression (8 women, 8 men;

mean age: 41.2 ±2.0 [SEM] years) and 16 age- and gender-matched healthy controls (41.1±2.1 years). They slept in the sleep laboratory after at least one adaptation night between ~ 22.30 and 06.30 h. Individuals with sleep apnea and/or nocturnal myoclonus, patients with significant co-morbid diagnoses, and healthy probands with a positive family history for psychiatric disorders were excluded. The EEG was obtained in both hemispheres from 3 bipolar derivations (fronto-central [FC], centro-parietal [CP] and parieto-occipital [PO]) along the antero-posterior axes (3). Sleep stages were visually scored from the C3-A2 derivation, and the EEG signals of all derivations were subjected to spectral analysis. Depressive symptoms were rated with the Hamilton Rating Scale of Depression (HRSD), Beck Depression Inventory (BDI) and Profile of Mood States (POMS). Differences between the groups were investigated by repeated measures ANOVA.

**Results:** The HRSD (22.3±1.1 vs. 0.7±0.3), BDI (23.3±2.3 vs. 0.5±0.2) and POMS (depression subscale: 26.8±3.7 vs. 1.1±0.7) revealed significantly higher scores in patients than in controls. No changes were found in visually scored sleep variables and all-night EEG spectra in non-REM and REM sleep. The ultradian modulation of SWA by the non-REM/REM sleep cycles, as well as the declining trend of SWA during sleep did not differ between the groups. For regional analyses in non-REM sleep, the spectral gradients between adjacent derivations were computed. A posterior dominance in the FC/CP ratios was present between 2.5-11.0 Hz in the controls, and between 2.0-13.5 and 15.0-20.0 Hz in the patients. The CP/PO ratios revealed an anterior dominance in delta (controls: 1.0-2.75 Hz; patients: 1.0-3.5 Hz) and alpha-sigma frequency bands (controls: 10.25-13.75 Hz; patients: 10.0-13.75 Hz). ANOVA disclosed no significant 'group' x 'derivation' interactions.

**Figure 1**



**Conclusions:** The lack of differences in sleep architecture, sleep EEG power spectra, the time course of SWA, and sleep EEG topography suggests that the homeostatic facet of sleep regulation is unchanged in moderately depressed outpatients when compared with healthy controls.

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Research supported by the Swiss National Science Foundation (823A-056616 and 3100-053005.97), the National Institute of Mental Health (MH38738), the UCSD Mental Health Clinical Research Center (MH30914), the General Clinical Research Center (M01-RR00827) and the Department of Veterans Affairs.

### 019.Q

#### EFFECTS OF HORMONAL REPLACEMENT THERAPY ON SLEEP IN HEALTHY AND DEPRESSED MENOPAUSAL WOMEN

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**Introduction:** The aim of this study was to examine the effects of hormone replacement therapy (HRT) on sleep polysomnography (PSG) in normal control (NC) and depressed (DP)(DSM-IV<sup>1</sup> criteria for a major depressive episode) menopausal women.

**Methods:** PSG measures were obtained pre- and post-treatment in 16 menopausal women (10 NC and 6 DP) randomized to 8 weeks of oral HRT: NC women received estradiol (E2)(Estrace 2mg daily), estradiol plus progesterone (P4)(medroxyprogesterone acetate 5 mg daily) or placebo. DP received E2, antidepressant (AD)(fluoxetine 20-40 mg daily), or E2 plus AD treatment.

**Results:** At baseline (BSL), DP (aged 54.85 ± 3.07) compared with NC (aged 57.20 ± 7.99) women, had decreased mean sleep latency (SL), stage 3 (S3), delta, total sleep time (TST) and sleep efficiency (SE) and increased REM latency (RL), REM density (RD), REM, and wake after sleep onset (WASO). In NC women, E2 compared with BSL, decreased SL and WASO and increased S2, S3, S4, delta, REM, TST and SE. E2 plus P4 decreased SL and WASO and increased S2, S4, delta, REM, TST and SE but not to the extent of E2 treatment alone. In DP, E2 compared with BSL decreased S1, S3, delta, REM, TST and WASO and increased SL, RD, S2, S4, and SE. AD treatment decreased RL, S2, S3, S4, delta, TST and WASO and increased SL, RD, and REM. E2 plus AD treatment decreased S2, S4, delta, REM, TST, WASO, and SE and increased SL, RD, S1 and S3.

**Conclusions:** DP vs. NC menopausal women have poorer sleep quality as reflected in decreased delta, TST and SE and more WASO. They also have more REM sleep and REM density, characteristic of sleep pathologies in depression. In NC women, E2 has beneficial effects on sleep as evidenced by changes in a wide variety of measures: It decreases SL and WASO and increases S2-4, delta, REM, TST and SE. P4 antagonizes the beneficial effects of estrogen on sleep. In contrast, E2 does not benefit the sleep of DP as it decreases delta sleep and TST and increases SL and RD (although it does decrease WASO and increases S4 and SE to some extent). AD treatment, although it improves mood in DP, does not improve

sleep quality as evidenced by decreases in delta and TST and increases in SL and the depressogenic measures of RD and REM sleep. The combination of E2 plus AD treatment, although the most efficacious in improving mood, generally does not benefit sleep in that S4, delta, TST and SE were decreased and SL and RD increased with the combined treatment. As other studies indicate, AD treatment is associated with decreased REM sleep and in this study, with decreased WASO. Although increasing attention is being paid to the effects of HRT on reproductive, cardiovascular and metabolic systems, further attention to the differential effects of HRT on the CNS and sleep are warranted in healthy vs. depressed women.

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Research supported by NIMH grant R01 MH59919, MH-42831, CRC grant MH-30914 and M01-RR-00827.

### 020.Q

#### POLYSOMNOGRAPHIC FINDINGS IN THE ACUTE AFTERMATH OF TRAUMATIC INJURY AND THE DEVELOPMENT OF PTSD.

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**Introduction:** The potential for chronicity and treatment resistance when PTSD becomes established has stimulated interest in understanding the early pathogenesis of the disorder. Arousal regulation and memory consolidation appear to be important in determining the development of PTSD, and both are functions of sleep. Sleep findings from chronic PTSD are complex and somewhat contradictory, and data from the acute phase are quite limited. The aim of the present study was to obtain polysomnographic recordings (PSGs) during an acute period following life-threatening experiences and injury, and to relate measures of sleep duration, maintenance, and architecture, and the timing, intensity and continuity of rapid eye movement (REM) sleep to the early development of PTSD.

**Methods:** Hospitalized injured subjects were recruited who could recall, and had been frightened by their recent life threatening experiences. Twenty one participants who could discontinue narcotic analgesics without pain significantly interfering with sleep received at least one PSG close to the time of medical/surgical stabilization and within a month of injury. PTSD symptoms were assessed concurrently and 6 weeks later. Sleep measures were compared between injured subjects with and without significant PTSD symptoms at follow-up, and 10 healthy, non-injured controls, and were also correlated with measures of PTSD severity.

**Results:** There was more wake time after the onset of sleep and a trend toward greater eye movement activity during REM sleep in injured trauma exposed patients compared to non-injured controls but these measures did not differ in relation to the development of PTSD. The injured group that developed PTSD symptoms had shorter average duration of REM sleep

prior to a stage change and greater number of REM periods. The average duration of "continuous REM sleep" correlated positively, and the number of REM periods correlated negatively with PTSD severity at follow-up. Percentage of slow wave sleep correlated positively with initial severity of PTSD avoidance symptoms.

**Conclusions:** General sleep disturbance was similar for injured subjects with recent trauma exposure who did and did not develop PTSD and there was an association of avoidance symptoms and greater slow wave sleep. The development of PTSD symptoms following traumatic injury was associated with a more fragmented pattern of REM sleep. This is consistent with the possibility that adaptive functions in processing traumatic memory that have been attributed to REM sleep, may be compromised by disruption of its continuity.

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## 021.Q

### PREVALENCE OF SLEEP-DISORDERED BREATHING IN TRAUMATIZED DISASTER SURVIVORS

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**Introduction:** Following the Cerro Grande Fire in Los Alamos, NM (May, 2000), sleep disorders were widespread and complex in 78 evacuees with posttraumatic stress seeking treatment for insomnia 10 months post-disaster (1). Symptom reports indicated that 95% of participants met Criteria A (EDS) or B (2 of 5 items listed last in Table 1) of the 1999 revised research diagnostic criteria for sleep-disordered breathing (SDB) (2). Of these 74 possible cases, 37 of 41 screened positive for SDB on a portable sleep-breathing assessment device (Autoset II Plus, ResMed). The current study investigated patients undergoing PSG to confirm SDB and compared them to those screened or suspected of SDB that did not undergo PSG.

**Methods:** In 41 screened with Autoset, mean (SD) AHI = 12.28 (9.93) and mean (SD) Flattening Index (FI) = 30.05 (14.71). Flattening is a measure of airflow limitation developed to facilitate auto-titration of CPAP. High FI in the context of low AHI seems to indicate a pattern of breathing consistent with UARS. Based on objective findings, the 41 tested were classified as: 21 predominantly UARS; 16 predominantly OSA; and, 4 without SDB. Fourteen of these 37 potential SDB cases underwent PSG at one of five different sleep labs in Los Alamos, Santa Fe, and Albuquerque. Self-report data were compared among three groups of patients: PSG tested (PSG-T, n=14), Autoset screened positive but not PSG tested (AT-S, n=23), or suspected of SDB but no screening or testing (SNT, n=33).

**Results:** All 14 PSG-T cases were diagnosed with SDB. The three-way comparison (Table 1) revealed no statistically sig-

nificant differences for age, gender, insomnia severity (ISI), functional impairment (FOSQ), loud snoring, depression (HSCL-25), or any of the five Criteria B symptoms (all  $p > .11$ , most  $p > .41$ ). Only BMI ( $p = .02$ ) (PSG-T was lower) and ESS ( $p = .07$ ) (PSG-T was higher) showed small differences.

Table 1

Variable	PSG-T (n=14)	AT-S (n=23)	SNT (n=33)
Age (M)	45.14	53.65	52.03
BMI (M)	25.45	23.82	27.07
Female (%)	43	39	30
ISI (M)	16.79	15.96	16.52
FOSO (M)	15.38	16.06	16.19
ESS (M)	11.64	8.87	7.67
Snoring (%)	43	30	39
HSCL-25 (M)	1.92	1.91	1.95
Obstructive Breathing (%)	14	35	24
Recurrent Awakenings (%)	93	91	91
Unrefreshing Sleep (%)	93	83	79
Daytime Fatigue (%)	50	48	48
Difficulty Concentrate (%)	57	78	82

**Conclusions:** The group testing positive on PSG was minimally different than the two groups suspected of SDB that did not undergo PSG. Thus, the likelihood of SDB in the latter two groups, all of whom met Criteria B (2), appears high. These findings suggest an important role for clinical sleep medicine in the treatment of trauma survivors. Sleep disturbance in post-traumatic stress patients appears fairly complex, owing in part to the presence of SDB, but SDB is not usually high on the differential diagnosis of trauma survivors with insomnia. Nonetheless, failure to treat SDB might contribute to refractory insomnia (3), which is common in PTSD patients. Last, a portable device to screen for SDB at-home may be an ideal pathway to engage trauma survivors concerned or fearful about sleeping in a lab. Future studies must explore how to facilitate treatment of SDB in trauma survivors and how such treatment impacts upon their physical and mental health.

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022.Q

LATERALIZATION OF REM SLEEP EEG IN AUTISTIC SPECTRUM DISORDERS

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**Introduction:** Atypical specialization of cerebral hemisphere has been described in autistic spectrum disorder (ASD) (1). The aim of the present study was to investigate hemispheric lateralization using quantified EEG analysis (qEEG) during REM sleep, a state characterized by an activation of thalamo-cortical neuronal networks.

**Methods:** Bilateral frontal (Fp1, Fp2, F7, F8), central (C3, C4), temporal (T3, T4, T5, T6) and occipital (O1 et O2) monopolar EEGs referred to linked ears were recorded in eight right-handed ASD participants with normal intelligence (7M, 1F; mean age 20.5 ± 3.3 years) and eight matched controls (7M, 1F; mean age : 21.8 ± 3.5 years) during two consecutive nights. Sixty to 90 seconds of artifact-free, quiescent REM sleep EEG samples were Fast Fourier transformed. Spectral analysis was performed on total frequencies and four frequency bands, namely: Beta (13.0-19.75 Hz), Alpha (8.0-12.75 Hz), Theta (4.0-7.75 Hz) and Delta (0.75-3.75 Hz). EEG lateralization was determined by computing a coefficient using the formula “right-left/right+left”, applied on spectral amplitude values (µ V) from homologous right and left electrodes. We first sought to verify in each group whether lateralization coefficients were different from zero. We then compared lateralization coefficients between groups.

**Table 1**—EEG lateralization coefficients in ASD and control participants (mean±s.e.m.). Negative values mean left lateralization. \* = Significantly different from zero. ♦ = Significant group differences

Areas of interest	Frequency bands	Controls	ASD
Fp	Delta ♦	-0,05±0.01	-2,58±0.00*
	Theta	1,19±0.01	-1,68±0.00*
	Alpha	2,32±0.02	-1,60±0.01
	Beta	1,86±0.02	-0,90±0.00
	Total	0,94±0.01	-1,99±0.00*
F	Delta	1,61±0.01	-1,68±0.01
	Theta	2,71±0.01*	-0,87±0.01
	Alpha	2,11±0.01	-1,12±0.01
	Beta	3,88±0.02 *	2,76±0.02
	Total	2,18±0.01	-0,39±0.01
O	Delta	2,74±0.01*	1,67±0.01
	Theta	2,08±0.01	0,84±0.01
	Alpha	0,77±0.02	1,48±0.01
	Beta	0,99±0.01	-0,05±0.01
	Total	1,74±0.01	1,23±0.01

**Results:** Control participants show a right frontal lateralization on Theta and Delta frequencies and a right occipital lateralization on Delta frequencies. ASD participants rather showed a left prefrontal lateralization on Theta, Delta and Total frequency bands. ASD participants showed a greater (left) Delta lateralization coefficient over the prefrontal area compared to controls.

**Conclusions:** This study supports the hypothesis of abnormal cerebral lateralization in ASD. Whether these observation are related to atypical lateralization of cognitive functions or to atypical dream reports from REM sleep (2) needs to be further investigated.

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023.Q

IS ANTIDEPRESSANT OR ANTIPSYCHOTIC MEDICATION USE ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA OR PERIODIC LEG MOVEMENTS OF SLEEP AS A CAUSE OF EXCESSIVE DAYTIME SLEEPINESS? A PROSPECTIVE CLINICAL AND POLYSOMNOGRAPHIC STUDY.

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**Introduction:** In the past, some case series have suggested antidepressant and antipsychotic medication use to be associated with, or precipitate obstructive sleep apnea(OSA) and periodic leg movements of sleep(PLMS). These were largely observational studies and the majority lacked polysomnogram(PSG) data. To address this question, we performed a prospective study(1998-2000) of all patients referred to the sleep center with excessive daytime sleepiness (EDS)and associated antidepressant/antipsychotic medication use.

**Methods:** Two hundred and eight-eight patients (63.5% males; mean age 51.56 years) were referred to the sleep center with EDS. Thirty one percent patients were on long term antidepressants/antipsychotic medications. Subjective sleep complaints using the Epworth Sleep Scale, modified depression scale and medication use were documented in all cases and all patients underwent a PSG. Data was analyzed using multivariate regression with apnea-hypopnea index(AHI) and the jerk index respectively as the dependent variables to determine which factors predicted OSA and PLMS.

**Results:** Factors predictive of severe OSA were obesity(p< 0.001), older age(p = 0.022), high ESS scores(p = 0.004), presence of depression (p = 0.044). Antidepressants and antipsychotic medications were not predictors (p =0.83). When depression was excluded (due to redundancy of depression and antidepressant use) from the model, antidepressants and

antipsychotic medications were still not predictors. Multivariate analysis using PLMS as the dependent variable yielded only older age as a predictor ( $p < 0.001$ ).

**Conclusions:** In the present prospective PSG supported study of patients with EDS, the known predictors included obesity and older age. The ESS was highly predictive of OSA. Depression was also correlated with OSA. However, in this study, antidepressant or antipsychotic medication use was not predictive of OSA or PLMS. EDS in patients with depression or psychosis taking medications is probably unrelated to OSA or PLMS and may be a directly related to depression or the sedating effect of antidepressant/antipsychotic medications.

## 024.Q

### CHANGES OF SEXUAL ACTIVITY, ERK, PERK, PP1 AND MPK-2 IN RAT MODEL OF DEPRESSION

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**Introduction:** It has been well documented that rats neonatally treated with REM sleep suppressant, clomipramine (CLI rats) have multiple behavioral abnormalities seen in human depression such as diminished sexual behavior, decreased aggressive behavior and decreased pleasure-seeking behavior (1). These findings imply that CLI rat may have weaker neuronal response to neuronal and humoral activation. Recent reports indicate that the initiation of a mitogen-activated protein kinases (MAPK) molecular cascade is an essential in synaptic activities during basic behavioral activation. Extracellular signal-regulated kinase (ERK) is one group of such protein kinase that belongs to the larger family of MAPK. ERK is localized to synapses and dendrites in neurons and activated by phosphorylation in response to many neurotransmitters and growth factors (2). Phosphorylation of ERK is reported to be increased by 5-HT, dopamine and by the treatment with psychostimulants including cocaine, apomorphine. The current study is aimed to disclose the possible relationship of MAPKs with depressive behavior.

**Methods:** Rats were treated with either CLI, 20mg/kg or equivolume saline, twice daily from age of 8 to 21 days. Sexual behavior was measured three times at the age of three to four months. After behavioral tests, rats were sacrificed and prepared for western blot. Brain levels of ERK1, ERK2, phosphorylated ERK1 (pERK1), pERK2, MAPK phosphatase-2 (MKP-2) and protein phosphatase 1 (PP1), which are involved in dephosphorylation of pERK, were determined. The pERK was determined with mouse monoclonal antibodies against pERK. The total ERK levels were evaluated with rabbit polyclonal antibodies against both ERK and pERK. The PP1 and MKP-2 were detected with corresponding antibodies. Proteins were detected using a chemiluminescence procedure. The integrated optical density was quantified.

**Results:** The major findings are: 1) CLI rats had significant lower sexual activity in all five variables (mount, mount latency, ejaculation, ejaculation latency and post ejaculation interval) compared with control rats; 2) CLI rats had significant

lower levels of pERK1, pERK2 and ERK2 in the frontal cortex compared with saline treated control rats; 3) CLI rats also had reduced level of pERK1 and pERK2 in the hippocampus but the difference is significant only for pERK1; 4) The levels of PP1 in both prefrontal cortex and hippocampus were significantly higher in CLI rats than in control rats; and 5) Differences of MKP2 between CLI and control rats were not significant.

Figure 1

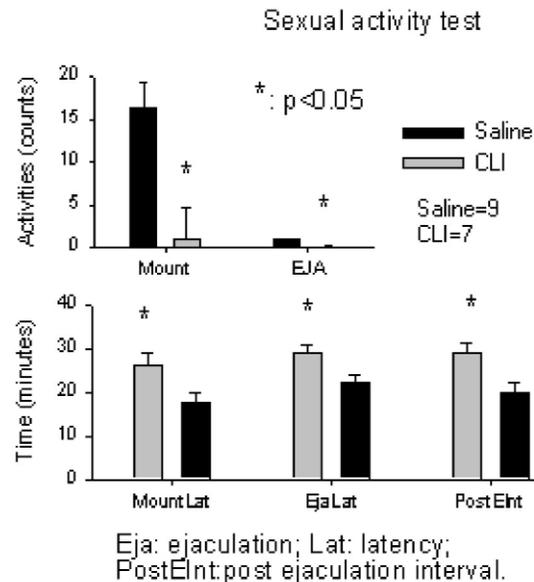
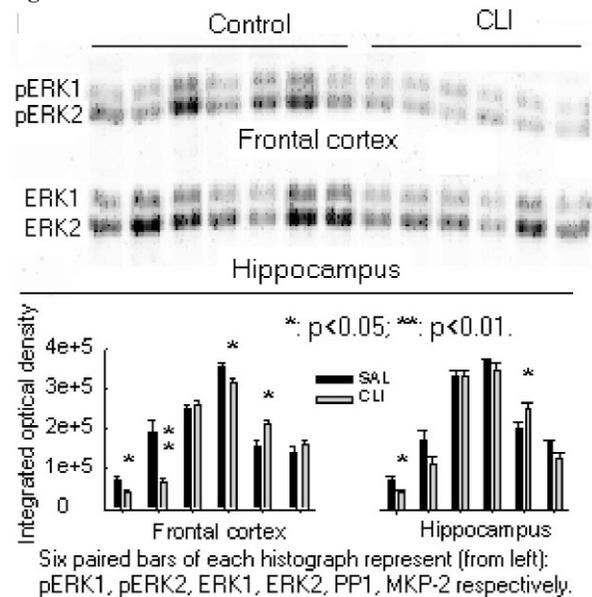


Figure 2



**Conclusions:** Our major finding is that the decreased level of ERK, ERK phosphorylation and enhanced ERK dephosphorylation (indicated by increased PP1) appear with the severe sexual deficits, which is one of the most common symptoms in human major depression, in CLI rats. These results are consis-

tent with the findings from human study of suicide depressants (3), which were reported to have lower level of ERK and pERK in the frontal cortex and hippocampus. These findings are consistent with the finding of increased cortical inhibition by transcranial magnetic stimulation in human depression, and indicate that 1) the depressive symptoms have reduced signal transduction in the cortex level and 2) CLI rats have the molecular changes in cortex similar as the severe depression in human.

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### Poster Symposium Treatment of Obstructive Sleep Apnea

#### 025.J

#### A LONGITUDINAL OBSERVATIONAL 3 YEAR COMPLIANCE STUDY OF PATIENTS TREATED WITH NASAL CONTINUOUS AIRWAY PRESSURE. (CPAP)

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**Introduction:** The gold standard non-invasive preferred treatment for sleep apnoea is nasal continuous positive airway pressure (nCPAP). Its efficiency however depends on long term effective use. There are no studies in this country regarding sleep apnea and the use of nCPAP. Many patients remain undiagnosed and untreated. This study was undertaken to assess long term compliance on nCPAP and to correlate this with symptom improvement on treatment. This was done by means of pre- and post-test questionnaires (identical questions). Our aims were to document the demographics of South African patients with sleep apnoea; to examine the financial implications as well as the impact of treatment versus no treatment. on nCPAP in patients with sleep apnea syndrome.

**Methods:** N=97 patients Mean age=48 yrs All males Indians=56% Whites=46% Blacks 0% Coloured 1.8%. Patients were referred by general practitioners and specialists. all patients completed a pre-test questionnaire on admission. All patients were diagnosed with sleep apnea syndrome on full polysomnogram. They were counseled, titrated on nCPAP on full polysomnogram. Mean A+HI index =60 Mean oxygen saturation low= 72% Mean follow up = 30 months. A Post-test

questionnaire identical to the pre-test questionnaire was completed telephonically. Only "yes" and "no" answers were required. A 56% return rate was realised.

**Results:** A Mc Nemar's test of variance was used to analyse and tabulate significant improvements in symptoms (p values). The patients were divided into 2 groups:G1=compliant (those who chose CPAP and stayed on the treatment)G2=non-compliant (those who did not choose treatment or stopped after 6 weeks. Drop off = 23%.The questionnaire outcomes were analysed according to: 1.No symptoms before or after treatment. 2.No symptoms before but developed after treatment. 3.Had symptoms before, but improved after treatment. 4.Had symptoms before treatment and symptoms persisted.For purposes of this study, group 3 was regarded as the most significant in terms of long term CPAP compliance. Conclusions showed significant improvements in symptoms such as snoring, breath holding, restlessness, concentration, headaches, and excessive daytime sleepiness. This correlates well with other research of this nature. Examination of the trend of the A+HI index related to long term compliance showed a positive correlation (p=.007).

**Conclusions:** Long term nCPAP compliance impacts on symptom improvement in sleep apnea patients.Long term compliance correlates with higher A+HI indexes.

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#### 026.J

#### THE EFFECT OF CPAP THERAPY ON SUBJECTIVE AND OBJECTIVE SLEEPINESS IN OBSTRUCTIVE SLEEP APNEA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS.

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**Introduction:** Although continuous positive airway pressure (CPAP) has become the standard of care in the treatment of obstructive sleep apnea (OSA), a systematic review has questioned its utility.<sup>1</sup> Since that review was published, a number of randomized controlled trials have been completed. We performed a meta-analysis to assess the effect of CPAP on sleepiness and update the current state of knowledge.

**Methods:** We conducted a thorough literature search of published, randomized controlled studies of CPAP in OSA including: a MEDLINE search, a review of the Cochrane database, and a review of all citations in identified studies. Meta-analyses were performed using the random-effects model of DerSimonian and Laird. Statistical heterogeneity was assessed using the Q statistic.

**Results:** a) Sixteen trials of CPAP in OSA were found. Two studies were excluded from analysis because endpoints did not include measures of sleepiness, one was excluded for recruiting only patients with positional OSA, and one crossover study was excluded for failing to randomize the order in which placebo and CPAP therapy were administered. b) The Epworth

Sleepiness Score (ESS) was reported in 11 studies (total of 706 subjects). In our analysis, CPAP reduced ESS an average of 2.87 more than placebo (95%CI [1.48,4.25],  $p<0.001$ , Figure 1). The heterogeneity ( $Q=62.3$ ,  $p<0.001$ ) found between studies could not be explained by differences in mean age, BMI, length of follow-up, or hours of CPAP use. However, trials of subjects with severe OSA plus sleepiness (i.e. mean apnea hypopnea index  $\geq 30$  and mean ESS  $\geq 11$ ) had a significantly greater change in ESS than the other trials ( $\delta$  ESS of 4.75 [2.97,6.53], versus 0.90 [-0.42,2.21],  $p<0.001$ , Figure 2). c) Objective measures of sleepiness were reported in 8 trials (6 MSLT and 2 MWT, total 482 subjects). Compared to placebo, CPAP increased sleep onset latency by 0.93 minutes ([0.10,1.76],  $p=0.04$ ) with little heterogeneity ( $Q=11.6$ ,  $p=0.12$ ).

Figure 1— All Trials

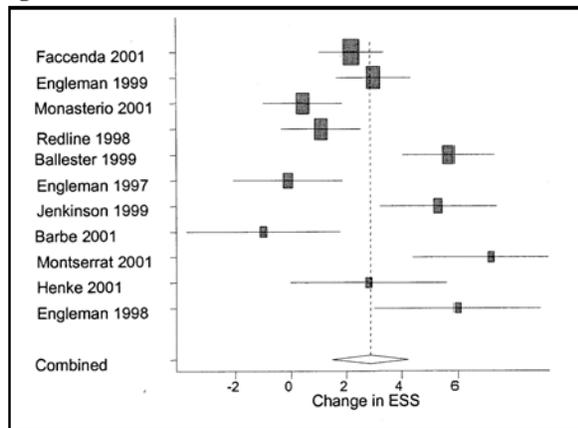
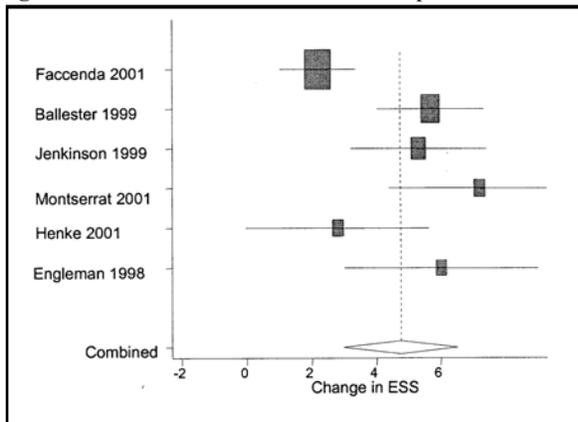


Figure 2—Trials with severe OSA and sleepiness



**Conclusions:** CPAP therapy significantly improves both subjective and objective measures of sleepiness in OSA. With respect to the Epworth Sleepiness Score, the effect of CPAP appears greater in populations with more severe sleep apnea and subjective sleepiness.

**References:**

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**027.J**

**EFFECT OF CPAP ON COGNITIVE FUNCTIONING IN PATIENTS WITH DEMENTIA AND SDB: PRELIMINARY RESULTS**

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**Introduction:** Patients with sleep disordered breathing (SDB) often suffer from some cognitive impairment. This observed impairment on cognitive tests has been attributed to nighttime intermittent hypoxemia and sleep disturbance. Studies examining the effect of CPAP on cognition in non-demented SDB patients have shown mixed results, however, many found that CPAP improved well-being (including depression), neuropsychological deficits (including improved vigilance) and quality of life. This study is examining whether CPAP treatment will improve cognitive functioning in patients with mild Alzheimer's disease (AD) and SDB.

**Methods:** The study is a randomized, double-blind, placebo-controlled trial of CPAP. Half the subjects receive six weeks of therapeutic CPAP. In a comparison group, half are first randomly assigned to three weeks of shamCPAP, followed by three weeks of therapeutic CPAP. Neuropsychological testing, including MMSE, is administered before the start of treatment, after three weeks, and after six weeks of treatment. Patients with mild probable AD (NINCDS-ADRDA criteria) are included. Each has sleep recorded in the home to confirm the diagnosis of (SDB; defined as an RDI>15), followed by a home MSLT and a comprehensive neuropsychological test battery. All are then admitted to the General Clinical Research Center (GCRC) for a CPAP titration night and a second night to sleep with the adjusted therapeutic or shamCPAP. They are then sent home with a CPAP machine. After three weeks, neuropsychological testing is repeated and subjects again return to the GCRC for a CPAP titration night and a second night to sleep with the adjusted CPAP. Subjects in the shamCPAP group then begin therapeutic CPAP. After another 3 weeks, a third neuropsychological test battery is administered and another home sleep recording is done. To date, two men (mean age 66.5 years; mean education 14 years; mean RDI = 16.9) have completed the protocol, one in each condition.

**Results:** Both subjects wore the CPAP for an average of over four hours a night, every night. Figure 1 shows the changes in Mini Mental Status Exam (MMSE), with the subject on therapeutic CPAP improving. The patient receiving CPAP had improvements on several of the cognitive tests, whereas the shamCPAP patient had deterioration in performance. For example, on the Category (Animal) Fluency Test (a test sensitive to the integrity of the semantic store as well as mental processing speed), the number of animal names generated improved over the three assessments for the subject on thera-

peutic CPAP but progressively decreased for the subject on shamCPAP.

Figure 1

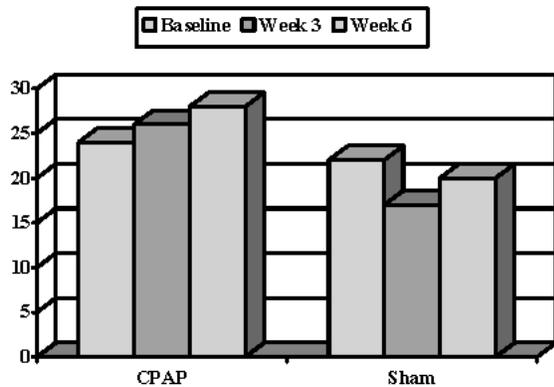
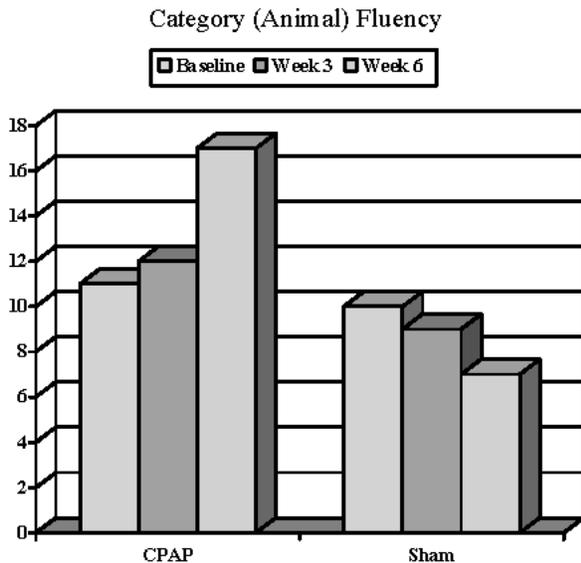


Figure 2



**Conclusions:** These results are very preliminary and are based on the first two subjects only. Nevertheless, the results suggest that CPAP treatment of SDB may yield improvement (or at least slow deterioration) in some aspects of cognitive functioning in AD patients with SDB. This study continues to enroll one-two subjects per month to further test this hypothesis with a goal of enrolling 100 patients by the end of the study.

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028.J

EFFECTS OF ESTROGEN REPLACEMENT THERAPY ON SLEEP-DISORDERED BREATHING IN POSTMENOPAUSAL WOMEN

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**Introduction:** Menopause is associated with increased prevalence of sleep-disordered breathing (SDB) with lower prevalence among postmenopausal women on hormone replacement therapy (HRT). A number of studies have supported the efficacy of HRT on sleep in postmenopausal women. Existing studies<sup>2,3</sup> evaluating the therapeutic benefits of estrogen replacement therapy (ERT) and other HRT regimens on SDB are based on very small samples and their results are inconsistent. The present study provides additional preliminary data on the impact of ERT on sleep and breathing in postmenopausal women.

**Methods:** Participants were 7 postmenopausal women who responded to newspaper ads and whose clinical presentation was consistent with a diagnosis of SDB, with an apnea-hypopnea index (AHI) > 10. Postmenopausal status was determined by cessation of menses at least 1 year before enrollment and confirmed by ovarian function lab test. Those with a current DSM-IV Axis I diagnosis, uncontrolled medical condition, BMI > 35 kg/m<sup>2</sup>, PLMS index > 5 per hour, RLS, a history of surgical menopause, or a history of taking ERT or HRT in the past 6 months were excluded from the study. Three single-night laboratory polysomnograms (PSG) were performed: screening/adaptation, baseline, and ERT. Within 2 weeks from the screening study, participants underwent a baseline study and then began ERT (a transdermal Vivelle dot patch (0.05 mg per day)). The third PSG occurred after 7-12 days on ERT. Respiration was measured by standard leads, including nasal cannula. Polysomnograms were scored without knowledge of treatment status. Sleep staging was based on Rechtschaffen and Kales (1968) criteria and respiratory events were scored based on the AASM (1999) criteria. Nonparametric Wilcoxon signed ranks test was used to compare sleep and respiratory measures at the two post screening nights (baseline versus ERT).

Table 1—Age, BMI, and Measures of SDB

	Age	BMI	AHI		AHI NREM		AHI REM		MinO <sub>2</sub> Sat		O <sub>2</sub> Sat* <90%	
			B	E	B	E	B	E	B	E	B	E
1	47	25.7	32.3	26.7	29.9	28.5	51.9	14.8	85.1	80.2	4.8	2.4
2	52	26.6	16.3	12.7	16.5	11.1	14.5	21.6	89.8	92.1	0	0
3	53	34.3	11.6	8.7	11.5	2.4	12.3	35.7	80.8	83.1	1.4	1.2
4	56	29.3	13.4	4.8	11.9	1.7	25.7	24.5	85.8	92.8	5.3	0
5	58	25.5	13.2	8.2	11.2	7.8	22.7	10.3	91.1	85.1	0	0
6	60	25.3	45.3	14.8	45.9	6.5	39.4	52.6	65.7	88.9	7.1	0.5
7	63	18.9	15.7	6.1	6.2	3.7	50.8	17.3	85.9	88.9	23.1	0.5
M	55.6	26.5	21.1	11.7	19.0	8.8	31.0	25.3	83.5	87.3	6.0	0.7
SD	5.4	4.6	12.8	7.5	14.0	9.3	16.4	14.5	8.5	4.7	8.0	0.9
p	-	-	.018		.018		.612		.397		.043	

\* Percent of TST O<sub>2</sub> saturation was below 90%

B Baseline; E ERT

**Results:** Results are summarized in Tables 1 and 2. Compared to baseline (B), ERT (E) was associated with significant reduction (44.5%) in the AHI and marked improvement in oxygen saturation. Overall, there were no significant differences between ERT and baseline on measures of sleep architecture, although there was a statistical trend for greater slow wave sleep (Stage 3 & 4) following ERT.

**Table 2—Sleep Parameters**

	TST (min)		SE (%)		SL (min)		WASO (min)		S REM (% TST)		S3&4 (% TST)	
	B	E	B	E	B	E	B	E	B	E	B	E
1	388	469	88.0	90.9	8	16	45	32	11.0	13.0	6.3	6.9
2	381	323	83.6	82.6	3	4	72	65	11.0	13.6	0.7	21.1
3	384	405	91.5	78.9	1	4	35	104	9.1	18.0	0.0	0.0
4	369	420	69.5	75.7	35	22	126	113	11.3	15.3	0.0	4.2
5	400	329	81.7	71.1	3	8	87	126	17.9	17.6	0.0	0.8
6	367	401	70.8	76.7	12	10	139	112	21.3	18.2	0.8	0.0
7	362	366	69.4	81.6	71	41	89	42	14.8	18.9	1.1	17.5
M	379	388	79.2	79.6	19	15	85	85	13.8	16.4	1.3	7.2
SD	13	52	9.3	6.3	26	13	39	38	4.4	2.4	2.3	8.7
p	.612		.866		.866		.735		.128		.093	

B Baseline; E ERT

**Conclusions:** The results suggest that short-term ERT improved disordered breathing in healthy postmenopausal women with SDB. The improvement appeared to occur predominately in NREM sleep. While the mechanisms underlie the improvement in SDB following ERT is unknown at this time, the data indicate ERT is an effective treatment. Differences in the types, dosages, drug-delivery modality and treatment duration of the HRT, differences in participant characteristics as well as small sample sizes might have contributed to the inconsistent findings in the limited existing literature. More studies investigating the effects of hormonal factors on the pathogenesis of SDB and the efficacy of HRT in treating SDB are needed.

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**029.J**

**AUTO-ADAPTING VS FIXED PRESSURE CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) IN CPAP NAIVE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL**

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**Introduction:** Auto-adapting CPAP has been advocated in patients with obstructive sleep apnoea (OSA) on the assumption that by adapting to the actual pressure needs of the patient at any given point in time, the overall pressure required to treat the OSA will be reduced, whilst the usage of CPAP will increase. We wished to assess whether these assumptions were correct during a trial of CPAP in newly diagnosed OSA patients.

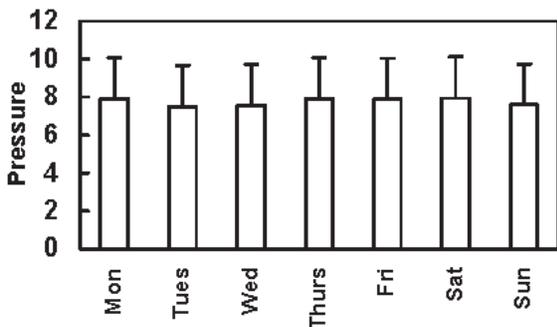
**Methods:** Patients were entered into the study if there was a clinical need to treat OSA. Each patient completed a single night auto-titrating CPAP study within the laboratory. They then undertook a 4-week trial of CPAP with the CPAP device (Goodnight 418P, Mallinckrodt) pre-programmed to 2 weeks of fixed pressure and 2 weeks of auto-adapting pressure, in a randomized design. The fixed pressure was calculated from Predicted Pressure = 4.44 + 0.0075Desats + 0.084BMi where Desats is the total number of 4% hypoxic dips from an overnight oximetry study and BMi is body mass index (1). Local ethics approval was obtained for the study. Data was analysed from the second week of each of the two weeks and are presented as mean ± standard deviation.

**Results:** Twenty-nine patients completed the study, and were aged 52.1 ± 10.6yr, had a BMi of 32.2 ± 4.8 kg.m<sup>-2</sup> and a pre-CPAP Epworth Score of 14.1 ± 3.3. Laboratory study: The number of 4% hypoxic dips decreased significantly (p<0.001) from 23.3/hr (1 – 85) to 1.8/hr (0.0 – 15.2). Usage was 6.3 ± 1.0 hrs, the auto-titrated CPAP pressure was 7.2 ± 2.8 cmH<sub>2</sub>O and with a mean pressure variation (δ P) of 7.5 ± 2.5 cmH<sub>2</sub>O. Auto-adapting vs Fixed Pressure: The results are summarized in Table 1. The Epworth was significantly lower (p < 0.005) after either treatment compared to the pre-CPAP Epworth score. There was no significant difference in Epworth scores between the treatment periods. The total number of hours usage/week was significantly less on the auto-adapting period (p<0.05) compared to fixed pressure, but there was no significant difference between the mean pressure over the week or the percentage of days used between the two treatment periods. The variation in auto-adapting pressure over the week is shown in Figure 1 and shows no significant variation in pressure demand per night.

**Table 1—Auto-adapting Fixed**

<b>Table 1</b>		
	<b>Auto-adapting</b>	<b>Fixed</b>
Epworth Score	10.9 ± 5.7	10.3 ± 5.7
Hours use/week	27.5 ± 14.8	34.6 ± 13.4
% Days Used	85.2 (44 – 100)	88.1 (44 – 100)
Mean Pressure	7.7 ± 2.8	7.9 ± 2.1

Figure 1—Pressure Variation



**Conclusions:** This study, in CPAP naive patients, shows that there is - 1. A significantly greater usage of CPAP for the fixed pressure period compared to the auto-adapting period, 2. No significant difference between a) the overall auto-adapted pressure compared to the fixed pressure, b) Epworth scores and c) the number of days used, 3. No significant night-to-night variation in auto-adapting pressure 4. Apparently little benefit in using auto-adapting CPAP as compared to fixed pressure CPAP

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**030.J**

**EFFICACY AND SAFETY OF MODAFINIL AS ADJUNCTIVE THERAPY FOR EXCESSIVE SLEEPINESS ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Obstructive sleep apnea (OSA) is a common cause of excessive sleepiness, which is associated with an increased risk of vehicular accidents and other negative outcomes. The standard treatment for OSA is nasal continuous positive airway pressure (nCPAP). However, some patients experience residual excessive sleepiness despite regular use of nCPAP. Modafinil (PROVIGIL®) is a novel wake-promoting agent that is chemically dissimilar to and has a pharmacological profile that differs from CNS stimulants, is well tolerated, and has a low potential for abuse. Modafinil has been shown to improve wakefulness in patients with OSA who were regular users of nCPAP. This 12-week study evaluated the efficacy and safety of modafinil for the adjunct treatment of residual excessive sleepiness in patients with OSA who were using nCPAP.

**Methods:** Patients with OSA and residual excessive sleepiness [Epworth Sleepiness Scale (ESS) score ≥10 at screening] who were using a stable nCPAP regimen with effectiveness during

use entered a 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Exclusion criteria included severe OSA or significant uncontrolled illness. Patients received placebo or modafinil 200 mg or 400 mg once daily, with the modafinil dose titrated as follows: 200 mg/d group: 100 mg/d on days 1 and 2 and 200 mg/d thereafter; 400 mg/d group: 100 mg/d on days 1 and 2, 200 mg/d on days 3 and 4, 300 mg/d on days 5 and 6, and 400 mg/d thereafter. Primary efficacy variables were the mean change from baseline in the sleep latency time on the Maintenance of Wakefulness Test (MWT) and improvement in overall clinical condition as assessed with Clinical Global Impression of Change (CGI-C) at week 12 or endpoint. Secondary efficacy variables included the mean change from baseline in the mean MWT latency time to the first epoch of sleep and ESS score. nCPAP use was monitored. Adverse events were recorded.

Figure 1

**MWT sleep latency**

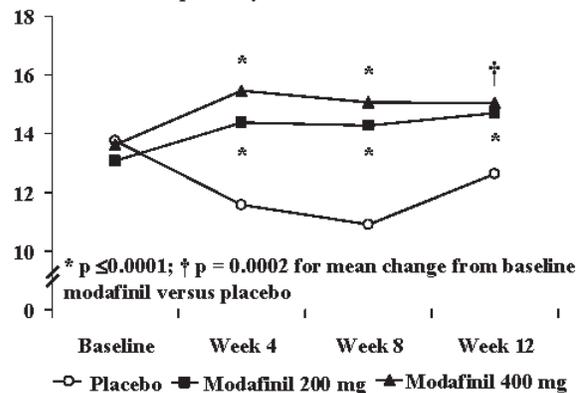
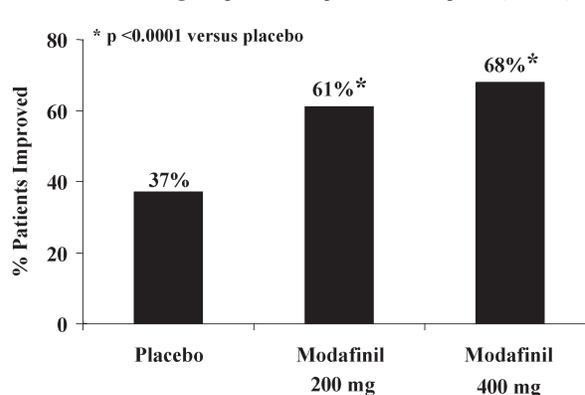


Figure 2

**Percentage of patients improved at endpoint (CGI-C)**



**Results:** 327 patients (mean age: 49 years; mean body-mass index: 36.2) were randomized; 323 received treatment (109 modafinil 200 mg/d; 106 modafinil 400 mg/d; 108 placebo). Mean change from baseline in the MWT sleep latency time was significantly greater at weeks 4, 8, and 12 of treatment with modafinil than with placebo (all p<0.0001; Figure 1). At week 12, overall clinical condition was improved for 64% of patients receiving modafinil compared with 37% of those receiving placebo (p<0.0001; Figure 2). The mean changes

from baseline in MWT sleep latency time to the first epoch of sleep and the ESS score (4.5-point decrease for modafinil 200 mg and 400 mg at week 12) also demonstrated significant improvements for patients receiving modafinil versus those receiving placebo (all  $p \leq 0.0001$ ). Modafinil treatment did not significantly affect nCPAP use (6 hours/night). The most common adverse events were headache (modafinil 26%; placebo 12%), nausea (modafinil 11%; placebo 2%), and anxiety (modafinil 8%; placebo 2%); 99% of these adverse events were mild or moderate in patients receiving modafinil.

**Conclusions:** Modafinil significantly improves wakefulness and overall clinical condition in patients with OSA who experience residual sleepiness despite nCPAP therapy. Modafinil did not significantly affect nCPAP use.

**References:**

(1) Pack AI, Black JE, Schwartz JRL, Matheson JK, for the U.S. Modafinil in OSA Study group. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* (In press).

Research supported by Cephalon, Inc., West Chester, PA.

### 031.J

#### MODAFINIL IMPROVES PSYCHOMOTOR VIGILANCE PERFORMANCE IN NCPAP-TREATED OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Untreated obstructive sleep apnea (OSA) causes sleep fragmentation that contributes to daytime sleepiness and impairments in psychomotor vigilance performance (1). Nasal continuous positive airway pressure (nCPAP) therapy reduces sleep fragmentation and improves sleep architecture and behavioral alertness. However, some patients with OSA who regularly use nCPAP continue to experience residual sleepiness that impairs daytime performance. In a previous 4-week, double-blind, placebo-controlled study, modafinil (PROVIGIL<sup>®</sup>) significantly improved wakefulness and psychomotor vigilance in patients with OSA who experienced residual sleepiness despite regular nCPAP therapy. Here we report the results of a 12-week, double-blind, placebo-controlled study designed to evaluate the effects of modafinil on psychomotor vigilance task (PVT) performance in patients with OSA who experienced residual sleepiness despite using nCPAP.

**Methods:** Patients with OSA and residual excessive sleepiness (Epworth Sleepiness Scale score  $\geq 10$  at screening) and who were using a regular nCPAP regimen with effectiveness during use were empanelled into a 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Exclusion criteria included severe OSA, significant uncontrolled illness, or a requirement for sedating medications. During the 12-week treatment period, subjects received once-daily placebo or

modafinil 200 mg or 400 mg. The modafinil dose was taken as follows: 200 mg/d group: 100 mg/d on days 1 and 2 and 200 mg/d thereafter; 400 mg/d group: 100 mg/d on days 1 and 2, 200 mg/d on days 3 and 4, 300 mg/d on days 5 and 6, and 400 mg/d thereafter. PVT performance was assessed 4 times/day on a baseline day and on a day during intervention weeks 4, 8, and 12. During each 10-minute PVT trial, visual stimuli appeared at variable intervals of 1 to 10 seconds. At baseline and weeks 4, 8, and 12, the median RT, the number of lapses transformed [by the square root of  $x + (\text{square root of } (-x+1))$ ], 1/RT of the 10% slowest RTs, and the 10% fastest RTs were evaluated. Treatment-emergent adverse events were recorded.

**Results:** 327 subjects were randomized (mean age 49 years, mean body-mass index 36.2) and 323 received treatment ( $n = 109$ , modafinil 200 mg/d;  $n = 106$ , modafinil 400 mg/d;  $n = 108$ , placebo). For subjects receiving modafinil, the median RT was significantly decreased (improved) at week 4 ( $p < 0.05$  for mean change from baseline versus placebo) and weeks 8 and 12 of treatment ( $p < 0.001$  for mean change from baseline versus placebo). Statistically significant improvements in the number of lapses transformed (Figure 1), the 10% slowest 1/RTs (Figure 2), and the 10% fastest RTs also were demonstrated at week 12 for subjects receiving modafinil (all  $p < 0.001$  for mean change from baseline versus placebo). The most common adverse events were headache (modafinil 26%; placebo 12%), nausea (modafinil 11%; placebo 2%), and anxiety (modafinil 8%; placebo 2%).

Figure 1

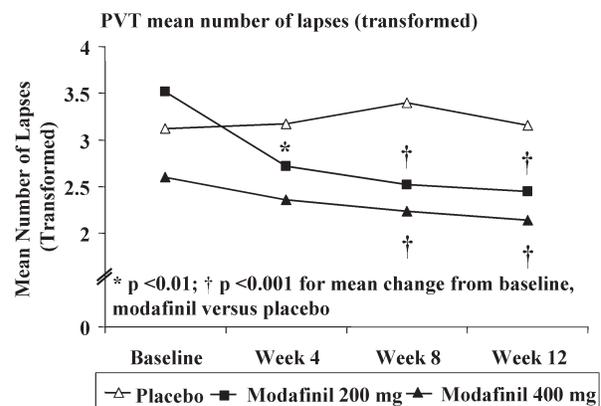
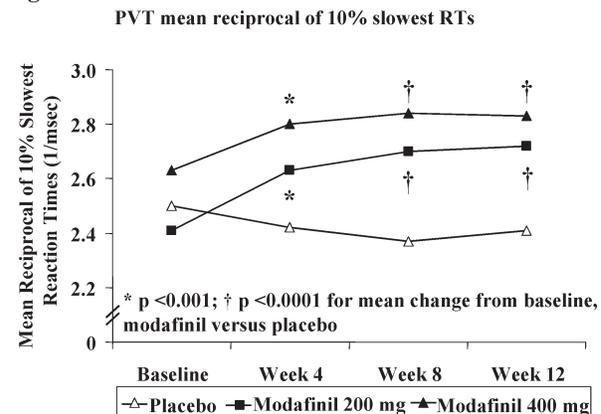


Figure 2



**Conclusions:** Adjunctive treatment with modafinil significantly improved daytime behavioral alertness as measured by PVT performance in subjects with OSA who experienced residual sleepiness despite nCPAP therapy. The findings are consistent with an earlier 4-kr outcome study, and with other data supporting the effectiveness of modafinil for reducing daytime sleepiness in this population (2).

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Research supported by Cephalon, Inc., West Chester, PA.

### 032.J

#### THE EFFECTIVENESS OF A MANDIBULAR REPOSITIONING APPLIANCE IN TREATING MODERATE SLEEP APNEA IN PATIENTS WHO ARE NCPAP FAILURES

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**Introduction:** Past studies have examined the effectiveness of mandibular repositioning devices for the treatment of obstructive sleep apnea. These studies provide evidence that mandibular repositioning can be beneficial to patients with RDIs in the mild to moderate range when they are used as an initial treatment. In this study we retrospectively investigated the efficacy of oral appliances in treating sleep apnea in 17 patients who were found to have an RDI in the moderate range of 15 - 50 per hour, but who had failed at treatment with NCPAP. These patients were initially titrated and prescribed NCPAP but discontinued its use due to various compliance issues.

**Methods:** Patients were initially evaluated and studied at the Baptist Sleep Institute in Knoxville, TN. Initial diagnostic data was obtained from overnight polysomnography after which an NCPAP titration study was conducted. All patients were titrated to normal RDIs with NCPAP but each failed to tolerate therapy following periods varying from 5 to 13 months. After all efforts to deal with compliance issues were exhausted, patients were referred for dental evaluation where upon a mandibular repositioning device (Klearway) was fitted and installed. This is an adjustable device fabricated of thermoactive acrylic which permits lateral and vertical jaw movement and provides full occlusal coverage of both arches. Prior to installation all subjects were found to have adequate dentition to support installation of the oral device, normal range of motion in the jaw, and minimal symptoms of TMJ. Following placement of the appliance patients were monitored for three months during which time regular adjustments were made to the device in order to obtain the maximum effective protrusion of the mandible without significant jaw discomfort. Patients continued usage for a period of 3 to 5 months then returned to

the Sleep Institute where they were tested by overnight polysomnography while using the oral device. There was no change  $> \pm 1\%$  in body mass index over the course of the study for any patient.

**Results:** The pre-treatment respiratory disturbance index for patients in this study group ranged from 15 to 42 events per hour with an average of 21.5 per hour. Low pre-treatment SpO<sub>2</sub> levels ranged from 69% to 87% with an average low of 80.3%. After completion of this study, overnight polysomnography revealed an RDI range of 1 to 20 events per hour with an average RDI of 7.7. (See table 1.) In 7 of the 17 patients RDIs were brought within a normal range of 5 or less per hour. All patients but one showed a decrease of at least 5 and as many as 19 events per hour. The one exception was a patient whose RDI increased from 18 to 20. The low SpO<sub>2</sub> levels for patients using the appliance during this post-treatment night was 84 to 94% with an average low SpO<sub>2</sub> of 87%.

Table 1

Pre RDI	Post RDI	Change
17	5	-12
25	7	-18
20	1	-19
15	9	-6
20	1	-19
25	10	-15
15	2	-13
20	2	-18
22	7	-15
23	5	-18
18	20	2
22	2	-20
25	5	-15
16	5	-11
19	6	-13
22	9	-13
42	28	-14

**Conclusions:** This analysis reveals an interesting lowering of RDIs in 16 out of 17 patients with RDIs in the moderate range who failed at NCPAP treatment. A total of 7 patients had RDIs lowered to within normal ranges. All patients but one showed marked improvement in RDIs. Average O<sub>2</sub> desaturation was improved and all patients reported better quality sleep and improvement in daytime sleepiness. Our plan is to follow up with a prospective study in which we will assign controls and more objectively define the effectiveness of mandibular repositioning appliances in reducing signs and symptoms of sleep apnea in patients who suffer from moderate sleep apnea and who are non-compliant with NCPAP.

## 033.J

**MODAFINIL DOES NOT AFFECT NIGHTTIME SLEEP IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Obstructive sleep apnea (OSA) is a common cause of daytime sleepiness, which is associated with decreased performance and quality of life. The standard treatment for OSA is nasal continuous positive airway pressure (nCPAP), which effectively treats the nighttime respiratory abnormalities. However, some patients experience residual daytime sleepiness despite regular use of nCPAP. Modafinil (PROVIGIL<sup>®</sup>) is a novel wake-promoting agent that is chemically dissimilar to and has a pharmacological profile that differs from CNS stimulants, is well tolerated, and has a low potential for abuse. Modafinil is effective in reducing the daytime sleepiness associated with narcolepsy. Previous study results also suggest that modafinil improves wakefulness in patients with OSA who are regular users of nCPAP therapy. In a 12-week, randomized, double-blind, placebo-controlled study, nocturnal polysomnography (NPSG) data were collected to evaluate the effect of daytime modafinil treatment on subsequent nighttime sleep parameters in patients with OSA who were using nCPAP.

**Methods:** Patients with OSA and residual daytime sleepiness (Epworth Sleepiness Scale score  $\geq 10$  at screening) and who were using a stable nCPAP regimen with documented effectiveness during use entered a randomized, double-blind, placebo-controlled, parallel-group study. Exclusion criteria included indicators of severe OSA, clinically significant uncontrolled illness, or a requirement for sedating medication. During the 12-week treatment period, patients were randomized to receive placebo or modafinil 200 mg or 400 mg once daily. NPSG data, collected with patients using nCPAP during overnight clinic visits at baseline and week 12, included sleep duration, sleep latency, sleep efficiency, sleep architecture, and number of arousals. Adverse events were recorded.

**Results:** A total of 327 patients (mean age, 49 years; mean body-mass index, 36.2) were randomized, and 323 patients received treatment (n = 109, modafinil 200 mg/d; n = 106, modafinil 400 mg/d; n = 108, placebo). After 12 weeks of treatment with modafinil, mean values for sleep duration, sleep efficiency, and the percentage of time in REM and non-REM stages of sleep were similar to those at baseline (Table 1). The most frequently reported adverse events were headache (modafinil 26%; placebo 12%), nausea (modafinil 11%; placebo 2%), and anxiety (modafinil 8%; placebo 2%).

**Table 1—Mean Sleep Parameters**

Parameter	Placebo		Modafinil 200 mg		Modafinil 400 mg	
	Week		Week		Week	
	0	12	0	12	0	12
Time in bed, min	445	445	445	445	441	435
Sleep latency, min	13.2	13.9	17.3	8.6	13.9	10.8
Sleep duration, min	368	383	386	389	379	379
Sleep efficiency	82%	86%	87%	87%	86%	87%
Sleep time, min						
Stage 1	43.7	40.7	40.6	41.7	40.6	38.3
Stage 2	213	225	227	228	222	224
Stage 3	24.9	24.9	21.9	24.0	23.7	25.1
Stage 4	15.7	15.9	13.2	15.2	13.8	12.1
REM stage	73.6	77.1	78.4	82.8	77.4	80.3

**Conclusions:** Treatment with modafinil to improve daytime wakefulness does not affect amount of nighttime sleep or measures of sleep quality in patients with OSA who are using nCPAP therapy. Modafinil is well tolerated by this patient population.

**References:**

- (1) Pack AI, Black JE, Schwartz JRL, Matheson JK, for the U.S. Modafinil in OSA Study group. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* (In press).
- (2) US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 1988;43:88-97.

**Research supported by Cephalon, Inc., West Chester, PA.**

## 034.J

**SLEEP EFFICIENCY DURING CPAP TITRATION PREDICTS SUBSEQUENT COMPLIANCE**

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**Introduction:** In order to investigate specific determinants of patient compliance with CPAP, studies have focused on diagnostic screening variables, side effects, health-beliefs, and measures of disease severity (2). Investigators have disregarded sleep parameters assessed during titration as potential predictors of compliance. As the titration night represents patient's initial exposure to CPAP treatment, we hypothesized that nocturnal PSG variables representing improved sleep during titration would be related to compliance.

**Methods:** Seventy-one consecutive patients with sleep apnea (REI > 10) aged 31-78 years (mean 50.68  $\pm$  10.63; 28 females, 43 males) participated. Patients had a mean REI = 47.5  $\pm$  29.2. PSG variables were measured during the titration night. Compliance was assessed at follow-up using pressure-on time counters. Compliance was calculated as mean hrs/nt over the initial follow-up period (mean 46.9  $\pm$  38.16 days). Standard PSG and subjective variables including sleep efficiency, sleep

stages as well as subjective measures of sleep quality were selected for inclusion as predictive variables. Multiple regression was used to determine the relative predictive power of each of the variables assessed.

**Results:** Objective compliance was  $5.04 \text{ hrs/nt} \pm 2.59$ . As previously reported, greater disease severity at screening was associated with higher compliance (AI [ $r = .32$ ], time sat below 85 [ $r = .25$ ], STG 1 [ $r = .28$ ], STG 2 [ $r = -.31$ ]). Consistent with our hypothesis, high sleep efficiency on the CPAP titration night was significantly associated with high subsequent compliance,  $F(1,66) = 11.49$ ,  $r = .39$ ,  $p = .001$ . Sleep efficiency on the initial diagnostic screening night was not associated with compliance  $r = -.09$ ,  $p = .45$  and the relationship between titration sleep efficiency and compliance continued to be strong after controlling for sleep efficiency on the screening night. Indeed, the best predictor of compliance was change in sleep efficiency from screening (mean =  $82 \pm 14\%$ ) to titration ( $80 \pm 12\%$ ),  $F(1,66) = 17.31$ ,  $p < .000$  ( $r = .48$ ), indicating that patients whose sleep improved most on the titration night had the highest levels of compliance. Separate analyses by gender indicated that for each sex, sleep efficiency remained a significant predictor of compliance. Also, in males, latency to persistent sleep ( $r = -.59$ ) and latency to stage 1 sleep ( $r = -.51$ ) were inversely correlated with compliance.

**Conclusions:** While greater disease severity at diagnostic screening is associated with increased compliance the converse is true during titration. Specifically, improvement in sleep during the titration night is associated with higher CPAP compliance. These findings suggest that patients' initial experience with CPAP treatment may be a crucial factor in determining their use of this treatment modality. The identification of sleep efficiency as a significant predictor of compliance despite the multiple variables impacting it speaks to the importance of a patient's first exposure to CPAP. The absence of a correlation between sleep efficiency at screening and compliance suggests the relationship between sleep efficiency at titration and compliance is not merely a reflection of initial disease severity. Focusing increased attention on compliance directly following patients' first use of CPAP may be warranted.

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## 035.J

### THE EFFICACY OF CONTINUOUS POSITIVE AIRWAY PRESSURE APPLICATION IN REDUCING GASTROESOPHAGEAL REFLUX IN A LARGE POPULATION OF OBSTRUCTIVE SLEEP APNEA PATIENTS

Kim H,<sup>1</sup> Vorona RD,<sup>1</sup> Winn MP,<sup>1</sup> Fishback NF,<sup>1</sup> Ware JC<sup>1</sup>

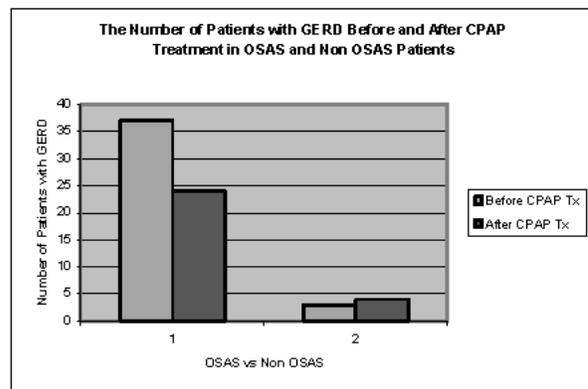
(1) Eastern Virginia Medical School/Sentara Norfolk General Hospital Sleep Disorders Center,

**Introduction:** Recently, the Eastern Virginia Medical School/Sentara Norfolk General Hospital Sleep Disorders Center (EVMS/SNG SDC) studied 1088 patients and found that there was no direct relationship between Gastroesophageal Reflux Disease (GERD) and Obstructive Sleep Apnea Syndrome (OSAS) (Kim et al, 2001). A study by Ing et al (2000) suggested that GERD responds to the application of Continuous Positive Airway Pressure (CPAP) irrespective of the presence or the absence of OSAS. Earlier studies investigating GERD and its response to CPAP had been limited in size. This large cadre of patients allowed further illumination of CPAP's efficacy in treating GERD.

**Methods:** For this study, we examined the above patients placed on CPAP. All patients entering EVMS/SNG SDC (Kim et al, 2001) had been prospectively administered a validated GERD questionnaire (Shaw et al., 2001). A score of  $\geq 15.5$  defined GERD. 186 patients diagnosed with OSAS (polysomnographically determined Respiratory Disturbance Index (RDI)  $\geq 10/\text{hour}$ ) and 11 patients without OSAS were administered CPAP. After one or more month of CPAP treatment, the questionnaire was administered again and the analysis of GERD scores pre and post CPAP treatment forms the basis of this abstract.

**Results:** Of 186 patients with OSAS, 37 patients had GERD before CPAP treatment. After CPAP treatment, this was reduced to 24 patients. This change was statistically significant as confirmed by Paired Samples Test (2-tailed significance of 0.023). Of 11 patients without OSAS, 3 patients had GERD before CPAP treatment and 4 patients after CPAP treatment (2-tailed significance of 0.341). This was not statistically significant. The average GERD score change for patients with OSAS was a decrease of 2.27 in GERD score while the average GERD score change for patients without OSAS was an increase of 1.80 in GERD score.

Figure 1



**Conclusions:** Patients with OSAS improved in GERD significantly with CPAP treatment while the patients without OSAS did not show a significant change in GERD. The latter conclusion on patients without OSAS is tentative as there was only a small number of patients in the analysis. If there is a relationship between OSAS and GERD, it may be mediated by other factors such as obesity. We are currently planning to better control the data set by including the patients who are not being treated with CPAP.

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**Oral Presentation**  
**Cardiovascular and Thermal Regulation**  
**During Sleep**

**036.B**

**HEART RATE VARIABILITY AS THE INDICATOR OF  
 CARDIOVASCULAR FUNCTION RESTORATION  
 DURING SLEEP**

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**Introduction:** Autonomic heart rate (HR) control evaluated by means of HR variability measures has been widely accepted as important information of cardiovascular function being a marker of sudden death.

**Methods:** Polysomnography was performed in 405 CAD pts (mean age 60.7 yr.) pts, including 200 pts with CHF (mean age 63.4 yr.). Sleep apnea syndrome (SAS) was observed in 46 pts (mean age 64.2 yr.), including 24 pts with CHF (mean age 65.4 yr.). Computerized HR analysis was performed by Poincare plots of RR intervals recorded during sleep as well as during active orthostatic test (AOT) just before and after sleep. Minimal (RRmax) and maximal (RRmin) HR frequencies, the difference between of them as maximal HR response (DRRr), maximal HR variability (DRRt) as maximal width between of tangential lines of square, parallel to diagonal, general HR variability (P) as the plot of all square were measured.

**Results:** Patients with CHF, as compared with pts without CHF, at evening-time during AOT demonstrated significantly reduced maximal HR response (DRRr 349 & 393 ms) due to higher minimal HR frequency (RRmax 1108 & 1146 ms) and significantly reduced HR variability evaluated as maximal and general HR variability (DRRt 94 & 103 ms and P 20700 & 24166 ms<sup>2</sup>). Maximal HR response and HR variability remained significantly reduced during sleep in CHF pts, as compared with pts without CHF. The difference between maximal HR response during AOT at morning- and evening-time was significantly lower in pts with CHF reflecting more reduced restoration of autonomic HR control. SAS pts demonstrated inability of restoration of cardiovascular function during sleep: maximal HR response to AOT did not differ significantly at evening- and morning-time. CHF pts with SAS, as compared without SAS, demonstrated significantly reduced maximal HR variability (DRRt 77 & 96 ms) during AOT at evening-time. During sleep minimal and maximal HR frequency was significantly lower (RRmax 1309 & 1237 ms and RRmin 746 & 711 ms) and general HR variability was higher in SAS pts, as compared with pts without SAS. In CHF pts with SAS, as compared without SAS, HR variability characteristics during sleep did not differed significantly. Sleep efficiency (85.0% & 88.9%), stage 4 (1.2% & 2.2%), and REM sleep (11.5% & 13.5%) were significantly decreased in CHF pts, as compared without CHF. Sleep structure was more disturbed in SAS pts, as compared without SAS, as well as in CHF pts demonstrating SAS, as compared without SAS, due to significantly decreased slow wave sleep and REM sleep in both group.

**Conclusions:** CHF patients demonstrated reduced restoration

of autonomic HR control due to depressed tonic and reflex control, especially parasympathetic one and disturbed sleep. Inability to restore cardiovascular function during sleep was observed in patients demonstrating SAS.

**037.B**

**INITIAL TEMPERATURE DROPS AT SLEEP ONSET  
 ARE MORE INFLUENCED BY POSTURE THAN  
 SLEEP**

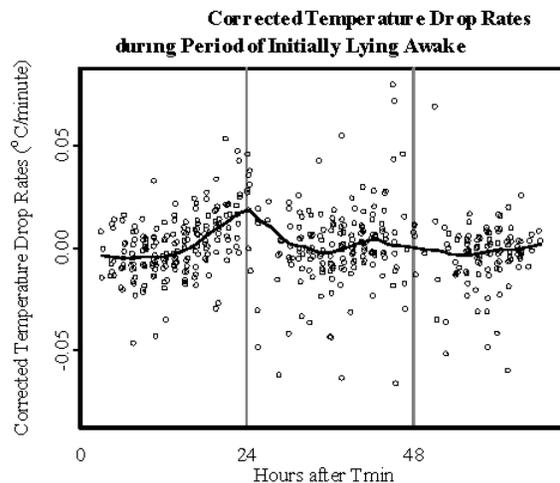
*Moul DE,<sup>1</sup> Chen X,<sup>1</sup> Ombao H,<sup>1</sup> Monk TH,<sup>1</sup> Begley AE,<sup>1</sup> Buysse DJ<sup>1</sup>*

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**Introduction:** Sleep propensity is influenced by circadian phase and declining temperatures near customary bedtimes (1). Temperature drops (TDs) associated with sleep have a circadian rhythm separate from the core body temperature (CBT) rhythm (2), and may influence sleep onset. In the present study, initial rates of temperature dropping between periods of lying awake and sleeping were compared to characterize their contributions to the TD rhythm.

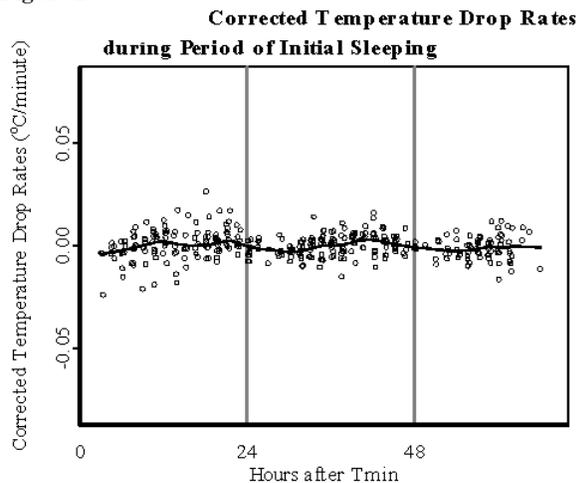
**Methods:** Eighteen young adult subjects (ages 20-30) underwent a 90-minute-day protocol of 40 sequential 60-minute enforced awake periods each followed by a 30-minute enforced recumbent period with encouraged sleep. CBT and polysomnographic parameters were collected throughout. Sleep onset was defined as Stage 2 or three consecutive one-minute epochs of Stage 1. Individuals' times of temperature minimum (Tmin) were established using cosinor analysis of the last 30 minutes of subjects' awake periods. Seventeen (9 male, 8 female) rhythms permitted rescaling to the initial Tmin. Episodes of initially lying awake and of initial sleeping were identified. TD rates were corrected for baseline effects during both kinds of episodes. These corrected rates were then regressed against potentially co-occurring linear (e.g. time-in-episode) and sinusoidal (e.g. 24-hour) effects using non-linear mixed effects regressions. The rhythms for the TD rates during these episodes were also compared to the rhythms of time spent asleep (TSA) and sleep latency (SL).

**Figure 1**



**Results:** The corrected TD rates were larger during initial recumbency (Figure 1) than after sleep onset (Figure 2). TD rate model parameters were uniformly larger before than after sleep onset, for both linear (TD acceleration rates during episode: 0.0064 vs. 0.0036 °C/min<sup>2</sup>) and sinusoidal (amplitudes 0.0084 vs. 0.0036 °C/min) effects. The circadian maximum of the TD rate rhythm of initial lying awake episodes occurred 2 hours before T<sub>min</sub>, whereas that of initial sleeping episodes occurred 7 hours before T<sub>min</sub>. The circadian maximum for the TD rhythm itself occurred approximately 3.4 hours before T<sub>min</sub>. The circadian maximum of TSA occurred at T<sub>min</sub>. The circadian maximum of SL occurred 8.6 hours before T<sub>min</sub>.

Figure 2



**Conclusions:** T<sub>min</sub> is well known as a critical influence over sleep propensity, but the time of maximum temperature dropping which occurs at customary bedtimes may also be an important influence (1). This study suggests that lying down itself plays a key role in facilitating sleep onset at customary bedtimes, and agrees with some prior data (3) that sleep onset itself may actually slow the initial TD rate.

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## 038.B

### FINGER WARMING AS PREPARATION FOR FALLING ASLEEP

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**Introduction:** Originally it was believed that the evening decline in core body temperature was the best predictor of sleep initiation (1). More recently the increase of distal skin temperature (hands and feet) has been shown to be a better predictor of sleep latency(2). However, most studies have examined distal skin temperatures over relatively long time intervals of measurement around the normal bed time. Therefore, the present study investigated the rapid changes of finger temperature from lights out to sleep onset at various circadian phases.

**Methods:** Fourteen good sleeping subjects (11 males, 3 females, mean age = 28.14 yrs) participated in a modified 48-hour wakeful bedrest constant routine while PSG and rectal temperature (RT) was monitored continuously. Skin temperature (ST) of the palmar distal surface of the right index finger was recorded at 30-second intervals with every multiple sleep latency test (MSLT) administered every half hour across the 48 hour period.

**Results:** Baseline finger ST was recorded before the start of each MSLT. There was a significant circadian rhythm of baseline ST with average peak of 33.5 deg C at 0300 hrs and nadir of 31.5 deg C at 1600 hrs. The core RT circadian rhythm nadir and peak respectively followed these ST phases by 2-3 hours. During the MSLT trials ST showed consistent and relatively rapid changes. During physical adjustment to supine position at the beginning of each trial there was a drop of ST of about 0.6-0.8 deg C over a period of one minute. This was followed by a steady rise of ST of 1 to 4 deg C. at a rate of about 0.6 deg C per minute until the trial was terminated at the third consecutive epoch of sleep or, in the case of longer sleep latencies, until ST leveled out at an asymptotic value.

**Conclusions:** The circadian rhythm of finger temperature is almost the reciprocal of core temperature, probably serving the function of helping to drive the circadian rhythm of core temperature through heat dissipation from vasodilation or conservation from vasoconstriction. The initial drop of ST with settling down may result from increased sympathetic vasoconstriction associated with the brief muscular effort required to adjust to the sleeping position. The subsequent, more pronounced increase of ST (1-4 deg C) would be a result of decreased sympathetic tone preceding sleep onset and be a part of what has been described as the "sleepening" process. It would be of interest to compare the magnitude of this normal response with that in sleep onset insomniacs who may instead show a sympathetic arousal as indicated by a further drop of ST when presented with an opportunity to fall asleep.

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Research supported by Australian Research Council

039.B

A MICROANALYSIS OF EMG AND EEG ACTIVITY DURING THE SLEEP ONSET PERIOD (SOP)

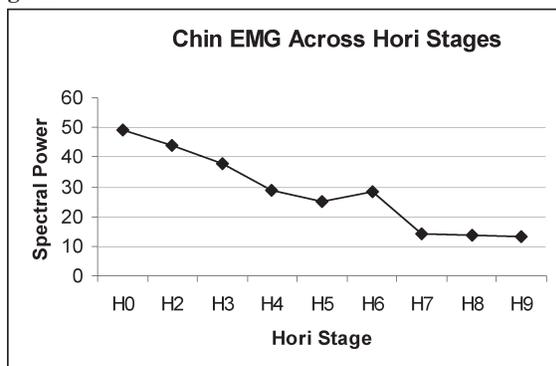
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**Introduction:** The Sleep Onset Period (SOP) refers to the process of falling asleep. Traditionally, this process has been defined by Rechtschaffen and Kales (1968) Stage One and more recently, and more precisely, by Hori's 9-stage model (2). Both Rechtschaffen and Kales and Hori have characterized the changes evident in EEG activity during the SOP. However, little work has focused on incorporating corresponding changes evident in EMG activity during this same period. And to the author's knowledge, no study has examined EMG changes as a function of Hori's 9 stages encompassing the SOP. The present study examines the changes evident in EMG activity measured from different sites (chin and wrist) during the SOP. It is theorized that EMG activity, of course, declines as one progresses towards sleep onset. However, using spectral analysis, the present study answers the questions of how quickly does this decline take place and at which points, if any, are large decreases in EMG activity measurable.

**Methods:** Twelve female undergraduates (aged 18 to 42 with a mean of 22), who were free of sleep disorders, spent two nights in the laboratory. Each participant was allowed 5 twenty-minute nap opportunities each night. FFT analysis was performed on F7, F3, Fz, F4, F8, T3, T5, T4, T6, C3, Cz, C4, P3, Pz, P4, O1, O2, A1, A2, submental EMG, and wrist EMG to assess changes in spectral power of EEG and EMG through each of Hori's 9 stages.

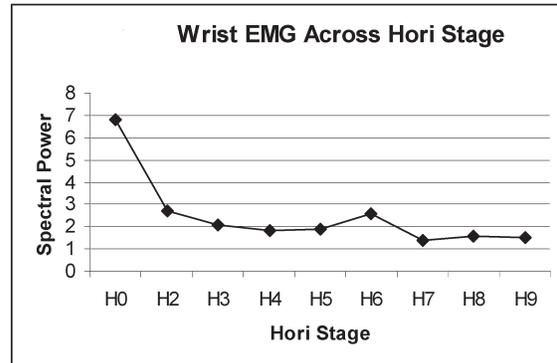
Figure 1



**Results:** Chin EMG significantly decreased as a function of Hori stage ( $F_{8,89} = 2.73, p = .010$ ; Fig.1). While there were no sequential stage differences, EMG activity at Hori Stage 0 (wake) differed significantly from Hori Stage 5 ( $t_{11} = 2.98, p = .012$ ) indicating a significant drop in chin EMG from wakefulness to the middle of Rechtschaffen and Kales' Stage 1. Additionally, wrist EMG also significantly decreased as a function of Hori stage ( $F_{8,89} = 2.82, p = .008$ ; Fig.1). Wrist

EMG activity showed a significant drop from Hori Stage 0 (wake) to Hori Stage 3 (< 50% alpha) traditionally associated with Rechtschaffen and Kales' Stage 1 indicating a much sharper decline in wrist EMG activity than exhibited by chin EMG activity. Chin EMG and wrist EMG were significantly correlated ( $r = .411, p < .001$ ) indicating that while EMG measured from the two different sites both declined, they did decline at different rates.

Figure 2



**Conclusions:** It is practical importance to relate the changes in EMG to the Hori stages to ascertain whether or not these changes are gradual or relatively abrupt (whether they occur early or late in the SOP) and whether they remain low or vary considerably. These characteristics could greatly affect the usefulness of monitoring EMG as a "sleepiness detector." The present study provides a more precise picture of the changes exhibited in EMG activity during the process of falling asleep.

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Oral Presentation  
Stress and Insomnia

040.L

INSOMNIA, STRESS, AND COPING SKILLS

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**Introduction:** Although stress is presumed to be one of the most common precipitant of sleep disturbances, little research has documented the specific role of stressful life events in primary insomnia. In addition, it is well recognized that hyperarousal is a core mediating factor of insomnia, yet it is unclear whether bedtime arousal is modulated by previous daytime stressors. If daytime stress is related to pre-sleep arousal and to sleep difficulties, it is plausible that these relationships are further mediated by the types of strategies used to cope with stress. The aim of the present study was to examine the relationship of stress and coping skills to pre-sleep arousal and sleep patterns in good sleepers and insomnia sufferers.

TUESDAY, JUNE 11, 2002

**Methods:** The sample was composed of 67 persons (38 women and 29 men; mean age = 39.6 years old), including 40 individuals with primary insomnia and 27 good sleepers. The insomniacs were divided in two subgroups, including 22 non-medicated and 18 medicated insomnia individuals. Their average insomnia duration was 9.8 years (range = 6 months to 35 years). All subjects completed prospective, daily, measures of stressful events (Daily Stress Inventory), pre-sleep arousal (Pre-Sleep Arousal Scale), and sleep (diary) for three consecutive weeks. In addition, they completed several retrospective and global measures of depression, anxiety, stressful life events, and coping skills.

**Results:** The results showed that poor and good sleepers reported equivalent number of minor daily stressors and major stressful life events. However, insomniacs rated both the impact of daily minor stressors and the intensity of major negative life events higher than did good sleepers ( $p < .05$ ). In addition, insomniacs perceived stress as more uncontrollable and unpredictable relative to good sleepers ( $p < .05$ ), and experienced higher pre-sleep somatic and cognitive arousal than good sleepers ( $p < .01$ ). Good sleepers tended to use task-oriented coping strategies while insomniacs relied more frequently on emotion-oriented coping strategies. The perceived impact of daily minor stressors and greater use of emotion-oriented coping strategies were the best predictors of pre-sleep arousal state, whereas the perception of lack of control over stress better predicted sleep quality.

**Conclusions:** The findings suggest that it is the appraisal of stressors and the perceived lack of control over stressful events, rather than the number of stressful life events per se, that enhance the vulnerability to insomnia. The main implication of these results is that insomnia treatments should not aim only at reducing stress; rather, treatment should also incorporate clinical procedures designed to teach more effective stress appraisal and coping skills.

#### 041.L

##### STRESS-RELATED INSOMNIA IN CAREGIVERS

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**Introduction:** Complaints of insomnia are commonly reported in caregiver studies. Men and women taking care of ill family members report difficulty initiating sleep, maintaining sleep, and feeling rested. We studied two samples of caregivers in order to document PSG-sleep in this ever-growing segment of the population.

**Methods:** Sample A consisted of 11 men and women caring for a family member who had received a liver transplant during the previous 6 months (transplant caregivers) and 13 age-matched, non-caregiver controls (mean age =  $49.9 \pm 7.6$  years). Sample B included 8 female spousal caregivers of patients with Alzheimer's Disease (AD caregivers) and an archival sample of 12 age-matched controls (mean age =  $67.7 \pm 9.7$  years). Stress measures were the Perceived Stress Scale (PSS) and the Intrusion subscale on the Impact of Event Scale (IES). Sleep was measured by polysomnography and self report. Sample A was studied in the sleep laboratory, whereas

sample B was studied in their homes. Within each sample, ANCOVA was used to quantify group differences on measures of stress and sleep. Between-sample comparisons were made on psychosocial data only, with age as a covariate. Correlations were used to characterize stress-sleep relationships in the larger sample of transplant caregivers.

**Results:** Caregivers in both samples complained of more difficulty coping with stress (PSS;  $F=7.01$ ,  $p<.01$ ), greater frequency of intrusive thoughts (IES;  $F=4.1$ ,  $p<.05$ ), and poorer sleep quality ( $F=5.9$ ,  $p<.01$ ). Objective sleep disturbances were also observed; caregivers in both samples exhibited poorer sleep efficiency (Sample A:  $F=6.0$ ,  $p<.05$ ; Sample B:  $F=6.4$ ,  $p<.05$ ) in comparison to their respective controls. In addition, sleep latency was significantly longer in caregivers in sample B, as compared to age-matched controls ( $F = 5.2$ ,  $p<.05$ ). Correlational analyses revealed that higher levels of intrusive thoughts were associated with poorer sleep efficiency ( $r=-.55$ ,  $p<.01$ ) and poorer sleep quality ( $r=.48$ ,  $p<.05$ ).

**Conclusions:** Results confirm that reports of insomnia among caregivers may be accompanied by significant changes in PSG-assessed sleep. During the night, caregivers were awake an average of 20 minutes longer than non-caregiver controls, and sleep quality scores among caregivers were above the cut-point for clinically-significant complaints. In addition, the older sample of AD caregivers took an average of 24 minutes longer to fall asleep than their age-matched control sample. Insomnia in caregivers may be an important pathway to the significant adverse health outcomes seen in caregiver populations including increased risk of psychiatric morbidity, greater morbidity in physical health outcomes, and mortality. Results suggest that caregiving may have a greater impact on insomnia in older adults whose sleep is already affected by advancing age. Results are also consistent with previous reports that intrusive thoughts are an important mediator of the stress-sleep relationship. These data suggest possible intervention targets for improving insomnia, and possibly health outcomes, in caregivers.

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#### 042.L

##### SITUATIONAL INSOMNIA: IN THE SITUATION OR IN THE PATIENT?

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**Introduction:** Situational insomnia (SI) is defined as poor sleep produced in an otherwise normal sleeper in response to specific environmental or stress factors. It has been hypothesized that chronic insomnia develops in response to repeated episodes of SI. However, little research has examined the nature of SI. Previous work has shown high variability in the response of normal sleepers to models of SI such as advance of sleep time or administration of caffeine<sup>1</sup>. The current study examined the response of a group of normal sleepers to the first night in the sleep lab and two advances in sleep time to determine consistency of response (i.e., reliability of SI across stressful settings) and characteristics of individuals suffering

from SI.

**Methods:** Participants to date have been 26 normal young adults (age 22 + 4; range 18 -32). Subjects slept in the lab for a screening night followed by a baseline night and an advanced sleep night (advance of normal bed time by 3 or 6 hours). On the following week, Ss returned for another baseline and advanced sleep night (whichever advance was not given in the first week). Ss remained in the lab for the day after each night for MSL T, mood, and psychomotor performance evaluation.

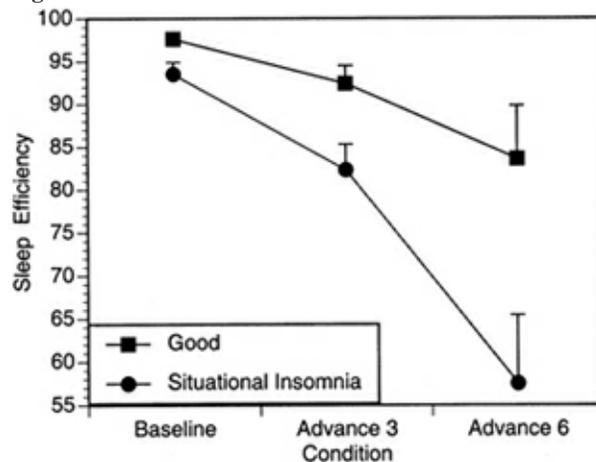
Table 1

Sleep Values for the group of 26 Ss

	Total Sleep	Time in Bed	Sleep Efficiency	Sleep Latency
Screen	439 (39)	480 (5)	92 (6)	11 (9)
Baseline 3	456 (16)	480 (4)	95 (3)	7 (7)
Advance 3	432 (36)	482 (6)	90 (7)	19 (24)
Baseline 6	447 (23)	479 (6)	93 (4)	12 (13)
Advance 6	359* (94)	480 (5)	75* (20)	16 (23)
F-Value	25.25*	2.61	25.3*	2.61

\*p < .01

Figure 1



**Results:** Global sleep times for the nights are presented in the Table. As hypothesized, variability in total sleep was increased on the screening night and both advance nights. Further, total sleep time on the screening and advance nights was significantly correlated ( $r_{screen-adv3} = .61$ ;  $r_{screen-adv6} = .65$ ;  $r_{adv3-adv6} = .57$  (all  $p < .01$ )). Ss with the best sleep (top 25%,  $n = 7$ ) and the worst sleep (bottom 25%,  $n = 6$ ) on the screening night have been examined in more detail. Sleep Efficiency data in these two groups across the study nights is presented in the Figure. The analysis of variance showed a significant Group by Condition interaction ( $F_{2,22} = 3.57$ ;  $p < .05$ ). SI Ss had a significantly worse sleep efficiency on the Advance 6 night as compared to the normals and compared to themselves on the baseline and Advance 3 nights. As implied by the significant interaction, those subjects who did not sleep as well on their first night in the lab (Screen night) had improved sleep on baseline nights that followed. However,

under the stress of an advanced bedtime, their situational sleep problem returned and was magnified. Preliminary analyses of demographic data have indicated that the SI Ss were significantly older than the good sleepers (26.8 vs 21 years) and tended to have a higher score on the MMPI Depression scale (62 vs 53). However, the groups did not differ in their own assessment of whether they would suffer from SI ( $t = -0.129$ ). Additional physiological and demographic variables are being reviewed.

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**043.L**

**A WITHIN-SUBJECT STUDY OF THE RELATIONSHIP OF NON-REM EEG SPECTRAL AMPLITUDE AND THE AGREEMENT BETWEEN SUBJECTIVE AND OBJECTIVE ASSESSMENTS OF SLEEP TIME**

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**Introduction:** The reasons why some individuals have a significant mismatch between subjective and objective, polysomnographic (PSG), assessments of their sleep remain unknown. Two recent studies suggest that such a mismatch may be associated with alterations in non-REM EEG frequency content.(1,2) Greater subjective underestimation of sleep has been reported to correlate with greater 14-35 Hz and 12.5-16 Hz and diminished 0.5-3.5 Hz non-REM EEG relative spectral amplitude. The present study sought to further examine these relationships by carrying out a within-subjects comparison of subjects who underwent PSG both at home and in the laboratory and had a mismatch at home but not in the laboratory. We hypothesized that diminished low-frequency and elevated higher frequency activity would be evident at home.

**Methods:** The subjects were 7 individuals (6 had a sleep complaint) who were part of a larger home vs. laboratory PSG study.(3) This subset underestimated their total sleep time at home (mean underestimation of 21%) but not in the laboratory (mean overestimation of 3.8%) as identified with a cluster analysis. All subjects underwent 3 consecutive PSGs at home and the laboratory with order randomized. Spectral analysis was carried out on nights 2 and 3 at home and in the laboratory, to avoid first-night effects, using 2 EEG channels (C3-M2 and Cz-Oz). FFT in 2 second epochs yielded six frequency bands: Delta (0.5-3.5 Hz), Theta (4.0-8.0 Hz), Alpha (8.5-12 Hz), Sigma (12.5-16 Hz), Beta (16.5-30 Hz), and Gamma (30.5-60 Hz). Absolute and relative amplitude (absolute amplitude normalized by total amplitude) were computed and compared for home vs. laboratory for Stage 2, Slow-wave Sleep, and REM sleep over the entire night using repeated

measures multivariate analysis of covariance controlling for the home-lab difference in total sleep time and time in bed.

**Results:** Significant home vs. laboratory effects were present only for non-REM sleep. For absolute amplitude data we found diminished Delta amplitude at home in Slow-wave sleep ( $F=10.8$ ,  $p<0.04$ ). For relative amplitude there was a trend for diminished Slow-wave sleep at home compared with the laboratory in both Stage 2 and Slow-wave sleep ( $F=6.1$ ,  $p<0.07$ ) and there was also evidence for significantly greater alpha relative amplitude at home for both Stage 2 and Slow-wave sleep ( $F=8.1$ ,  $p<0.05$ ).

**Conclusions:** This pilot study provides further support for the hypothesis that non-REM EEG frequency spectral alterations are associated with a mismatch in subjective vs. objective assessments of sleep. The results particularly reinforce that subjective underestimation of total sleep time may be associated with decreased non-REM EEG Delta amplitude.

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#### 044.L

##### RELATIONSHIP BETWEEN DEPRESSION, ANXIETY AND EPWORTH SLEEPINESS SCORES WITH SUBJECTIVE AND OBJECTIVE SLEEP MEASUREMENTS OF ELDERLY INSOMNIACS

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**Introduction:** Insomniacs have been found to overestimate sleep latency and underestimate total sleep time<sup>1</sup>. A variety of factors, including greater depression<sup>2</sup> has been associated with more disturbed sleep. Therefore it was suggested that higher depression scores would be associated with larger discrepancies between subjective (sleep log) estimations and objective (actigraphic) measures of sleep in our sample of older insomniacs. Furthermore, as depression symptoms are positively associated with Epworth Sleepiness Scores (ESS)<sup>3</sup>, the association between ESS and objective-subjective sleep parameter differences were explored.

**Methods:** Total sleep time (TST), sleep efficiency (SE), and wake after sleep onset (WASO) data were gathered from an average of  $6.82 \pm .451$  consecutive days of sleep logs and actigraphy of 39 (11 m, 28 f) elderly subjects (age 54-78) with

a complaint of insomnia. These measures were compared with ESS data, as well as depression and anxiety scores, as measured by the Geriatric Depression Scale (GDS) and the Spielberger State-Trait Anxiety Inventory respectively.

**Results:** SE as measured by actigraphy was significantly higher than subjective recollections of SE ( $p<.0001$ ); actigraphy measured TST was also significantly higher than sleep log TST ( $p=.0003$ ). There was no significant difference in WASO between the two methods of data collection. No correlation was uncovered between GDS and ESS ( $r=.199$ ) with this sample. Multiple linear regression analysis found that there was a positive significant effect of GDS score on the actigraphy TST - sleep log TST difference ( $p=.0029$ ). There was no effect for gender on any sleep parameter. ESS negatively and significantly impacted differences between actigraph and subjective reportings of SE ( $p=.0406$ ); ESS also significantly related negatively to a TST actigraphy, sleep log difference ( $p=.0011$ ).

**Conclusions:** These data suggest that in insomniacs with higher depression scores, the difference between actigraphically measured and subjectively estimated TST increases. Because it was found that insomniacs tend to underestimate the amount of TST more as their depression scores increase, it is important to consider the potential impact of depression when relying on subjective estimations of sleep. Interestingly, higher ESS scores significantly predicted smaller differences between actigraphic and subjective data on TST and SE parameters. This confirms reasoning that as sleepiness increases, subjective estimations more closely mirror physiological manifestations. These findings suggest that the lower the ESS score, the more likely insomniacs underestimate their TST and SE. It is recommended that if low ESS scores are present in insomniac subjects that objective measures be considered as an adjunct to subject recollections for sleep quality measurements.

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#### 045.L

##### THE ROLE OF ANXIETY IN SLEEP STATE MISPERCEPTION

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**Introduction:** When evaluating patients with anxiety and depression, clinicians often rely on subjective complaints of

sleep disturbance. However, little is known about how reliably patients report sleep disturbance. Some individuals with complaints of insomnia have normal sleep when evaluated objectively with polysomnographic measures. This divergence between subjective and objective perception of sleep is called sleep state misperception. Depression reportedly is associated with sleep state misperception in older patients. Further, it is widely believed that increased anxiety is associated with distortions in time interval judgment. We therefore hypothesize that patients with higher anxiety will have less accurate sleep state perception. The purpose of the present study was to determine the extent to which anxiety is associated with sleep state misperception. We also explored the relationship between sleep state misperception, alexithymia, and depression.

**Methods:** One hundred and twenty consecutively evaluated patients with sleep related breathing disorders were surveyed as an addendum to their standard clinical workup. The survey included questionnaires that indexed anxiety, alexithymia, and depression. Patients were age 21 years or older. We excluded patients taking medication known to affect sleep, patients with alcohol or drug abuse within the last 2 months, and patients concurrently diagnosis of any anxiety, mood, or thought disorder. In addition to routine evaluation procedures (which includes the Beck Depression Inventory (BDI), subjects completed a State-Trait Anxiety Index (STAI) and Toronto Alexithymia Scale (TAS) on the evening of their sleep study. Subjects then slept one night at the clinic while undergoing standard polysomnographic monitoring as part of our evaluation for sleep apnea. In the morning, patients completed a post-sleep questionnaire in which they subjectively evaluated, among other things, their sleep latency, sleep duration, and number of awakenings. Objective measures of sleep latency, total sleep time, and nocturnal awakenings were calculated from polysomnograms.

**Results:** The first step was to compare questionnaire and objective data to index the accuracy of sleep state perception. This was accomplished by subtracting the subjectively estimated parameter from the objectively calculated one. Patients were sorted on the basis of STAI, TAS, and BDI scores. Significant ( $p < 0.05$ ) correlations were found between the STAI-State score and misperception in total sleep time and sleep latency; BDI and sleep latency misperception; and TAS and sleep latency misperception. Patients with STAI-state anxiety scores in the top 20th percentile were compared to patients with scores in the bottom 20th percentile. Total sleep time and sleep latency misperception was significantly ( $p < 0.05$ ) greater for patients with higher state anxiety scores and for patients with higher depression scores than those with the lowest anxiety and depression scores, respectively. Total sleep time misperception was also marginally ( $0.10 > p > 0.05$ ) greater among patients with the highest alexithymia scores.

**Conclusions:** These pilot study data provide a clue about the mechanisms underlying sleep state misperception. It appears that anxiety level plays a role in sleep state misperception. This information enables us to better understand the relationship between complaints of insomnia in some patients and their levels of anxiety; their mood; and their ability to assess their own emotional state.

## 046.L

### A COMPARISON OF OBJECTIVE AND SUBJECTIVE MEASURES OF INSOMNIA IN MONOZYGOTIC TWINS DISCORDANT FOR CHRONIC FATIGUE SYNDROME

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**Introduction:** Chronic fatigue syndrome (CFS) is a heterogeneous disorder of excessive fatigue of  $\geq 6$  months duration occurring in the absence of a clear physical or psychiatric etiology<sup>1</sup>. Although insomnia is a common complaint among individuals with CFS, the evidence supporting objective deficits is conflicting. We studied monozygotic (MZ) twins discordant for CFS to detect the presence of differences in objective and subjective measures of insomnia. This co-twin control study design permitted us to control for genetic variability, which has a strong influence on sleep.

**Methods:** Overnight polysomnography (PSG) with a full recording montage was performed in 21 sets of MZ twins discordant for CFS for two consecutive nights with the first night used for acclimatization. Visual PSG scoring was performed according to standard criteria by a single technician blinded to illness status. Data was obtained for sleep latency, total sleep time, sleep maintenance efficiency, arousal index, REM latency and sleep stages. Both twins filled out a 175-item Attitudes and Beliefs Questionnaire that explores subjective themes and beliefs regarding sleep (0=does not apply, 1=disagree or never, 2=rarely, 3=sometimes, 4=usually, 5=true or always). Data was analyzed using parametric and non-parametric methods for continuous and non-continuous variables using matched pair analytic techniques.

**Results:** There was no difference in the following objective measures of insomnia between CFS patients and their healthy co-twins: sleep latency (13.0 vs. 10.6 min,  $p=0.52$ ), total sleep time (380 vs. 388 min,  $p=0.36$ ), sleep maintenance efficiency (88.1 vs. 89.3%,  $p=0.50$ ), arousal index (18 vs. 19/hr,  $p=0.63$ ), REM latency (63.4 vs. 88.7 min,  $p=0.13$ ), stage 1 (8.4 vs. 9.2%,  $p=0.48$ ), stage 2 (44.7 vs. 48.6%,  $p=0.10$ ), and slow wave sleep (18.9 vs. 17.3%,  $p=0.28$ ). Stage REM sleep was increased in the CFS twins (28.1 vs. 25.0%,  $p=0.02$ ). The following subjective measures of insomnia and poor sleep were endorsed more frequently by the CFS twins: "I often have a poor nights sleep" (3.8 vs. 2.2,  $p < 0.001$ ), "I wake up often during the night" (3.7 vs. 2.2,  $p < 0.001$ ), "my nights sleep is often restless and disturbed" (3.8 vs. 1.8,  $p < 0.001$ ), "I feel that my

sleep is abnormal" (3.7 vs. 1.4,  $p < 0.001$ ), "I have trouble getting to sleep at night" (3.5 vs. 2.1,  $p < 0.001$ ), "I have been unable to sleep at all for several days" (1.7 vs. 1.0,  $p = 0.02$ ), "I feel that I have insomnia" (2.2 vs. 1.3,  $p < 0.01$ ), and "I take a prescription drug to help me sleep" (3.5 vs. 1.0,  $p < 0.001$ ).

**Conclusions:** CFS patients had worse subjective sleep than their co-twin controls despite a lack of objective findings to support this discrepancy. CFS patients may suffer from a type of sleep state misperception. CFS patients have a higher percentage of REM sleep, suggesting high REM pressure may play a role in this condition. The co-twin control design highlights the importance of using well-matched control subjects in the study of CFS and sleep.

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Research supported by grant U19AI38429 from the National Institutes of Health (Dr. Buchwald).

### 047.L

#### TRYPTOPHAN DEPLETION AND SLEEP IN PRIMARY INSOMNIA

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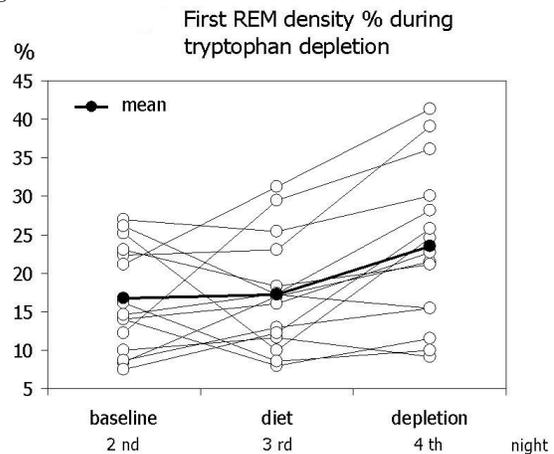
**Introduction:** The tryptophan depletion test has been established as a research tool to gain insight into the functional consequences of supposedly decreased brain serotonin levels by applying a drink containing a mixture of aminoacids without tryptophan which results in a 70 to 90% decrease of plasma tryptophan levels (Moore et al., 2000). Recently, the test has been applied to investigate the role of serotonin for normal sleep regulation and disturbed sleep in depression (Moore et al., 2000; Voderholzer et al., 1998). In the present study the tryptophan depletion test was used to investigate its impact on sleep in patients with primary insomnia to test whether tryptophan depletion reveals depression-like sleep abnormalities in this patient group, as it has been hypothesized that primary insomniacs are at risk for developing major depression (Riemann and Berger, 1998).

**Methods:** Fifteen patients (7 males, 8 females) with primary insomnia according to DSM-III-R criteria completed the protocol. Mean age  $\pm$  SD was  $40.1 \pm 11.3$  years. Subjects had suffered from insomnia for 1 to 35 years (average duration of insomnia was  $11.1 \pm 11.1$  years). All subjects were free of any kind of psychoactive medication prior to the study for at least 7 days. Subjects slept for 4 consecutive nights in the sleep laboratory. During the first laboratory night patients were screened for sleep apnea or PLMS. The second night was considered as a baseline night and the third and fourth night were experimental nights. On day 3 and on day 4 until midday subjects received standard nutrition consisting of a low protein diet. On day 4 subjects at 18.00 hours drank the tryptophan-

free aminoacid drink. Sleep was measured according to standard procedures and scored visually.

**Results:** Compared to the baseline night prior to night 4 at 22.00 hours serum tryptophan levels were decreased by 82%. When calculating contrasts (t-tests) between the fourth night and the baseline night it became obvious that the tryptophan depletion significantly increased stage 1 ( $p < 0.01$ ) and decreased stage 2 ( $p < 0.05$ ) and increased REM density ( $p < 0.05$ ) (see figure 1). REM latency remained unaltered.

Figure 1



**Conclusions:** As revealed by serum tryptophan concentrations the test procedure was successful in reducing serum tryptophan levels and supposedly also brain tryptophan levels. Effects in primary insomniacs were in the same direction and partly stronger than in our study with healthy subjects (Voderholzer et al., 1998). Sleep continuity was impaired whereas slow wave sleep remained unaltered. An increase of REM density was observed, whereas REM latency did not change. It is concluded that with this test procedure at least some similarities to depressed sleep can be provoked in primary insomniacs.

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**Poster Symposium**  
**Is There a Better Way? New Ideas on Instrumentation and Methodology**

**048.R**

**AN AUTOMATIC AMBULATORY DEVICE FOR DETECTION OF ASDA DEFINED AROUSALS FROM SLEEP: THE WP100**

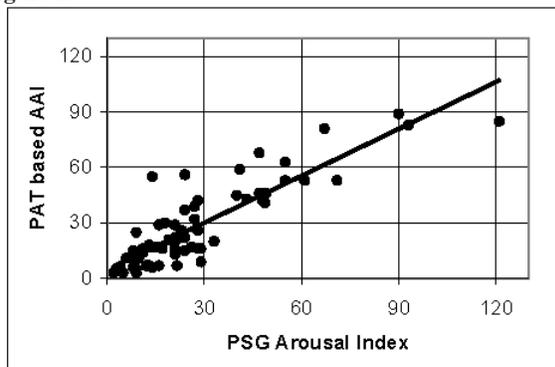
Pillar G,<sup>1</sup> Betito M,<sup>1</sup> Bar A,<sup>2</sup> Sheffy J,<sup>2</sup> Lavie P<sup>2</sup>

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**Introduction:** Arousals from sleep are associated with increased sympathetic activation and are therefore associated with peripheral vasoconstriction. Recent years have proposed that sleep fragmentation in the form of multiple arousals is associated with daytime somnolence and cognitive impairment. Manual scoring of arousal is a time consuming and is problematic because of the low interscorer reliability. Thus, a development of an automatic algorithm to detect arousals may be of great clinical value. We hypothesized that digital vasoconstrictions as measured by peripheral arterial tonometry (PAT), would reflect accurately arousals from sleep, and can provide a basis for such an algorithm. Based on a previously studied group of 40 sleep apnea patients simultaneously recorded by both polysomnography (PSG) and PAT systems, an automatic algorithm using the PAT signal (and pulse rate derived from it) was developed for detection of arousals from sleep. This was further validated in a separate group of 96 subjects studied by an in-lab system.

**Methods:** In the present study, 68 subjects (mean age 47.1 ± 14.1) underwent a whole night PSG with simultaneous recording of PAT signal by the ambulatory WP100 device. The ambulatory device consists of two finger probes, a PAT and oximeter, and a wrist mounted actigraph to record sleep and wake periods. The PSG recordings were blindly manually analyzed for arousals based on ASDA criteria, while PAT was scored automatically based on the algorithm developed previously.

**Figure 1**



**Results:** There was a significant correlation between ASDA arousals derived from the PSG and PAT automatic arousals

derived from the ambulatory WP100 ( $R=0.87$ ,  $P<0.001$ , fig) with a good agreement across a wide range of values, with an ROC curve having an area under the curve (AUC) of 0.87. The sensitivity and specificity of PAT to detect patients with at least 20 arousals per hour of sleep, were 0.80 and 0.79, respectively.

**Conclusions:** We conclude that automatic analysis of peripheral arterial tonometry signal derived from the ambulatory device WP100 can accurately identify arousals from sleep, in a simple, reproducible and time saving fashion.

**Research supported by a grant from Itamar Medical L.T.D., Caesarea, Israel.**

**049.R**

**CIRCADIAN CHANGES IN EEG THETA POWER BY YOSS PUPIL STAGE**

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**Introduction:** Significant increases in theta activity in awake EEG by Yoss pupil stage (percent of maximum diameter, Stage 1 "awake"= 95-100% to Stage 4 "sleepy"= 64-75%) have been found both within and between sleep disorder and normal subject groups when pupil diameter and EEG data were collected concurrently at 1400 hours<sup>1</sup>. The purpose of this study was to determine if theta increased by pupil stage and time of day in a sample of healthy subjects (8 F, 6 M, 21-58 years of age, usual hours of sleep = 6.5 to 9 hrs/night) who underwent one day of the pupillographic Alertness Level Test (ALT) with concurrent polysomnography (PSG) at 1000, 1200, 1400 and 1600 hours.

**Methods:** Pupil diameter and PSG data were collected concurrently at 256 Hz for 15 minutes with the subjects seated in a quiet, dark room at each of the four time periods. Pupil diameter data were cleaned off line and down sampled to 8 Hz, and C3/A2 EEG data to 64 Hz. Power spectral density functions (FFT) were calculated on 2 sec epochs for minutes 5-11, and standardized for each individual by dividing each 2 sec epoch by the mean theta power obtained for the first minute of dark recording. The mean pupil diameter for each 2 sec EEG window was calculated, divided by the largest pupil diameter found for each subject during the fourth minute of dark recording, and classified according to the appropriate Yoss pupil stage. The 2 sec theta values for each Yoss stage were aggregated for each subject regardless of when they occurred during the 5-11 minute period. During visual scoring, EEG epochs with significant muscle or eye movement artifact were removed from the analyses.

**Results:** ANOVA revealed that there were significant differences in theta power ratios by time of day (4 times) and pupil stage (4 stages) [ $F(15) = 17.66$ ,  $p .000$ ]. Post Hoc Least Significant Difference testing with Bonferroni correction (critical  $p .008$  or  $<$ ) revealed there were significant differences in the amount of theta activity both within and between testing times by pupil stage. Within time of day, statistically significant differences in theta power ratios were as follows: 1000 hr - Stage 4 > Stages 1-3; 1200 hr - Stage 4 > Stages 1-3; 1400 hr - Stage

4 > Stages 1 & 3; 1600 hr - Stage 2 < Stage 1 and > Stage 4. Between testing periods, the theta power ratio tended to be significantly greater for the afternoon testing periods and the sleeper pupil Stages 3 and 4.

**Conclusions:** These data replicate earlier findings which suggest that the pupillographic ALT, like the EEG-based physiologic sleepiness measures (the MSLT and the MWT), is a measure of increasing sleepiness in awake individuals, and is a sensitive measure of a lowered level of alertness at mid-afternoon in normal subjects.

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Research supported by Mr. J. A. Piscopo.

**050.R**

**VALIDATION OF THE KICKSTRIP™: A NOVEL SCREENER FOR PERIODIC LIMB MOVEMENTS DISORDER (PLMD)**

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**Introduction:** The KickStrip™ disposable diagnostic device for patients suspected of PLMD has been described previously in detail (1). It is based on the "smart sensor" electronic technology, which includes a strain gauge flex sensor, a CPU with real time software, and a display that presents the score (Kscore), which reflects the number of PLM events per hour of use. In the present study, the Kscore is validated against the PLM index (PLMI) based on inlab polysomnography (PSG).

**Methods:** Eighty-two patients (Male/Femal 65/17 age range – 18-74 yrs) suspected of sleep disorders of any kind from two sleep laboratories (31 from Loewenstein Rehabilitation Hospital (LRH) and 51 from Rambam Medical Center (RMC)) participated in the study. All patients underwent an overnight sleep recording with full PSG, including anterior tibialis electromyogram (EMG) concomitantly with a KickStrip™ for each leg. Kscores and PLMI (based on standard scoring criteria) from each leg were collected. Analyses were performed for the data of each of the sleep labs and/or both laboratories combined. Analyses were based on all legs beyond patients (LG analysis) and/or on the higher score of the two legs for each patient (PT analysis). Pearson correlations (r) were computed between Kscores and PLMI. Sensitivity (SENS) and Specificity (SPEC) values were computed for various thresholds (>5, >10, >20, >40) representing increasing severity levels of PLMD. For the entire sample only, receiver-operating characteristic (ROC) curves were plotted by LG and area-under-the-curve (AUC) was computed for the various thresholds to determine overall accuracy. A Bland-Altman plot was produced by PT only, to show the distribution of the differences between the Kscores and PLMI against their means.

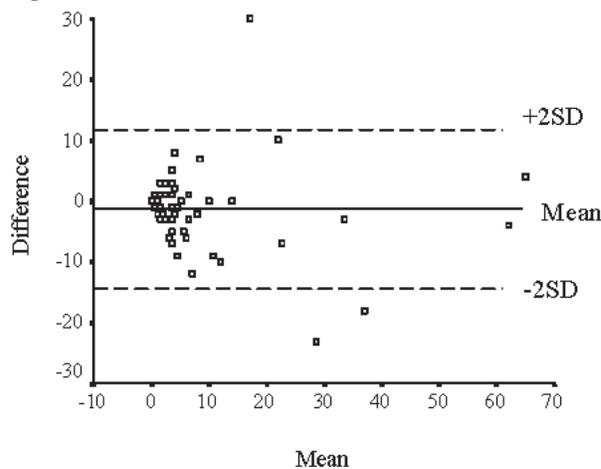
**Results:** Table 1 shows results for each lab separately and for both combined. Measures of accuracy generally increased

with severity level. Figure 1 shows a Bland-Altman plot of the differences between the methods against their means. A mean bias of -1.27 (95% CI -2.9 to 0.37), indicates a slight overestimation of the severity of the PLMD by the KickStrip™.

**Table 1**

		RMC (n=51)		LRH (n=31)		ALL (n=82)	
		LG	PT	LG	PT	LG	PT
SENS	>5	.74	.75	.58	.80	.69	.76
	>10	.73	.83	.63	.75	.70	.80
	>20	.57	.50	1.00	1.00	.70	.67
	>40	1.00	1.00	1.00	1.00	1.00	1.00
SPEC	>5	.87	.83	.88	.83	.87	.83
	>10	.95	.91	.98	1.00	.96	.94
	>20	.96	.97	.96	.95	.96	.97
	>40	.99	1.00	.98	.95	.99	.98
AUC	>5					.82	
	>10					.86	
	>20					.92	
	>40					1.00	
r		.78	.82	.91	.95	.84	.88

**Figure 1**



**Conclusions:** The comparisons between the KickStrip™ Kscores and PLMI based on PSG recordings show high correlations and overall accuracy, excellent specificity at all levels, excellent sensitivity at the severe level and medium to good sensitivity in the mild to moderate levels. Clinically, differences between the methods are trivial. We conclude that the KickStrip™ is a valuable device for PLMD home screening and for monitoring the efficacy of drug treatment.

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**051.R****VARIABILITY IN HOME-ADMINISTERED BRIGHT LIGHT TREATMENT**

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**Introduction:** With few exceptions (e.g., Martin et al. 1998), studies using bright light therapy for treatment of sleep disorders provide few details regarding light delivery. Manufacturers claim that their bright light equipment delivers specific light intensities (lux) at standardized distances. In our current research on bright light treatment for older insomniacs, we were concerned about how much light subjects actually received, particularly since treatment conducted in the home is typically of longer duration than that of laboratory studies.

**Methods:** Nineteen older adults (13 women, 5 men) aged 65.2 /pm 8.9 years were studied. The subjects were screened for major sleep, medical, or psychiatric disorders through questionnaire data, clinical interviews, physical examinations, and ambulatory polysomnography. We followed a specific protocol for light delivery in the subjects' homes. Curtains and shutters in the homes were closed. The subjects determined the minimum light intensity they needed for personal safety; this intensity was used as the standard ambient light during treatments. A research assistant set up a 10,000- or 50-lux Satellite Lamp (Northern Light Technologies, Montreal, CAN), according to a randomization scheme. The lamp was placed on a table covered by white, reflective photographic paper. Each subject sat in front of the lamp, eighteen inches between the lamp face and the subject's forehead. A flexible arm supports and allows rotation of the lamp head (containing two light tubes covered by a UV filter) to alter the direction of light; the other end of the arm is connected to a rectangular base. Initially, the lamp head was bent completely downwards, and then gradually rotated upwards until the subject could see both light tubes through the UV filter. Subjects were instructed to place reading material on the table so that they were facing but not directly viewing the light source. We collected 10 readings of ambient light at each eye using a professional light exposure meter, positioning the light sensor in the direction of the subject's gaze. We collected an additional 10 readings at each eye after switching on the lamp (either dim or bright).

**Table 1**—ANOVA results of light measurements

Light Level	N	Mean (SD)	Range
Ambient (no lamp)	6	19.1 (12.0)	2.5-41.5
Dim Lamp (50 lux)	6	44.9* (5.4)	34.0-53.0
Ambient (no lamp)	13	51.3 (108.5)	0-497.5
Bright Lamp (10,000 lux)	13	3062.2* (974.0)	2707.5-6943.0

\* P < .0001

**Results:** As expected, differences between ambient vs. dim light, ambient vs. bright light, and dim vs. bright light were

significant (see table). However, even within a given light level, significant differences ( $p < .001$ ) were detected between subjects. For two subjects, we could not reduce ambient light in their homes to levels comparable to other subjects; however, both subjects were in the bright light condition where this discrepancy had minimal impact.

**Conclusions:** Although we followed a standard protocol for lamp setup at the home, we found high variability in the amount of light actually received by subjects at eye level. We do not know the extent to which this variability affects treatment outcome; variability issues are particularly acute when treatment is based at home. Few studies using bright light treatment report detailed data either on the specifics of lamp arrangement, or on the amount of light actually received. Questions about light treatment effectiveness cannot be satisfactorily answered unless this information is provided.

**References:**

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**Research supported by the Medical Research Service of the Palo Alto Veterans Affairs Health Care System, by the Department of Veterans Affairs Sierra-Pacific MIRECC, and by AG 12914.**

**052.R****SLEEP LABORATORY ENVIRONMENT HAS LITTLE EFFECT ON PARAMETERS OF SLEEP IN PATIENTS UNDERGOING OVERNIGHT POLYSOMNOGRAPHY.**

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**Introduction:** Overnight polysomnography (PSG) is used for evaluating disorders of hypersomnia, most commonly obstructive sleep apnea. Some aspects of the indoor sleeping environment (bed type, pillow type, room temperature and humidity) have been examined in the sleep laboratory. None, however, have evaluated the effect that the sleep facility itself has on sleep parameters. Here, the effect that the physical indoor environment has on sleep in the sleep laboratory is examined. We speculated that the change in the lab would result in better sleep quality.

**Methods:** 196 consecutive patients were evaluated during the spring of 2001 when the sleep laboratory at the University of Utah changed from a traditional, hospital-based, 3 bed lab to a new, updated, modern, 6 bed facility off campus. All staff, procedures, and protocols were maintained between the 2 facilities. These patients were placed into 2 groups: Group 1 had 97 consecutive patients evaluated 1 month before the switch over and prior; Group 2 had 99 consecutive patients 1 month after the switch and beyond. All individuals were studied with overnight PSG. Patients were excluded if they were under the age of 15, were undergoing PSG for CPAP titration or split night study, or if they were to undergo MSLT the next day. These 2 groups were then analyzed statistically regarding demographics, diagnosis, sleep efficiency, total sleep time, total time in bed and percentage of time spent in REM sleep,

non-REM sleep, wakefulness, stage 1 sleep and slow wave sleep.

**Results:** The 2 groups are well matched for age and gender. Approximately 2/3 of patients in both groups had a diagnosis of obstructive sleep apnea with a mean RDI in group 1 of 29.7 and 25.7 in group 2. All measured parameters of sleep during overnight PSG showed no significant difference between the 2 groups (table 1).

**Table 1**

	Group 1	Group 2	p-value
Age	51.8	52.6	0.70
Gender(% Male)	75%	74%	
% OSA	67%	66%	
RDI	29.7	25.7	0.26
Sleep Efficiency(%)	79.2	78.4	0.71
Total Time in Bed (min)	453.7	465.4	0.76
Total Sleep Time (min)	358.5	367.2	0.43
Sleep Onset (min)	21.6	21.4	0.94
REM Latency (min)	171.6	136.1	0.19%
Time Awake	20.8	21.5	0.74%
REM Sleep	12.9	12.1	0.45%
NREM Sleep	87.1	87.9	0.45%
Stage 1 Sleep	21.5	21.8	0.87%
Slow Wave Sleep	7.1	7.7	0.62

**Conclusions:** The indoor sleep laboratory environment does not have an effect on common parameters of sleep in individuals evaluated for primary sleep disorders. This may have implications in establishing laboratory-based normals within a given medical system or areas with similar physical environments.

**053.R**

**A WITHIN-SUBJECTS COMPARISON OF A NEW SLEEP APNEA HOME-DIAGNOSTIC SYSTEM AND POLYSOMNOGRAPHY**

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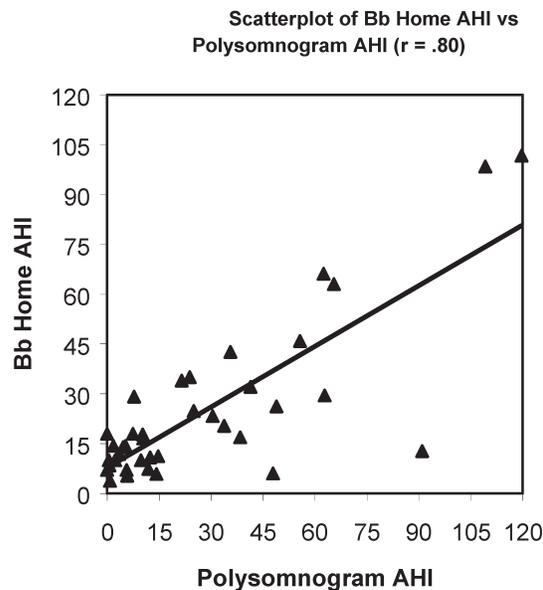
**Introduction:** Sleep apnea is a serious and common disorder that challenges healthcare resources<sup>1,2</sup>. Portable home apnea-testing devices have been promoted as simpler, less costly alternatives to polysomnography even though limited data are available regarding their validity and reliability in the home environment<sup>3</sup>. We evaluated the portable Bedbuggtm Home Diagnostic System by comparing Bedbugg (Bb) home results to laboratory polysomnogram, and Bb laboratory results to simultaneous polysomnogram. We compared SaO2 nadir recorded by Bb vs. polysomnogram, and we calculated the sensitivity, specificity, and predictive values of Bb compared to polysomnogram at apnea/hypopnea index diagnostic thresholds 5, 15, and 30, respectively.

**Methods:** Thirty-eight subjects received simultaneous Bb and clinical polysomnogram in the laboratory, and used Bb at home for three nights. Through random assignment, half of the subjects used Bb at home prior to the laboratory polysomnogram and half of the subjects used Bb at home following the

laboratory polysomnogram. Because no systematic differences were apparent between the two home-study groups, the data were pooled for analysis. Subjects were asked to complete a questionnaire regarding ease of use of the Bb system in the home. For each subject, apnea/hypopnea indexes and SaO2 nadirs were averaged across all three nights of home testing for comparison to laboratory polysomnogram results. The apnea/hypopnea index and SaO2 nadir scores were correlated with and compared to the automated scores of Bb using Pearson's product-moment correlation "r".

**Results:** Apnea/hypopnea index correlations were: Bb-lab vs. polysomnogram, r =.86; Bb-home vs. polysomnogram, r =.80 (figure 1); Bb-lab vs. Bb-home, r = .94. Sensitivity, specificity, positive and negative predictive values are shown in table 1. At apnea/hypopnea index 5, Bb-lab scored zero true negatives resulting in undefined specificity and undefined negative predictive value. SaO2 nadir correlation was r =.93 for Bb-lab vs. polysomnogram, and r =.87 for Bb-home vs. polysomnogram. Ninety five percent of the subjects (36 of 38) found the Bedbugg system simple to use at home without Technician assistance.

**Figure 1**



**Table 1**

*Sensitivity, specificity and predictive values of Bb.*  
 L=Bb-in lab, H=Bb-home, U=undefined.

	RDI ≥ 5		RDI ≥ 15		RDI ≥ 30	
	L	H	L	H	L	H
<b>Sensitivity (%)</b>	100	100	94	88	86	50
<b>Specificity (%)</b>	U	11	86	76	88	92
<b>Positive Predictive Value (%)</b>	76	78	84	75	80	78
<b>Negative Predictive Value (%)</b>	U	100	95	89	91	76

**Conclusions:** The correlation between home and lab recordings was high, with Bb demonstrating acceptable to good sensitivity and positive predictive value. Bb's specificity and negative predictive value were good at apnea/hypopnea index criteria levels corresponding to moderate and severe sleep apnea, but undefined to poor at the mild sleep apnea diagnostic criteria level. Future studies of Bb should include non-clinical subjects and event-by-event correspondence analysis to better define specificity at a mild level of apnea/hypopnea index. The authors concluded that Bb is a valid and reliable home testing device for adults suspected to have sleep apnea.

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**Research supported by the Sequoia Hospital Pulmonary Research Fund.**

## 054.R

### NEW INSTRUMENTATION FOR DETECTING CENTRAL APNEA

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**Introduction:** Chest and abdominal strain gauges are generally used for detecting respiratory problems during polysomnography. However, the data obtained from strain gauges are qualitative and their calibration may change markedly during a night. Intraesophageal pressure(Peso) monitoring is accepted as a quantitative method. However, inserting a pressure transducer is considered to be slightly invasive for the patients. To correct this problem, an air pad sensor(APS) was developed to diagnose the respiratory problems of subjects non-invasively.

**Methods:** The APS consists of three pads(size:20x60x1cm) containing 150 ml air inside. The APS is simply put under the subject's bodies or mattress during the examination. Acoustic signals received by the pad are converted to electric signals. Then the signals are filtered with 0.5Hz low pass(80 dB/decade) and differentially analyzed. Nine obstructive sleep apnea(OSA) patients(9 men; average AHI in supine, 56.0/hr.; average age, 54.0 years; mean BMI, 26.6 kg/m<sup>2</sup>) and two healthy subjects were examined using APS and daytime polysomnography, including Peso, simultaneously. The agreement ratio in terms of the central apnea time among the APS, Peso, and abdominal strain gauge was compared. The sensitivity to detect the respiratory rate was also compared among them. Cosecutive data during 10 minutes of sleep in supine position was analyzed.

**Results:** Four cases out of 9 OSA indicated obstructive and mixed apnea episodes. The remaining 5 cases showed only obstructive apnea. In 4 cases with mixed apnea, the agreement ratio in terms of central apnea time between the APS and the Peso was 93.4%, although the ratio between the Peso and the abdominal strain gauge was 40.7%. The agreement ratios in terms of respiratory rate among the Peso & the APS and the Peso & the strain gauge were 99.4% and 93.4% respectively, in 5 obstructive apnea subjects. In 4 subjects with mixed apnea, the agreement ratio was 97.5% in the APS & the Peso and 74.4% in the strain gauge and the Peso. Two healthy subjects showed complete coincidence among the Peso, strain gauge, and APS.

**Conclusions:** Peso monitoring is accepted as a gold standard to evaluate respiratory effort quantitatively and is used as an A-class reliable sensor for polysomnography. This study showed a high agreement ratio between the APS and the Peso in the central apnea period. If the APS is applied with strain gauge during polysomnography, the central apnea period may be identified easily. Further study on the APS is necessary to evaluate its reliability in various sleep related breathing disorders and sleep positions.

## 055.R

### SELF-REPORTED SLEEP QUALITY IN THE US GENERAL POPULATION

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**Introduction:** Studies have shown that Americans increasingly report getting less sleep ("2000 Sleep in America poll"). This study sought to gain a further understanding of self-reported sleep quality in the US and the demographic characteristics associated with sleep quality using the Medical Outcomes Study (MOS) Sleep Scale.1

**Methods:** The MOS-Sleep is a 12-item, patient-completed questionnaire with six subscales: sleep disturbance, snoring, awaken short of breath or with headache, quantity of sleep, sleep adequacy, and somnolence as well as a 9-item sleep problem index. Scores range from 0-100, with higher scores indicating more of the domain being measured. The MOS-Sleep was administered by telephone to 1,011 US adults 18 and older in January 2001. Demographics including age, race/ethnicity, gender, education, household income and a single general health rating item were collected. Analyses were performed using t-test, chi-square, GLM and multivariate regression models. Results reported were statistically significant at the minimum of p<0.05.

**Results:** Average age was 46; 51% were female and 74% were white. Fifty-four percent reported that their household income was <\$50,000 year and 35% stated that their highest education level was a high school (HS) diploma. Mean scores (SDs) were sleep disturbance: 24(23), sleep adequacy: 61(30), somnolence: 22(19), quantity of sleep: 6.8 hrs(1.5), and the sleep problems index: 26(18). No difference in sleep quantity was seen between men and women, however women had more sleep disturbance, less adequate sleep, and more overall sleep problems. Men were more likely to snore, but there was no gender difference in somnolence. Those with household

income <\$50,000/year were more likely to have disturbed sleep, somnolence and overall sleep problems, but reported no difference in quantity compared to those with a household income >\$50,000/year. No differences were found by race/ethnicity on any of the scores. Those aged 65+ tended to have better sleep scores, with the exception of somnolence, where they and the 18-29 age group had higher scores than those 30-49 and 50-64. Few differences were seen by education, with the exception of those with <HS diploma reporting more sleep disturbance, somnolence, overall sleep problems and less adequate sleep than those with a HS diploma, those who attended some or completed college and those who had postgraduate training. Individuals in excellent or very good health had less sleep problems than those in good, fair or poor health. Multivariate analysis confirmed these findings, with the exception that lower household income was not associated with more sleep problems after controlling for age, gender, race/ethnicity, education and health status.

**Conclusions:** These results provide a greater understanding of sleep quality in the US general population. Few differences between groups were found on sleep quantity, yet differences in quality were found by gender, age, education and health status. Further work is needed to understand these differences in sleep quality among the general population.

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## 056.R

### VALIDITY OF THE SLEEP-EVAL SYSTEM IN THE ASSESSMENT OF RESTLESS LEGS SYNDROME

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**Introduction:** Restless legs syndrome is characterized by disagreeable leg sensations occurring most often at sleep onset that provoke an urge to move the legs. This disorder would affect between 6% and 10% of the population and is more prevalent in elderly individuals. This study aims to assess the validity of the Sleep-EVAL system, a diagnostic tool specialized in the recognition of sleep disorders in the general population, for the restless legs syndrome diagnosis.

**Methods:** Three hundred twenty patients of two sleep disorders centers were interviewed by telephone using the Sleep-EVAL system (1). Information collected by the system included several aspects of sleep disorders: insomnia symptoms, daytime sleepiness, leg symptoms (pain, creeping, discomfort, cramps, jerks), medical and psychiatric history, medications, and sleep and mental disorders diagnoses according to the DSM-IV and ICSD classifications. The Sleep-EVAL diagnoses were compared to the diagnosis given by the physicians of the patients.

**Results:** The sample is composed of 320 patients: 163 of them were diagnosed with a restless legs syndrome by a sleep spe-

cialist. 57.7% of RLS patients were women. The mean age for the RLS patients was 59.73±12.48 years while the other patients were younger with a mean age of 46.59±18.68 years (p<.001). Overall, 72.4% of RLS patients entered into the RLS decisional tree of the Sleep-EVAL System with a positive answer on a question about unpleasant sensations in the legs at night. This sole question was not specific to RLS patients and was answered positively by 37.6% of the other patients. The other RLS patients entered into the tree based on positive answers on leg pain associated with difficulty initiating sleep. This symptom was reported mostly by RLS patients: 46% compared with 7% for the other patients. Based on the information collected during the interview, the Sleep-EVAL system recognized adequately 82% of the RLS patients.

**Conclusions:** Our aim was to measure the ability of Sleep-EVAL to identify RLS individuals based on self-report information. The results show that Sleep-EVAL was performing adequately.

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## 057.R

### CAN OBSTRUCTIVE SLEEP APNEA BE DIAGNOSED IN THE HOME USING A WRIST-MOUNTED DEVICE WITH AUTOMATED ANALYSIS OF PERIPHERAL ARTERIAL TONOMETRY, PULSE OXIMETRY, AND ACTIGRAPHY?

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**Introduction:** Ambulatory monitoring for the detection of OSA in the home is an attractive alternative to polysomnography in the sleep laboratory. Ideally, such technology should be simple to use for the patient with limited instruction and require minimal post-acquisition analysis. Peripheral arterial tonometry (PAT) employs a finger-mounted, pneumo-optic sensor that measures the digital arterial pulse volume. Arterial vasoconstriction, a marker of sympathetic nervous system activity which is often associated with the termination of OSA events, induces PAT signal attenuation. Based on our previous laboratory studies [1,2], we concluded that OSA could potentially be diagnosed in the home using automated analysis of PAT when combined with pulse oximetry and actigraphy.

**Methods:** We prospectively studied (n=19 to date, 8 in Boston and 11 in Haifa) subjects with suspected OSA. Subjects were studied one night in the home with the Watch\_PAT100 (PAT device) and one night in the laboratory with polysomnography. The PAT device includes a PAT probe and pulse-oximetry sensor worn on separate fingers and a wrist-mounted recording unit that includes an accelerometer for actigraphy measurement (to differentiate sleep from non-sleep). PSGs were scored using recent AASM criteria with the scorer blinded to the results of the PAT device. Automated analysis of the PAT, oximetry, and actigraphy signals calculated a PAT-RDI. We



059.R

**DIRECT CURRENT EEG IS NEEDED FOR ACCURATE RECORDING OF SLOW EEG WAVEFORMS DURING SLEEP**

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**Introduction:** The EEG activity patterns during human sleep have been extensively studied for several decades. Characteristic EEG features of nonREM sleep include many different, long lasting phenomena (K-complexes, V-waves, spindles, positive occipital sharp transients and slow-wave activity). In addition, invasive animal studies have clearly indicated the presence of infraslow (< 0.5Hz) EEG frequencies, which are coupled to faster activity patterns like K-complexes. Conventional EEG (AC-EEG) techniques, due to high-pass filtering, only detect frequencies above approximately 0.5Hz, while most of the EEG events specific to sleep are longer lasting and may contain significant amount of slower frequencies. Hence many if not all of these well recognized EEG waveforms are likely distorted in conventional EEG recordings. Faithful detection of slower frequencies requires a direct current EEG (DC-EEG). We have recently developed a technique capable of performing stable bedside DC-EEG recordings.

**Methods:** We recorded sleeping, healthy volunteers and epileptic patients during afternoon naps and overnight sleep. We used a custom made DC-EEG amplifier with 6 to 16 channels, using Ag/AgCl electrodes. For analysis the derivations were referenced to a calculated linked mastoid. Skin potentials ("galvanic skin responses") were eliminated by short-circuiting them by penetrating the basal lamina layer with a tiny needle. In most experiments, DC-EEG traces were compared with simultaneous AC-EEG recordings.

**Results:** We found consistently that both K-complexes and arousal transients in DC-EEG have waveforms that differ considerably from those acquired with conventional AC-EEG techniques. Most notably, DC-EEG demonstrated clearly that these waveforms were mainly unidirectional, cortex-negative transients, rather than bidirectional waves as seen in AC-EEG. These transients appeared to be in phase with simultaneous infraslow oscillations (0.1-0.4Hz). Spectral analysis by the fast Fourier transform showed a strong underlying oscillatory pattern with peak frequencies varying between 0.1Hz and 0.7Hz.

**Conclusions:** A comparison of our findings with published invasive recordings obtained from cats (e.g. M. Steriade and co-workers) reveals close similarities in both the waveforms of fast events and in the infraslow oscillatory activity, which may enable a direct comparison between the cellular/network mechanisms studied in animals and the DC-EEG activity observed in humans. DC-EEG is a practical bedside technique in our hands, providing a new, clinically applicable and straightforward approach to characterize brain activity during human sleep. Future areas of study include the mechanisms coupling sleep phenomena and epileptic events, as well as possible derangements of the synchronization between infra-

slow and higher frequencies activity in sleep disorders.

Research supported by Finnish Academy

**Oral Presentation**  
**The Ups and Downs of Clinical Pharmacology**

060.C

**METHYLPHENIDATE PREFERENCE AND SUBJECTIVE EFFECTS: TIME-IN-BED AND DOSE**

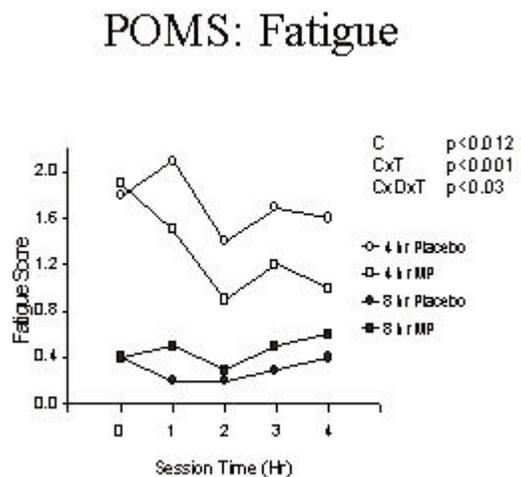
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**Introduction:** A previous study found that methylphenidate (10 mg) preference and subjective effects varied as a function of prior amount of sleep and associated level of daytime sleepiness. This study assessed the dose-dependent differences in preference and subjective effects as a function of level of daytime sleepiness.

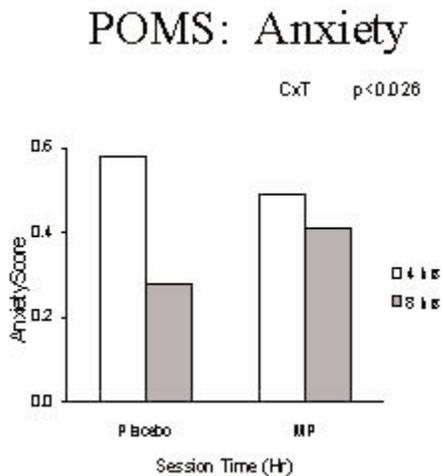
**Methods:** Eighteen healthy, normal adults, 21-45 yrs old, participated. All were in good medical and psychiatric health with no history of alcoholism or drug abuse. Subjects were randomly assigned to a methylphenidate dose (5, 10, or 20 mg). On each of 2 sampling days at 0900 hrs subjects received, in a counter-balanced order, a color-coded methylphenidate (at the assigned dose) or placebo capsule. On each of 5 subsequent choice days they chose 1 of the 2 color-coded capsules. For the duration of all 7 days at 2-hr intervals subjective effects, performance, and MSLT testing was done. Subjective effects were assessed with the Profile of Mood States (POMS), Addiction Research Center Inventory (ARCI), and visual analog scales (VAS). All Ss completed this 7-day assessment after 8 hrs time-in-bed (TIB) and 4 hrs TIB each of the 7 nights with order of TIB counter-balanced and 1 week of recovery between TIBs.

Figure 1



**Results:** Overall, methylphenidate (MP) was chosen more frequently after 4 hrs TIB than 8 hrs TIB (53% vs 37% of days) ( $p < .04$ ). In the 8 hrs TIB, placebo was preferred at all doses on 57- 66% of the choice days. In the 4 hrs TIB, 5 and 10 mg methylphenidate were preferred to placebo (51 and 60% of days), while at 20 mg, MP preference was not evident (49% of days). Analyses of subjective effects for 10 mg, the most preferred dose, in addition to showing main effects of TIB (i.e., POMS Vigor reduced after 4 hrs,  $p < .01$ ) and MP (i.e., VAS drug liking increased,  $p < .01$ ), revealed significant TIB by MP interactions. As illustrated below, MP reduced POMS Fatigue only after 4 hrs TIB ( $p < .03$ ). On POMS Anger and Anxiety (illustrated below) scales the scores were elevated after 4 hrs relative to 8 hrs prior to capsule administration and MP decreased these scores relative to placebo ( $p < .03$ ).

Figure 2



**Conclusions:** Methylphenidate was preferred to placebo only after 4 hrs TIB and preference was strongest at the 10 mg dose. The subjective effects of methylphenidate 10 mg were consistent with choice behavior and showed it reversed the dysphoric effects of sleep restriction.

Research supported by NIDA grant # R01-DA11448

061.C

**ESOPICLONE: PHARMACOKINETIC AND PHARMACODYNAMIC EFFECTS OF A NOVEL SEDATIVE HYPNOTIC AFTER DAYTIME ADMINISTRATION IN HEALTHY SUBJECTS**

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**Introduction:** Esopiclone (ESO) is a novel, isomerically pure, non-benzodiazepine, cyclopyrrolone agent that rapidly induces sleep and improves total sleep time with an absence of residual morning effects.

**Methods:** This daytime, randomized, double-blind, placebo (PBO)-controlled study in healthy subjects reports single dose, pharmacodynamic and pharmacokinetic parameters of ESO at

escalating doses of 1.0, 2.0, and 3.0 mg ( $n=6$  per dose level), as part of a larger dose escalating study. Psychomotor impairment was evaluated using the Digit Symbol Substitution Test (DSST) and daytime sleepiness was assessed using the Stanford Sleepiness Scale (SSS).

**Results:** ESO appeared rapidly in systemic circulation ( $t_{max}$  of 1.0 to 1.5 hrs for each ESO dose level) following oral administration. Terminal phase half-life ( $t_{s1/2s}$ ) was between 4.5 and 5.8 hours for each dose level. The mean DSST scores mirrored the PK profile. At 6 hours post-dose, the mean DSST score returned to baseline and showed no impairment at the 1.0, 2.0 or 3.0 mg doses (Table 1). The SSS results at 6 hrs post dose were generally consistent with the results of DSST, demonstrating no subjective daytime sleepiness as measured by mean change from baseline score (Table 2). Adverse events were limited primarily to somnolence and unpleasant taste. Somnolence was expected following daytime administration of ESO and consistent with the pharmacology of the drug. Unpleasant taste was mostly noted during ingestion and probably attributable to the liquid formulation.

Table 1—Mean DSST Score Following ESO Administration

Treatment	DSST <sup>a</sup>			
	Baseline	Maximum Change	Time of Maximum Change <sup>b</sup>	6 Hours Post Dose
ESO 1.0 mg	57.7	-11.5	1 hour	56.7
PBO 1.0 mg	66.7	0.7	2 hours	75.3
ESO 2.0 mg	57.2	-6.2	2 hours	62.2
PBO 2.0 mg	59.0	-2.0	2 hours	61.3
ESO 3.0 mg	60.2	-11.5	2 hours	63.7
PBO 3.0 mg	57.3	1.7	2 hours	67.0

For each dose level,  $n=6$  for ESO and  $n=3$  for PBO.

a: DSST scores represent number of correct substitutions in 90 seconds; higher score is indicative of higher function.

b: Median is presented for the time of maximum change.

Table 2—Mean SSS Score Following ESO Administration

Treatment	SSS <sup>a</sup>	
	Baseline	6 Hours Post Dose
ESO 1.0 mg	2.7	2.7
PBO 1.0 mg	2.0	2.0
ESO 2.0 mg	1.7	1.3
PBO 2.0 mg	2.3	2.0
ESO 3.0 mg	1.8	1.7
PBO 3.0 mg	2.3	1.3

For each dose level,  $n=6$  for ESO and  $n=3$  for PBO.

a: SSS scores are measured in a scale of 1-7; lower score is indicative of more alertness.

**Conclusions:** ESO demonstrated rapid onset with a half-life of less than 6 hours. The pharmacodynamic profile of ESO mirrored its pharmacokinetic profile. ESO was generally safe and well tolerated over the therapeutic dose range and did not show any impairment at 6 hrs post dose by subjective and objective measures.

Research supported by Sepracor Inc., Marlborough, MA.

**062.C****EFFECTS OF A FIXED VALERIAN-HOPS EXTRACT COMBINATION (ZE 91019) ON QUANTITATIVE EEG DATA IN HEALTHY SUBJECTS WITH CAFFEINE INDUCED HYPERAROUSAL**

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**Introduction:** Beneficial effects on sleep quality have been demonstrated for Alluna (Ze91019), a fixed valerian-hops combination, in an exploratory trials(1) and a post marketing study. As an additional outcome no significant daytime sedation was reported (2). Also, the combination suggests lack of interaction with alcohol(3). These trials have shown beneficial effects after nightly use of two weeks or more. However, consumers have reported beneficial effects of single doses, especially when they felt too hyped, nervous or anxious. Therefore, additional data, preferably from placebo controlled trials to enhance the understanding of the effects of a single dose are desirable.

**Methods:** The effects of Ze91019 on the pharmacodynamic characteristics of EEGs were evaluated in a blinded PCT in 48 healthy male volunteers (18-35 years). The subjects consumed a dose of 200mg caffeine to generate pharmacodynamic, central-nervous characteristics typical for an anxious state. The subjects then received either a single dose of the treatment (2 tablets plus matching placebo, 6 tablets of active/no placebo, or placebo only). Quantitative 18-channel-EEGs were recorded directly for a 10 min. baseline prior to ingestion of caffeine and treatment as well as after 30, 60, 90 and 120 min. using a multichannel electrocap (Electrocap Coop. USA, Medtronic-Neurodiagnostics, Denmark). Spectral power data were calculated using FFT (BrainVision-Analyzer, Brain Products, Germany, 2000).

**Results:** The pharmacodynamic effects of caffeine were measurable as a decrease in alpha-1-power already 30 min. after drug intake while beta-2-power increased continuously. Ze91019 neutralized this caffeine effect dose-dependently. Two tablets reduced the effects caused by caffeine while the intake of six tablets resulted in power changes opposite to the effects caused by caffeine. Six tablets of Ze91019 increased alpha-1-power from 11,82 to 18,15  $\mu V^2$ , whereas the absolute power decreased from 17,65 to 5,70  $\mu V^2$  after placebo. The beta-2-power increased after placebo from 4,45 to 5,21  $\mu V^2$  while six tablets caused a decrease from 4,17 to 2,84  $\mu V^2$ .

**Conclusions:** The trial has shown that a single dose of a fixed valerian-hops combination has a measurable effect on the CNS in subjects who displayed pharmacodynamic characteristics similar to a nervous state. The effects appeared to be dose dependent, which contributes to the evidence that Ze91019 is a pharmacologically active herbal preparation.

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**063.C****THE EFFECTS OF MODAFINIL ON SIMULATED DRIVING PERFORMANCE IN ADHD SUBJECTS COMPARED TO CONTROLS**

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(1) Eastern Virginia Medical School,

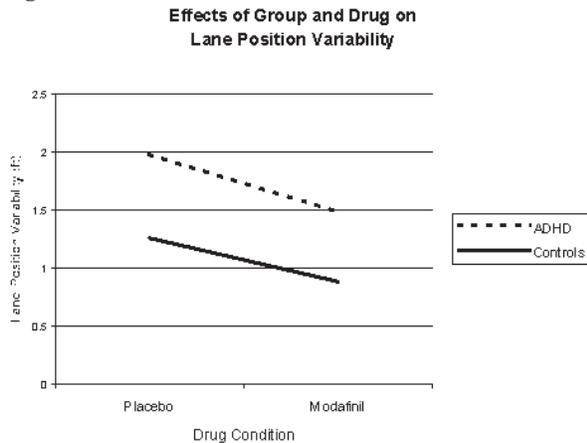
**Introduction:** Fatigue effects simulated driving performance in several populations. Post-call male residents have poorer driving performance putatively due to sleep deprivation (1). Sleep apnea patients also have poorer driving performance when compared to controls (2). The present study investigated whether ADHD subjects have similarly impaired driving performance. An earlier study showed poor driving performance in ADHD subjects that normalized on methylphenidate (3). This study examined whether modafinil, a stimulant drug with longer-lasting effects, could improve driving performance in the ADHD population. We hypothesized that 1) ADHD subjects would perform worse on the driving simulator than control subjects, 2) modafinil would improve driving performance for both groups, and 3) ADHD subjects on modafinil would perform similarly to control subjects on placebo.

**Methods:** Participants included 8 ADHD and 8 control subjects, matched for gender, between the ages of 18 and 35. Subjects possessed a valid drivers license and had normal vision, or vision corrected to normal. Subjects were administered the Structured Clinical Interview for the DSM-IV Axis Disorders to determine a diagnosis of ADHD. Participants completed a simulated drive on two separate occasions, one week apart. Subjects were asked to discontinue any stimulant medication two-days prior to the test and not to consume any nicotine or caffeine 3 hours prior to their visits. All subjects received both modafinil (200 mg) and placebo. Drug condition was counter-balanced and double-blind. One hour after receiving the medication, subjects completed a 10-minute practice drive through a city scenario followed by a 60-minute drive designed to replicate a highway-driving scenario. Lane position variance (ft) was continuously sampled. The within factors were drug condition (modafinil versus placebo), and time (six 10-minute blocks).

**Results:** A 2 (group) x2 (drug condition) x6 (time) ANOVA was used for analysis, with repeated measures for drug condition and time. Lane position variability was significantly greater in ADHD subjects compared to controls ( $p = .042$ ). Subjects on Modafinil had significantly less lane position variability than subjects on placebo ( $p = .001$ ). There were no significant interactions, and no significant difference across time. An independent samples t-test showed no significant differ-

ences between ADHD subjects on modafinil and control subjects on placebo ( $t = 0.26$ ,  $p = n.s.$ ).

**Figure 1**



**Conclusions:** These results indicate that ADHD subjects perform more poorly on a driving simulator than normal subjects, and that modafinil can improve driving performance for both controls and ADHD populations. ADHD subjects on modafinil perform similarly to control subjects on placebo. Analysis of EEG for attention lapses may help determine if fatigue/sleepiness contribute to poorer performance.

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Research supported by Eastern Virginia Medical School, Department of Psychiatry Grant

**Oral Presentation  
Sleep Apnea Diagnosis**

**064.J**

**A COMPARISON OF SLEEP LABORATORY ACTIVITY IN THE UNITED STATES AND JAPAN**

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**Introduction:** Despite the apparent increase in sleep laboratory activity for over the last 20 years, there has been no quanti-

tative assessment of the number of yearly polysomnograms (PSG) in industrialized nations. This study was designed to determine the number of sleep laboratories and sleep studies conducted in the United States (U.S.) at the current time, and to compare this with another industrialized nation, Japan.

**Methods:** For the US, a survey was sent to all American Academy of Sleep Medicine (AASM) members and accredited laboratories detailing the number of full overnight in-laboratory PSGs performed. The actual number of PSGs performed in three index states (MA, OR, LA) was determined by telephoning or emailing all known sleep laboratories in those states. Using the ratio of [(total # laboratories or PSG) divided by (# labs or PSG from the original mailed survey)] in these three states, we extrapolated the total numbers for the entire U.S. For Japan, we mailed a similar survey to all clinical members of the Japanese Society of Sleep Research, attendees of the Sleep Disordered Breathing Study Group who are in charge of their departments or sleep laboratories, departments affiliated to medical schools who claimed involvement in sleep disorders, and other local physicians introduced by reliable informants.

**Results:** In the US, 633 laboratories returned mailed questionnaires; they reported performing 677,404 PSG/year. The actual number of PSGs performed in the three index states was 1.72 times as many as reported from the mail survey. By extrapolation, we therefore estimated that 1.17 million studies are performed in the U.S. In 2001 (430 PSG/yr/100,000 population). Similarly, we estimated that there are 1292 American sleep centers. The number of PSGs performed in each state was highly variable (range: 121-1161 PSG/yr/100,000). Only AASM membership density ( $r=0.32$ ,  $p=0.02$ ) correlated with the state rate of PSG. The number of PSGs performed in Japan was much less (18.3 PSG/yr/100,000 population).

**Conclusions:** There are 23 times more PSGs performed in the USA versus Japan. This may be due to differences in: disease prevalence, reliance on ambulatory studies, flexibility of the health care system to in establishing a new field, standardization of diagnostic/therapeutic procedures, physician reimbursement, physician/patient knowledge of sleep disorders, and attitudes towards sleep disorders. We doubt this represents an excessive number of PSGs in the US with a more appropriate utilization of services in Japan, because the vast majority of individuals with OSA in the US remain undiagnosed despite 1.17 million studies per year. We speculate, therefore, that the proportion of undiagnosed sleep apnea must be greater in Japan than the U.S. The wide variability between states (U.S.) in the number of PSGs/100,000 population remains unexplained but does not relate to apnea risk factors (age, gender), socioeconomic status, Medicare reimbursement or population density.

Research supported by Pfizer Health Research Foundation

**065.J**

**AUTOMATIC DETECTION OF SLEEP APNEA BASED ON PERIPHERAL ARTERIAL TONOMETRY: IN LAB POLYSOMNOGRAPHIC VALIDATION**

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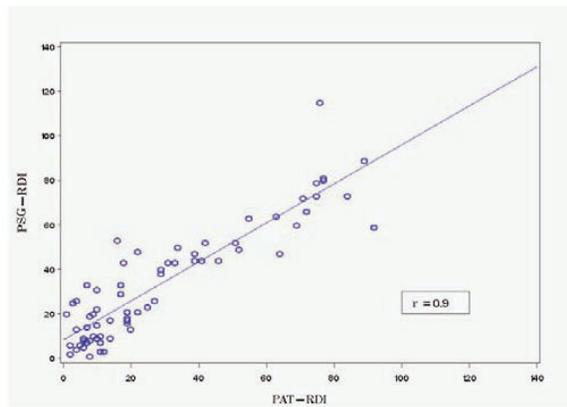
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**Introduction:** There is a growing need for the development of an ambulatory unattended diagnostic system for sleep apnea syndrome. The WATCH PAT 100 (WP100), a portable device, based on the peripheral arterial tonometry (PAT), is designed for unattended home sleep studies. The objective of the present study was to validate the efficacy of the WP100 as an ambulatory device for the diagnosis of OSAS.

**Methods:** Seventy-six subjects (69 OSAS patients and 7 normal volunteers, men/women 60/16, age 47.1±14.1 years, BMI 28.3±5.3) underwent in lab polysomnography (PSG) simultaneously with WP100 recording. The PSG recordings were blindly scored for apnea/hypopnea according to the AASM criteria (1999), and respiratory disturbance index (RDI) was calculated (PSG-RDI). The WP100 data was analyzed automatically for RDI (PAT-RDI) by a proprietary algorithm, which had been developed on recordings from a former group of subjects.

**Results:** Across a wide range of RDI levels the PAT-RDI was a highly correlated to the PSG-RDI (R=0.90, P<0.0001), with an area under the ROC curve (AUC) of 0.87 for both diagnosis thresholds of 10 and 20 events/hour.

**Figure 1**—A scatter plot of PSG-RDI vs. PAT-RDI



**Conclusions:** The Watch PAT 100 provides an accurate automatic diagnostic measure for suspected OSAS.

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**Research supported by Itamar Medical Ltd.**

**066.J**

**MALLAMPATI SCORE - A USEFUL CLINICAL TOOL FOR ASSESSING THE RISK OF OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** The Mallampati score is a simple airway classification used primarily in anesthesiology to predict the difficulty of endotracheal intubation. The score is easily obtained by asking the patient to open the mouth as wide as possible while protruding the tongue as far as possible, and is scored on a scale of I-IV (I-entire uvula visible, II majority of uvula visible, III-only soft palate visible, IV-only hard palate visible). A tongue depressor is not used, and the patient should be instructed not speak or emit sounds during the assessment. Scoring is the same for men and women. The goal of this study was to determine if Mallampati score has practical value in the assessment of patients with possible obstructive sleep apnea.

**Methods:** Mallampati score was prospectively determined in 151 patients who had been referred for a sleep apnea evaluation. Height and weight were also measured and body mass index was calculated. Each patient subsequently underwent polysomnography. Obstructive sleep apnea was defined by an apnea-hypopnea index greater than or equal to 10 events/hr. Hypopnea was defined as a measurable decrease in airflow for 10 seconds or more, associated with a 4% or more decrease in oxygen saturation. Bivariate logistic regression was used to examine the relationship between Mallampati score and sleep apnea. Multivariate logistic regression was used to adjust for patient body mass index. Spearman rank correlations were done to further examine the relationship between Mallampati score and body mass index.

**Results:** Obstructive sleep apnea  $\beta$  (apnea-hypopnea index  $\geq 10$ ) was present in 62 of 151 subjects (41%). The mean apnea-hypopnea index for all subjects was 19.3  $\pm$  27.0 events/hr (range: 0-156). The mean Mallampati score for all subjects was 2.5  $\pm$  0.8, and the mean body mass index (BMI) was 32.1  $\pm$  7.5 kg/m<sup>2</sup> (range 17.1- 61.8). For every one point increase in Mallampati score, the odds of having sleep apnea increased by 66% (bivariate OR = 1.66; P=.027). When adjusted for subject BMI, the odds were identical (Table 1). There was no association between body mass index and Mallampati score (P=.12).

**Table 1**—Mallampati Score Predicts OSA

	OR	P	95% CI
Mallampati Score	1.66	.029	1.05 - 2.62
Body Mass Index	1.07	.009	1.02 - 1.12

**Conclusions:** Few physical parameters that are independent of body mass index have been shown to be useful in the evaluation of obstructive sleep apnea. Based on these results, Mallampati score predicts the presence of obstructive sleep apnea and the association is independent of patient body mass index. The scoring system is easily mastered, simple to use, and

requires no special equipment. Thus, use of this scoring system may be of practical clinical value when assessing patients prior to polysomnography. Mallampati score could also be useful in future clinical studies, allowing for a better assessment of patients prior to intervention and for more detailed analyses based on the prior odds of obstructive sleep apnea.

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**067.J**

**BIOBEHAVIORAL QUANTIFICATION OF ALERTNESS AND MEMORY IN PATIENTS WITH SLEEP APNEA**

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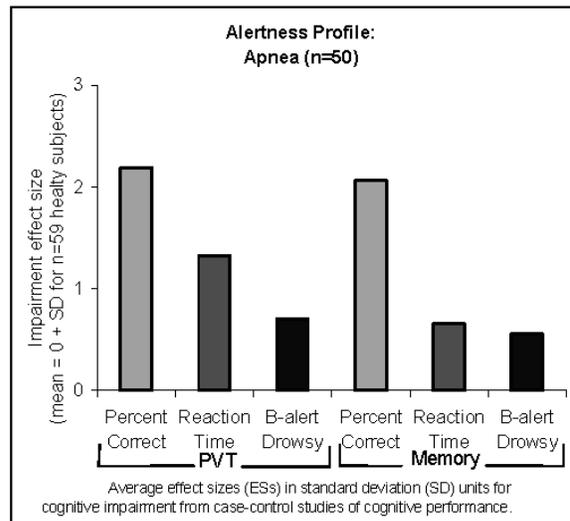
**Introduction:** An alertness profiling (AP) system simultaneously acquired electroencephalographic (EEG) indices and neurobehavioral performance measures to quantify alertness in Sleep Apnea (SA) patients and healthy subjects. Measures of alertness included: B-Alert EEG classifications [1], accuracy and reaction time on psychomotor vigilance and memory tests and a modified Maintenance of Wakefulness Test (MWT) [2].

**Methods:** Fifty-nine healthy subjects (37 males; 22 females; mean age = 33.0, range 23 - 63) and 50 patients (32 males; 18 females; mean age = 45.9, range 22 - 66) diagnosed with SA (mean RDI = 55, range 12 - 165) completed the AP study between 8:00AM and 12:30PM. Continuous EEG (CzOz-Differential) and EOG recordings were acquired during: Psychomotor Vigilance Tests (PVT), Paired Associate Learning-Memory tests (PAL) and a modified MWT. B-Alert classifications, reaction times and percentage of correct responses were averaged across each of the PVT and PAL sessions. MWT was terminated following 90 consecutive seconds EEG evidence of sleep and absence of finger-tapping.

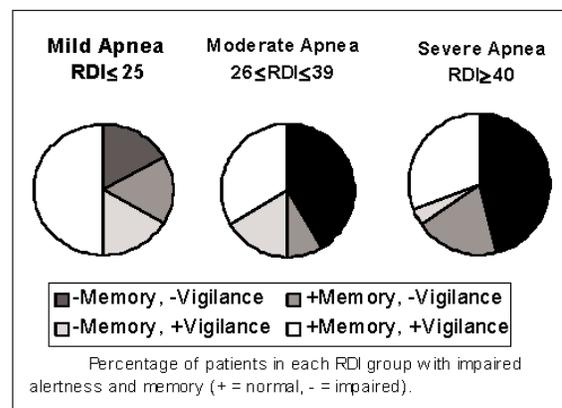
**Results:** T-test comparisons revealed that SA patients were significantly less accurate on all performance measures: PVT-ABM (t=4.09, p£.001), PAL-memory (t=5.52, p£.001) with slower reaction times: PVT-ABM (t=-5.22, p£.001), PAL-memory (t=-2.36, p£.05). During the MWT, all healthy subjects remained awake for the full 40 minutes, while SA patients were significantly more likely to fall asleep prior to completion (t=3.98, p£.001). B-Alert identified significantly more drowsy epochs for the SA patients during PVT-ABM (t=-3.03, p£0.01) and PAL-memory (t = -2.26, p£.05). Impairment effect sizes ranged from 0.55 to 2.2 standard deviations

(S.D.) from the means of the healthy group (Fig 1). RDI values were used to stratify patients into mild (£25, n=12), moderate (26 - 39, n=12) and severe (≥40, n=26). Figure 2 illustrates the percentage of patients in each RDI sub-group with impaired (> 1.5 S.D. from normal) alertness (B-Alert or PVT) and/or memory (PAL).

**Figure 1**



**Figure 2**



**Conclusions:** Excessive daytime drowsiness (EDS) and neuropsychological impairments can significantly impact SA patient safety, quality of life and prognosis. This study revealed that the B-Alert classifications, vigilance and memory performance parameters clearly discriminated SA patients from healthy subjects. Although there was substantial variability across patients, a relationship between severity of SA (as measured by RDI) and the alertness measures was observed. A closer inspection of the data suggested sub-groups of patients, some characterized by impaired vigilance and/or accompanying memory deficits (Fig. 2). Impairment was not, in all cases, directly correlated with the RDI, suggesting that individuals may differ in their vulnerability to the sleep fragmentation caused by SA. The B-Alert EEG indices and neuropsychological performance, derived during a one-hour AP

TUESDAY, JUNE 11, 2002

clinical protocol, may have applications in the diagnostic assessment and subsequent treatment outcome evaluation of SA and other sleep disorders.

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**Oral Presentation  
Pediatric Sleep and Behavior**

**068.G**

**DO FACTORS ASSOCIATED WITH CONSOLIDATED SLEEP CHANGE WHEN THE CHILD GROWS UP?**

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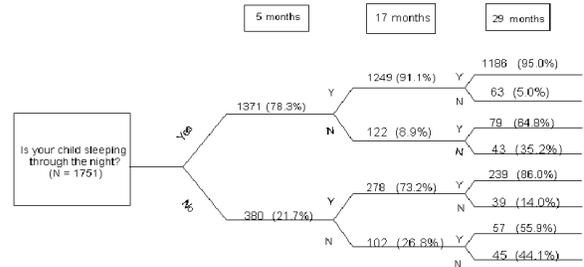
**Introduction:** Infant sleep disorders are one of the parent's major concerns (1). Moreover, a significant continuity in frequent night wakings from 6 months of age until school years was observed (2-3). To our knowledge, it is still unclear as to what predicts the development and maintenance of nocturnal awakenings. Our aim was to evaluate the evolution of the factors likely to impede or foster the process of sleeping through the night at 5, 17 and 29 months of age.

**Methods:** Longitudinal data on 1751 children were collected by questionnaires and interviews. The mother's opinion on whether the child was sleeping through the night or not classified children into good or bad sleepers (5, 17 and 29 months). Logistical regressions were used to determine the most determinant factors associated with consolidated sleep at each age.

**Results:** The most comprehensible way of presenting measurements of stability from longitudinal data is a probability tree (see Figure). The upper branch represents the good sleepers group: 91% of good sleepers at 5 months are still good sleepers at 17 months and 95% of good sleepers at 17 months are still good sleepers at 29 months. The lower branch represents the bad sleepers group: 27% of bad sleepers are still bad sleepers at 17 months and 44% of bad sleepers at 17 months are still bad sleepers at 29 months. The table presents the most influential factors likely to impede the process of sleeping through the night for each age with the corresponding odd ratios. Overall, the determinants correctly classified 72,0% of the infants at 5 months, 72,3% at 17 months and 69,2% at 29 months. For all ages, the most factors which impede sleep consolidation were comforting the child outside his bed and putting him to bed already asleep or staying with him until he falls asleep.

**Figure 1**

**Figure. Evolution of "good" and "bad" sleepers at 5, 17 and 29 months of age.**



**Table 1**

**Table. Factors which impede sleep consolidation**

Variables – 5 months	Odds ratio
1) Comforting child outside his bed/feeding	5,24
2) Infant's temperament (difficult)	1,46
3) Co-sleeping	1,41
4) Sex (boy)	1,43
Variables – 17 months	Odds ratio
1) Putting the child to bed already sleep or staying with him until asleep	4,18
2) Comforting child outside his bed	2,16
3) Child's temperament (difficult)	1,17
4) Co-sleeping	1,78
Variables – 29 months	Odds ratio
1) Putting the child to bed already sleep or staying with him until asleep	2,93
2) Comforting child outside his bed	2,26
3) No mother's feeling of efficacy	1,12
4) Child's bad health	1,64

**Conclusions:** Our results suggest that when a child is a good sleeper, he has excellent chances to continue to be a good sleeper. When a child is a bad sleeper at 5 months, he has good probabilities to become a good sleeper too. Otherwise, if he is a bad sleeper at 17 months, he has increased probability of staying a bad sleeper at 29 months. Moreover, parental behaviors surrounding sleep periods were the most important ingredients in the recipe for a good sleep. In other words, infants must learn to fall asleep on their own to be able to go back to sleep without signaling their awakenings.

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**069.G****A COMPARISON OF POLYSOMNOGRAPHIC CHARACTERISTICS BETWEEN CLINICAL AND COMMUNITY SAMPLES OF CHILDREN WITH ADHD.**

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**Introduction:** A growing number of studies have recently addressed the prevalence of sleep problems among children with Attention-Deficit/Hyperactivity Disorder (ADHD)(1,2). However, only a few have objectively quantified the sleep characteristics in the ADHD population. Furthermore, most studies have used highly selected samples and inadequate controls. Therefore, the aim of this study was to compare objective sleep data for two groups of pre-adolescent children with ADHD (a sleep clinic referral sample and a community sample) with control children.

**Methods:** The clinical sample of ADHD children was selected from the pediatric population referred to the Sleep Medicine Center and underwent polysomnography as part of their clinical assessment (ADHDcl). The community sample was recruited from a survey of sleeping habits conducted among parents of first-grade students attending Jefferson County Public Schools system and using a previously validated questionnaire. Community children with reported ADHD (ADHDcom) and controls were randomly selected, and invited for an overnight polysomnographic assessment in the sleep laboratory.

**Results:** A total of 45 pre-adolescent children with ADHDcl (34 male), 54 ADHDcom children (38 male) and 54 controls (24male) were studied. Mean ages were  $7.5 \pm 2.1$ ,  $6.6 \pm 0.6$  and  $6.7 \pm 0.5$  years respectively. Statistically significant differences were observed between the groups for REM latency and REM percentage, percentage of Stage 2 sleep, respiratory arousal index (Aresp), periodic leg movement index (PLMI), apnea-hypopnea index (AHI) and mean oxygen saturation (mSpO<sub>2</sub>). Specifically, REM latency was shorter in controls than in ADHDcl ( $p < 0.05$ ) and ADHDcom ( $p < 0.001$ ); REM % was greatest in controls and least in ADHDcl with all groups being significantly different from each other ( $p < 0.01$ ). All groups were also different from each other for AHI, with ADHDcl having the highest AHI ( $p < 0.05$ ), and Aresp ( $p < 0.001$ ). PLMI was also higher in ADHDcl than the other groups ( $p < 0.05$ ) but there were no differences in PLMI between ADHDcom and controls.

**Conclusions:** In all ADHD children, some sleep characteristics differ from controls, in particular the high prevalence of sleep-disordered breathing. However, ADHD children from the community are significantly different from ADHD children referred to a Sleep Clinic with regards to PLMI and AHI. Elevated PLMI has been previously documented in clinical populations of children with ADHD but our data illustrate that these findings cannot be extrapolated to all children with hyperactivity. The altered percentage of REM sleep across all three groups has not been previously reported and warrants further investigation.

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**070.G****LATER BEDTIMES AND HIGHER BMI'S ARE ASSOCIATED WITH HIGHER AHI'S IN MINORITY CHILDREN**

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**Introduction:** Obesity, African-American race, sinusitis and persistent wheeze, are risk factors for moderate sleep-disordered breathing (SDB) defined by an Apnea/Hypopnea Index (AHI) of 10 or more events per hour of sleep in children and adolescents (1). Given the relative preservation of sleep architecture in children and adolescents with SDB (2), we questioned whether the presence of SDB might adversely affect reported bedtimes and/or total sleep duration.

**Methods:** A retrospective analysis of clinical and polysomnographic data on 202 children and adolescents (18-months to 18 years) evaluated at our Sleep Center for complaints of snoring and daytime somnolence was performed. Body Mass Index (BMI) was available in 132 patients. Data on AHI, SaO<sub>2</sub> nadir, Reported Bedtime and Total Sleep Duration for weeknights were extracted. Weekend sleep patterns were omitted from the analysis since they are different and often complicated by recovery sleep (3). Since the AHI and SaO<sub>2</sub> nadir were highly correlated ( $r=0.73$ ,  $F(1, 153)=174.01$ ,  $p=.0000$ ,  $\text{Adj R-squared}=0.5291$ ), separate multiple linear regression models were employed. The first regressed the SaO<sub>2</sub> nadir by Race, Sex, BMI, Age, Bedtime, and Total Sleep Duration. The second, regressed the AHI by Race, Sex, BMI, Age, Bedtime, and Total Sleep Duration.

**Results:** The database demographics are presented in Table 1. The database consisted of 92.4% Minority children and adolescents. The only independent variable that correlated significantly with the SaO<sub>2</sub> nadir was BMI - the more obese the child, the lower the SaO<sub>2</sub> nadir with SDB events during polysomnography ( $t=-2.20$ ,  $p=0.029$ , 95% confidence interval, -0.00385 to -0.00021). The regression of AHI by Race, Sex, Age, BMI, Bedtime, and Total Sleep Duration was a much better linear fit ( $r=0.46$ ,  $F(8, 123)=5.35$ ,  $p=.0000$ ,  $\text{Adj R-squared}=0.2098$ ). Age, BMI, and Bedtime, all correlated with the AHI. The younger the child the higher the AHI ( $t=-3.47$ ,  $p=0.001$ , 95% confidence interval, -3.16905 to -0.86521), the

heavier the child the higher the AHI ( $t=4.99$ ,  $p=0.000$ , 95th confidence interval, 0.60328 to 1.39683), and the later the child's reported Bedtime the higher the AHI ( $t=2.22$ ,  $p=0.028$ , 95th confidence interval, 0.54689 to 9.47393). Table 2 looks at the relationship by pre-school, pre-teen, and adolescent age groupings.

Table 1

Sex	Number	Percentage
Males	71	53.4%
Females	62	46.6%
Race	Number	Percentage
African American	76	57.1%
Hispanic	47	35.3%
Caucasian	10	7.5%

Table 2

	Ages 1-5	Ages 6-12	Ages 13-18
Number (M,F)	49 (30,19)	66 (30,36)	18 (11,7)
Mean BMI	18.3	25.5	34.2
Mean AHI	21.6	16.8	22.9
Mean SaO2 Low	88%	87.6%	86%
Mean Bedtime	9:37pm	9:19pm	10:16pm

**Conclusions:** The presence of moderate, SDB in toddler/preschool minority children would underscore the need for early diagnosis and treatment prior to entering elementary school where adverse neurocognitive effects are likely to become manifest. Furthermore, early intervention may also facilitate earlier bedtimes and sleep offset rise times, which are often difficult to advance in children by the time they reach school age.

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**071.G**

**SLEEP QUALITY AND PSYCHOSOCIAL FUNCTIONING IN A COMMUNITY SAMPLE OF PRESCHOOL CHILDREN**

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**Introduction:** The present study concerns the relationship between sleep quality and psychosocial functioning in pre-

school children. Understanding this relationship is important to the investigation of the role of sleep in development and is needed to help establish criteria for defining normal and abnormal sleep (1). Previous studies of children's sleep and daytime functioning have been limited by the lack of comprehensive, cost-efficient, and standardized measures of sleep quality. This problem was addressed by using the newly developed Children's Sleep-Wake Scale (2). The present study also broadly examined children's daytime status by using standardized measures of emotional, behavioral, social, and adaptive functioning.

**Methods:** Caretakers of preschool children were recruited from a variety of sources (community activities, shopping centers, schools, and daycares). Data were collected on 111 children (59 male, 52 female), ages 3 to 5 years. Seventy-six percent of the children were Caucasian, 31% were African American, and 4% were Hispanic and multiracial. Children with physical or developmental disabilities or taking stimulant medication were excluded. Caretakers were administered the Behavioral Assessment System for Children (BASC), the Social Skills Rating Scale (SSRS), the Vineland Adaptive Behavior Scale (VABS), and the Children's Sleep-Wake Scale (CSWS). The CSWS is a 42-item pencil-and-paper instrument that assesses behavioral sleep quality in 2- to 8-year-old children. Caretakers report how often sleep behaviors occur using a 6-point scale (Always, Frequently-if not Always, Quite Often, Sometimes, Once in Awhile, and Never). Five subscale scores [Going to Bed (GTB), Falling Asleep (FA), Maintaining Sleep (MS), Reinitiating Sleep (RS), Returning to Wakefulness (RTW)] and a total scale score can be obtained. Higher scores are indicative of better sleep quality.

Table 1

Correlation coefficients for BASC subscales and CSWS subscales and total scale scores						
BASC Domains	GTB	FA	MS	RS	RTW	CSWS Total
<b>Externalizing</b>						
Hyperactivity	.55**	.46**	.30**	.28**	.32**	.53**
Aggression	.53**	.45**	.31**	.37**	.26**	.54**
<b>Internalizing</b>						
Anxiety	.14	.14	.08	.06	.15	.16
Depression	.39**	.39**	.28**	.29**	.44**	.51**
Somatization	.20*	.26**	.34**	.23*	.37**	.40**
<b>School</b>						
Attention	.39**	.31**	.18	.13	.23*	.35**
<b>Other</b>						
Atypicality	.25**	.21**	.31**	.31**	.35**	.41**
Withdrawal	.06	.21	.16	.07	.04	.15

\*\* p<0.01; \*p<.05  
Note: All correlations are negative

**Results:** Tables 1 and 2 present the correlations between the five behavioral dimensions of sleep as measured by the CSWS and the BASC subscales (Table 1) and the SSRS and VABS subscales (Table 2). Inspection of scatter plots revealed that each of the significant relationships was linear. It can be seen

that there is a weak to moderate relationship between sleep quality and all of the BASC subscales except the anxiety and withdrawal subscales. Sleep quality was also related to social skills and adaptive functioning. The strongest relationship was with self control (SSRS), and the weakest relationships involved motor skills and daily living skills (VABS).

**Table 2**

Correlation coefficients between SSRS subscales, VABS subscales and CSWS subscale and total scale scores

	CSWS Subscales					CSWS Total
	GTB	FA	MS	RS	RTW	
<b>SSRS Subscales</b>						
Cooperation	.35**	.37**	.19*	.16	.31**	.39**
Assertion	.18	.29**	.18	.09	.22*	.27**
Responsibility	.29**	.27**	.27**	.09	.13	.29**
Self-Control	.45**	.47**	.31	.27**	.29**	.50**
<b>VABS Subscales</b>						
Communication	.22*	.27**	.27**	.22*	-.04	.25**
Daily Living	.16	.23*	.25**	.27**	-.21*	.18
Socialization	.26**	.31**	.26**	.18	.08	.30**
Motor Skills	.17	.20*	.24**	.26**	-.02	.23*

\*\* p<.01; \*p<.05

**Conclusions:** Relationships between sleep and daytime behavioral problems have been documented in previous studies (3). The results presented here replicate and extend these findings by showing that the sleep of preschool children is importantly related to multiple aspects of daytime psychosocial functioning, including social and adaptive functioning. All of the observed relationships were linear. That is, poor sleep quality was associated with low levels of daytime functioning, while good sleep quality was related to high levels of functioning.

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**072.G**

**POLYSOMNOGRAPHIC EVIDENCE OF NORMAL SLEEP RELATED RESPIRATION IN PATIENTS WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER**

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**Introduction:** There has been some speculation about the relationship between attention deficit-hyperactivity disorder (ADHD) and obstructive sleep apnea syndrome (OSAS) (1,2,3). To further explore this, we performed polysomnogra-

phy on 16 children with ADHD.

**Methods:** Six to 15 year old patients were enrolled as part of an ongoing study examining the effects of pharmacologic treatment of ADHD on sleep and cognitive function. They met DSM-IV criteria for ADHD (inattentive, hyperactive, or combined). They had scores on the ADHD rating scale (ADHD-RS, consisting of 9 inattention items rated from 0-3 for a possible total score of 27, and 9 hyperactivity items similarly rated) at least 1.0 SD above age and gender norms. They had a Clinical Global Impression (CGI) score of at least 4 (moderately ill). They met the same criteria at a subsequent visit 10-24 days later. They had normal lab results and ECG, and had no clinical evidence of primary sleep disorders including OSAS (evidenced by snoring accompanied by excessive daytime sleepiness or observed apneic episodes), bipolar disorder, major depression, hypertension, or drug or alcohol abuse. Only one patient was excluded because of reports of snoring and daytime sleepiness. All subjects also had actigraphic monitoring during the interval between the visits described above. A subset of patients (16 out of 31) volunteered for two nights of polysomnography (PSG) as part of the latter visit. The first night recording included EEG, EOG and submental EMG, ECG, nasal pressure, piezo abdominal belt, oximetry, and leg movement recordings.

**Results:** The 16 patients (mean age 11.1, SD 2.0, range 7-14.6, 12 boys and 4 girls) had severe ADHD. On the ADHD-RS, patients had mean inattention score of 22.4 (SD 3.2, range 16-27) and mean hyperactivity score of 17.5 (SD 7.1, range 3-27). The table shows the minimum, maximum, mean and standard deviations for polysomnographic variables. There was no evidence of OSAS.

**Table 1**

**PSG Characteristics of ADHD patients**

	Mean	SD	Min	Max
Age	11.06	2.03	7	14.58
Time in bed (min)	550.1	28.3	490.5	585.3
Sleep efficiency (%)	90.8	4.5	76.9	95.0
Stage 1 (%)	3.0	2.2	0.8	7.6
Stage 2 (%)	51.6	8.6	28.4	66.3
Stage 3 (%)	4.5	2.2	1.1	8.3
Stage 4 (%)	23.6	9.3	14.4	44.2
Stage REM (%)	17.5	5.4	8.2	25.1
Lat to 1 <sup>st</sup> epoch sleep	22.3	11.0	6.0	41.0
Lat to persistent sleep	26.1	13.0	6.0	51.5
Lat to REM sleep	174.4	66.1	91.0	320.0
REI (NREM)	2.2	1.5	0.0	5.2
REI (REM)	3.5	3.7	0.0	12.0
REI (Total)	2.5	1.6	0.0	4.9
PLM Index	3.7	4.0	0.0	11.0

**Conclusions:** ADHD is likely a multi-etiological syndrome. However, there was no evidence of OSAS being one of the significant etiologies in this sample of patients. Clinical screening for snoring accompanied by EDS or observed apneic episodes successfully eliminated any patients who might have had OSAS. Patients did not have to be excluded simply for snoring. Of course, ADHD does not protect patients from OSAS, and the two may co-exist in some patients. Since

OSAS is known to cause cognitive impairment, when it coexists with ADHD, treatment of OSAS may well improve some cognitive symptoms. However, ADHD is clearly a separate entity from OSAS, with its own clinical picture and treatment, and it can be diagnosed without having to perform a PSG.

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### 073.G

#### SLEEP AND NEUROBEHAVIORAL FUNCTIONING IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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**Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) has been universally established as an immensely prevalent childhood disorder. It is characterized by impaired attention, impulsivity, and excessive motor activity. Sleep problems have often been associated with ADHD. Disrupted or shortened sleep has been associated with ADHD-like symptoms in late childhood. In addition, increased variability of the sleep measures reflecting instability of the sleep-wake system was found in children with ADHD. Sleep problems have been found to profoundly affect the neurobehavioral functioning (NBF) of children and adults. However, the relationships between sleep and NBF in children with ADHD has not been investigated. The aim of the present study was to investigate the neurobehavioral correlates of sleep patterns and sleep variability in boys diagnosed with ADHD.

**Methods:** Sleep and NBF of 35 non-referred boys and 32 boys diagnosed with ADHD from 2nd, 4th grade classes, were assessed using objective methods. Sleep was monitored using actigraphy for 5 consecutive nights. Actigraphic sleep measures included means and standard deviations (night-to-night variability) of sleep quality, (sleep percent, true sleep time, longest sleep period, quiet sleep, and number of night wakings); sleep quantity (sleep onset time, and total sleep time); and Sleep schedule (sleep onset time) measures. A computerized neurobehavioral evaluation system was used to assess children's NBF. The battery assesses attention, short-term memory, working memory and motor functioning.

**Results:** Sleep. Children diagnosed with ADHD had increased instability of sleep duration, sleep efficiency, true sleep, and sleep onset time compared to the non-referred children ( $F$ 's range from 8.17 to 24.5,  $p < .05$ ). In addition, whereas the night-to-night variability of sleep onset time and sleep duration was smaller for the older children in the control group compared to the younger ones, it was greater for the older children

in the ADHD group compared to the younger ones. Age effects were found for the regular sleep measures, with older children having shorter sleep compared to younger children. ( $F$ 's range from 8.17 to 24.5,  $p < .05$ ). NBF functioning. The performance of children with ADHD was poorer compared to the children from the normative group ( $F$ 's range from 3.5 to 9.7,  $p < .05$ ). In addition, older children performed better than younger children on the NBF measures ( $F$ 's between 4.49 to 22.3,  $p < .05$ ). Sleep and NBF. Different patterns of associations between sleep and NBF were found for the 2 groups. In the normative group, greater night-to-night variability of sleep was strongly associated with attention and working memory tasks ( $r$  between  $-.37$  to  $-.59$ ,  $p < .05$ ). In the ADHD group, greater night-to-night variability of sleep was associated with poorer motor functioning and short-term memory ( $r = -.42$  and  $.37$ , respectively,  $p < .05$ ). In the control group, measures of sleep quality, quantity and schedule were associated with attention and visual-motor measures ( $r$  between  $-.37$  to  $-.59$ ,  $p < .05$ ). In the ADHD group, only one measure of sleep efficiency was associated with one measure of attention ( $r = -.38$ ,  $p < .05$ ).

**Conclusions:** The results highlight different nature of associations between sleep and NBF in children with ADHD compared to non-referred children. In addition, they replicate the finding regarding increased sleep variability as characteristic of children with ADHD. These findings will be discussed with regard to the roles of the noradrenergic system and locus coeruleus in sleep, attention and ADHD.

### 074.G

#### SLEEP DISTURBANCE AND ASSOCIATED COGNITIVE PROBLEMS IN CHILDREN WITH NOCTURNAL ASTHMA

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**Introduction:** Sleep-related asthma occurs in 61 to 74 percent of asthmatics. The consequences of nocturnal asthma are frequent arousals and hypoxemia which may contribute to poor sleep, daytime sleepiness, fatigue, and impaired cognitive functioning. Reports suggest that individuals with nocturnal asthma may exhibit memory problems, inattention, and irregular performance. Despite these reports, little evidence is present in the literature to document the daytime consequences of this disorder, particularly in children. Stores and colleagues (1998) found that children with nocturnal asthma performed more poorly on a measure of delayed recall than age- and gender-matched controls. The children with nocturnal asthma rated themselves as significantly more depressed and were rated by their parents as having increased learning problems and psychosomatic symptoms. Performance on measures of memory and attention improved with the increased control of the nocturnal asthma symptoms and the ensuing reduction in sleep disruption.

**Methods:** We prospectively studied 24 children with nocturnal asthma and 14 controls matched for age, intelligence, and socioeconomic status. The children were admitted to the Gen-

eral Clinical Research Center of Texas Children's Hospital. They underwent pulmonary function tests and measurement of eosinophils, NO, and plasma cytokines at determined time points. Sleep diaries were completed for the week prior to their admission as well as an Epworth Sleepiness Scale (modified for children) and a Sleep Questionnaire. The children were administered a battery of neuropsychological measures including measures of intelligence (Wechsler Intelligence Scale for Children-III), memory (Wide Range Assessment of Memory and Learning), attention (Conners' Continuous Performance Test), and academic development (Kaufman Test of Academic Achievement).

**Results:** The results of the sleep measures indicated that the children with nocturnal asthma displayed more problems with sleep as compared to controls on the Sleep Questionnaire ( $F = 9.56, p = .006$ ). In addition, the nocturnal asthma group endorsed problems with sleep whereas the controls did not ( $\text{Chi-Square} = 9.29, p = .002$ ). The children with nocturnal asthma demonstrated more fluctuations in their attention over time ( $F = 3.11, p = .004$ ). In addition, they displayed more problems with impulsivity ( $F = 2.23, p = .03$ ). No differences were noted on measures of intelligence, academic development, or memory. Increased sleepiness, as assessed by the Sleep Questionnaire, was associated with increased problems with impulsivity during the day ( $p = .03$ ). Parents tended to endorse greater subjective daytime sleepiness for their children with nocturnal asthma than parents of controls ( $F = 3.98, p = .057$ ).

**Conclusions:** Children with nocturnal asthma were reported to have increased disruption in their sleep and demonstrated daytime problems with inattention and impulsivity. Sleep disturbance was associated with increased impulsivity during the day.

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**075.G**

**SLEEP AND NEUROCOGNITIVE FUNCTION IN 6-YEAR OLD HYPERACTIVE CHILDREN**

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**Introduction:** There is increasing evidence that snoring and sleep disordered breathing (SDB) in children are associated with behavior problems, such as hyperactivity (1). Children with ADHD also exhibit more sleep disturbances than other children (2). While improvements in learning and behavior have been documented following treatment for SDB (3), the frequency of SDB among hyperactive children and the nature of the relationship between SDB and behavior are less well understood in ADHD children. To determine the relationship between SDB and daytime neurocognitive function we studied a community sample of hyperactive/ADHD children and controls.

**Methods:** Parents of 1st grade children in public schools were surveyed about their child's sleeping habits using a validated questionnaire. The questionnaire also asked if they believed their child to be hyperactive or have ADHD. Randomly selected hyperactive and control children underwent overnight polysomnographic assessment and a battery of neurocognitive tests. Three groups of hyperactive (index) children were therefore included: 1) ADHD and taking medication (ADHD/med); 2) ADHD and not taking medication (ADHD/nomed); 3) hyperactive but not ADHD (hyper).

**Results:** 84(56 male) hyperactive children (ADHD/med n=37, ADHD/nomed n=18, and hyper n=29) were recruited with 26 (9 male) controls. Sleep studies indicated that SDB was present in 12% of index and in none of the control children. Analysis of variance revealed that REM latency, REM density (%TST) and respiratory arousal index were more likely to be affected in ADHD ( $p < 0.01$ ). Correlations between the affected sleep variables and domains of neurocognitive function are shown in Table 1. Exclusion of children with OSA did not alter the correlations. A stepwise logistic regression model revealed that REM latency predicted only 9.2% of the variance between the groups ( $r = 0.3, p < 0.01$ ), and that all other sleep-related variables were excluded by the model.

**Table 1**—Correlation between sleep and neurocognitive variables.

Sleep variable	(+) correlation	(-) correlation
REM latency	Conners' ADHD index* DSM-IV hyperactive-impulsive*	Attention/Executive function*
REM %	Language* Visuospatial** Memory**	Conners' ADHD index* Global Index restlessness-impulsivity* Global Index total* DSM-IV hyperactive-impulsive** DSM-IV total*
Respiratory arousal index	Externalizing total score*	

\* $p < 0.05$ , \*\* $p < 0.01$

**Conclusions:** In a community sample, 90% of the variance observed between the groups of hyperactive and control children is not explained by any one or more of the sleep measures. However, the prevalence of SDB is higher than that expected in the general population. These findings suggest that SDB may adversely affect pre-existing ADHD. However although REM sleep disturbances are more likely to occur in ADHD, they appear to impose little if any effect on daytime neurobehavioral functioning.

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**Oral Presentation  
Sleep and Aging**

**076.H**

**LINEAR RATES OF DELTA DECLINE ACROSS SLEEP AND DELTA INCREASE ACROSS WAKING IN YOUNG AND ELDERLY NORMAL SUBJECTS DO NOT DIFFER WHEN NORMALIZED FOR DELTA CAPACITY**

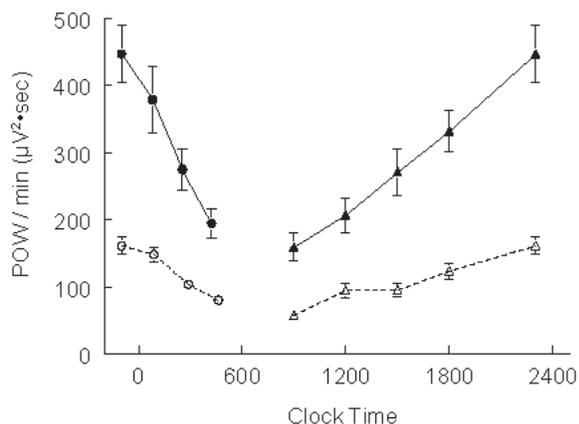
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**Introduction:** In 1974 one of us proposed that NREM delta is a correlate of a homeostatic process by which sleep reverses the effects of waking brain activities, and that changes in delta across sleep reflect the kinetics of this process. Assuming that the process is metabolic, we hypothesized that delta levels would be high early in sleep, declining exponentially. Borbely and coworkers incorporated these ideas into their quantitative “two-process” homeostatic model, postulating that delta increases across waking as a saturating exponential, and declines exponentially across sleep. Although this model has been fit to empirical data, it is not clearly established that the exponential model is significantly superior to a linear fit. This study was aimed, in part, at investigating this question.

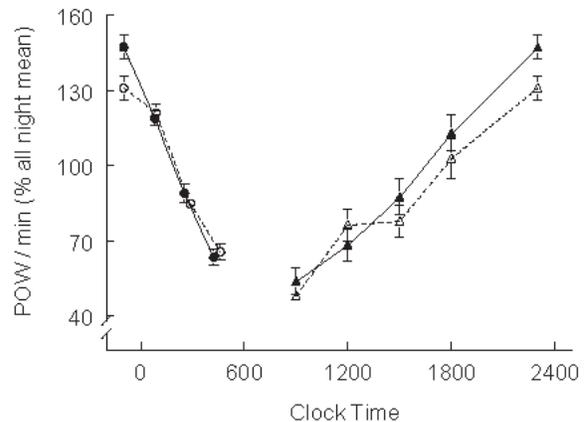
**Methods:** Young normal (YN) Ss (N=19, mean (sd) age = 22.4 (1.4)) and elderly normal N Ss (N=19, 71.4 (4.9)) underwent four separate sleep recording sessions consisting of a baseline night, nap, and post-nap night. Nap times were 0900, 1200, 1500 and 1800; nap order varied across Ss. EEG was scored visually and delta was measured by PA and FFT (PASS PLUS, sleepsoftware.com). The delta production rate was measured as absolute power/min and this value was also normalized as a percent of the S's 4-night baseline mean. ANOVAs with orthogonal components were performed. Preliminary findings were presented at APSS 2000.

**Figure 1**—Figure 1 absolute NREM delta (0.3-3 Hz) power/min plotted across baseline sleep NREM periods (circles) and daytime naps (triangles) for YN (solid line, filled symbols) and EN (dashed line, open symbols) Ss. Final data point in nap line is NREMP1 value. Both groups show linear— not exponential—rates of change with steeper linear slopes in the YN Ss.



**Results:** ENs produced delta power in baseline sleep at a significantly lower rate than YNs (123 vs 310  $\mu\text{V}^2\text{sec}/\text{min}$ ,  $p < 0.0001$ ). Figs. 1 and 2 plot absolute and normalized delta decline across NREMPs and increase across daytime naps. Linear trends were highly significant ( $p < 0.0001$ ), with no significant curvature, for both absolute and normalized measures. Absolute growth and decay curves were significantly ( $p < 0.0001$ ) less steep in ENs than in YNs, but normalized curves were strikingly similar. Similar results (not shown) were obtained for average sample amplitude and wave incidence in delta.

**Figure 2**—Figure 2. Normalized (%) curves for delta decline across sleep and increase across waking. Format is the same as Fig. 1. Delta declines and increases linearly and the slopes of the curves do not differ for YN and EN groups. Thus, the striking differences in slope seen in Fig. 1 are eliminated when each S's values are normalized to his total baseline night pow/min.



**Conclusions:** The significantly flatter decline of absolute delta power across NREMPs in ENs confirms previous results. But YN and EN linear curves of normalized delta power are similar and do not differ in slope. Thus, ENs and YNs both “consume” and “accumulate” delta power at similar rates when data are normalized to each S's total delta “capacity”. This similarity is missed if the data are not normalized or are normalized to a biologically irrelevant standard. Our original assumptions and those in the 2-process model, of exponential rates of increase and decline of delta, were not confirmed in our data. Questions are raised as to 1. what underlying biological processes might give rise to linear growth and decay curves for NREM delta, and 2. why ENs, despite a 50% reduction in delta production, maintain normalized rates of delta growth and decay about equal to those of Ss half a century younger.

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## 077.E

## CIRCADIAN PHASE-RESPONSE CURVES IN YOUNG AND OLDER ADULTS

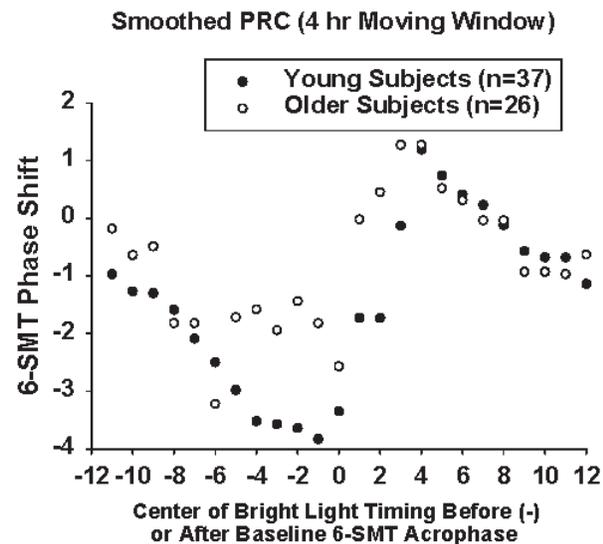
Youngstedt SD,<sup>1</sup> Kripke DF,<sup>1</sup> Elliott JA,<sup>1</sup> Huegel GO,<sup>1</sup> Cress AC,<sup>1</sup> Kinimaka C,<sup>1</sup> Del Prado G,<sup>1</sup> Rex KM<sup>1</sup>

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**Introduction:** Previous human phase-response curves (PRCs) for bright light have been mainly limited to young males (1,2). Older individuals may be less responsive to phase-shifting effects of light due to loss of SCN neurons or impairment of the retinohypothalamic pathway resulting from glaucoma, cataracts, and other eye problems. An aim of our ongoing research is to compare light PRCs in young and older adults.

**Methods:** We have examined 63 volunteers: 37 young adults ages 18-30 years and 26 older adults ages 60-75 years. Volunteers were screened extensively to ensure good health and abstinence from melatonin-altering drugs. During the week prior to laboratory recording, volunteers maintained stable sleep-wake schedules, verified by continuous Actillum recording (AMI, Ardsley, NY). Mood was assessed at the end of baseline with the Center for Epidemiologic Studies-Depression Scale (CES-D). Following home recording, volunteers spent 4.7-5.6 days in the laboratory, and followed a 90 min "ultra-short" sleep-wake cycle consisting of 30 min for sleeping in 0 lux followed by 60 min of wake in 50 lux. A baseline period lasted at least 30 hr. Baseline circadian phase was assessed over 24 hr through measurement of urinary 6-sulphatoxymelatonin (6-SMT). The best-fitting cosine curves determined the acrophases (peaks) for these data. During the next 3 days, volunteers were given 3 consecutive 3-hr bright light pulses at 3,000 lux, centered at one of 8 randomly assigned times around the 24 hr day. Following the third treatment volunteers spent 30 hr in the lab. Final circadian phase was determined during the last 24 hr in the lab. The CES-D was completed on days 1 and 5.

Figure 1



**Results:** Sixty-three of the 65 volunteers who began the laboratory study completed it. The experiment resulted in no significant decline in mood, and volunteers reported feeling recovered after 1-2 days of normal rest at home. PRCs for the young and older volunteers are displayed in the Figure. Hourly data were smoothed by applying a 4-hr moving window of stimulus timing.

**Conclusions:** A PRC difference is emerging between the young and older volunteers, which might account for advanced circadian and sleep timing in older adults. The data support recent results of Benloucif et al. showing greater phase delays in young vs. older adults (3). One interpretation of the present data is that the young have a larger delay response to evening light. An alternative, less compelling, interpretation might be that the young have a larger light response in both delay and advance regions, but their mean shift, resulting from free-run during the experiment, is greater, due to a longer circadian period ( $\tau$ ). As we acquire more subjects (total  $n=112$ ), we will explore these interpretations, as well as the hypothesis that light-induced shifts may be correlated with visual sensitivity.

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## 078.E

## RELATIONSHIP BETWEEN CIRCADIAN MELATONIN RHYTHM AND SLEEP TIMES IN OLDER AND YOUNG ADULTS

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**Introduction:** Sleep disturbances and day-to-day variability in sleep are common among older individuals. It has been postulated that these age-related sleep changes are due to alterations in circadian rhythmicity and/or changes in sleep homeostatic regulation. The objective of the present study was to investigate age-related alterations in the relationship between the circadian phase of the melatonin rhythm and the timing of sleep.

**Methods:** Thirty-one healthy young ( $28.4 \pm 4.3$  years, mean  $\pm$  SD; 16 men) and 19 healthy older ( $65.1 \pm 7.1$  years; 9 men) adults kept a self-selected, consistent sleep schedule for 7 days and wore actiwatches during this time. Then they were admitted to the general clinical research center (GCRC) at Northwestern Memorial Hospital and began a modified constant

routine (recumbent posture, dim light  $\leq 50$  lux, consistent caloric intake), with sleep occurring at the habitual time. After an adaptation night, blood was sampled at regular intervals, and plasma was analyzed for melatonin using radioimmunoassay. The dim light melatonin onset (DLMO; time of first melatonin level  $\geq 20\%$  of maximum melatonin level) and offset (DLMOff; time of first melatonin level  $\leq 20\%$  of maximum melatonin level) were calculated for each subject. Average sleep onset and wake times were calculated for each subject for the week prior to admission using the data collected by the actiwatch.

**Results:** Table 1 summarizes the findings for the young and older subjects (mean  $\pm$  SD) and figure 1 shows the average timing of the DLMO and the DLMOff relative to average sleep times in the two groups. Older subjects had an earlier sleep onset time and an earlier DLMO when compared to young subjects. In both young and older subjects, the DLMO occurred approximately 2 hours before sleep onset. Wake times were slightly (but not significantly) earlier, and the DLMOff was slightly (but not significantly) later in older subjects relative to young subjects. These differences resulted in the DLMOff occurring on average over an hour after wake in older subjects, but less than a half-hour after wake in young subjects.

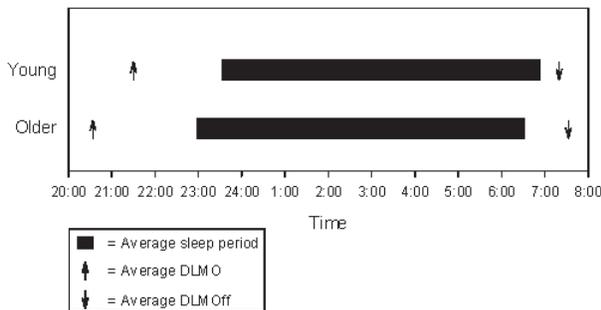
**Table 1**

	Young Subjects	Older Subjects
Sleep onset time **	23:34 $\pm$ 9 min	22:57 $\pm$ 13 min
DLMO **	21:25 $\pm$ 16 min	20:34 $\pm$ 14 min
Sleep onset - DLMO	133 min $\pm$ 18 min	135 min $\pm$ 16 min
Wake time	06:51 $\pm$ 13 min	06:27 $\pm$ 16 min
DLMOff	07:20 $\pm$ 16 min	07:36 $\pm$ 19 min
DLMOff - Wake *	27 min $\pm$ 12 min	65 min $\pm$ 21 min

\*\* p < 0.05 for young vs. older

\* p < 0.10 for young vs. older

**Table 2**



**Conclusions:** Results of this study indicate that there is an age-related advance of both the DLMO and sleep onset. The phase-angle relationship between these two variables was consistent between the older and young subjects. In contrast, the phase-angle relationship between wake and DLMOff was larger for the older compared with the young subjects. Thus, dif-

ferential age-related relationships were noted at the beginning of the night versus the end of the night. These findings suggest that aging may alter the interaction between the circadian and homeostatic processes that regulate sleep.

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**079.H**

**EVENING NAPS OF OLDER PEOPLE IN RELATION WITH EARLY MORNING AWAKENING**

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**Introduction:** Earlier bedtimes and wake-up times are well-known features of sleep in normal aging. Advance of circadian rhythms is reported to have some relation with these sleep features. We wanted to know the relationship between home sleep timing and circadian rhythms in older people as measured in an ultra-short sleep-wake cycle which minimizes interference from sleep and postural masking (1). As a possible factor influencing the earlier wake-up times in older people, we evaluated nap characteristics of older people.

**Methods:** Fifty-five older volunteers ages 60-75 years (66.2  $\pm$  5.0; 34 women, 21 men) and 67 young adults ages 18-32 years (23.7  $\pm$  3.9; 43 women, 24 men) participated in this study. Subjects had few sleep complaints, and were healthy and physically active. Each subject wore an ActiLume wrist-activity monitor and kept daily sleep logs for 7 days at home. Times of sleep onset and offset of both nocturnal sleep and napping, and number and duration of napping episodes were obtained based on the ActiLume and sleep logs. Phase angles between midpoint of nocturnal sleep and 24-hour sleep acrophase were calculated to evaluate the effect of napping on nocturnal sleep. The sleep acrophase was derived from a 24-hour cosine fit to sleep/wake data. After home recording, all subjects entered the laboratory where a 90-min sleep-wake schedule was followed for 32 hours. The 90-min sleep-wake schedule consisted of 30 min for sleep, followed by 60 min awake. During this schedule, urine samples were collected every 90 min and 6-sulphatoxymelatonin (6-SMT) was assayed to estimate the circadian rhythm of each subject. Melatonin acrophase was computed from a 24-hour cosine fit to 6-SMT data.

**Results:** There were differences between young and older groups in nocturnal sleep onset, nocturnal sleep offset, and 6-SMT acrophase (young; 00:22  $\pm$  1:14, 08:04  $\pm$  1:23, and 03:56  $\pm$  1:29, old; 22:54  $\pm$  1:19, 06:29  $\pm$  1:07, and 03:08  $\pm$  1:44, all p<0.01). In reference to the 6-SMT acrophase, sleep onset and offset were more advanced by 40 and 47 minutes, respectively, in the older group. Number of nap episodes were nearly significantly increased in the older group (young; 1.32/wk, old; 1.82/wk, p=0.068). Both onset and offset times of naps were significantly later in the older group (young: 15:08  $\pm$  3:21, 17:35  $\pm$  4:01; old: 17:02  $\pm$  3:09, 19:22  $\pm$  3:19, p<0.01, p<0.01). A nearly significant difference in nocturnal sleep offset was observed between the older people with evening naps (offset time of naps later than 18:00) and the older people without ones (06:12  $\pm$  0:58, 06:45  $\pm$  1:11, p=0.063). Twenty-four hour sleep acrophase was advanced compared to the mid-

point of nocturnal sleep by 71 minutes in the older group but it was delayed by 25 minutes in the young group.

**Conclusions:** These results indicate that older people nap more in the evening whereas young people nap more in the afternoon. Evening naps are thought to contribute to a phase advance of sleep timing (2), possibly through early awakening. The sleep-advancing effect of evening naps in the older people may underlie the finding that bedtimes and wake-up times are more advanced than the melatonin circadian rhythm in the older people. When we evaluate sleep and decide treatment options in the older people, 24-hour sleep monitoring of evening naps should be considered.

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## 080.H

### EVENING LIGHT NORMALIZES PHASE BUT MORNING LIGHT IMPROVES DAYTIME PERFORMANCE IN OLDER ADULTS

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**Introduction:** Scheduled exposure to bright light in the evening has been shown to normalize circadian phase and improve sleep and neuropsychological performance in elderly subjects with sleep maintenance insomnia [1]. In addition, exposure to light in both the morning and the evening can improve mood in older adults [2]. In the present study, we compared the effect of scheduled bright light exposure in either the morning or the evening on measures of circadian phase and performance in older adults with advanced circadian and sleep phase.

**Methods:** Seven elderly subjects (1 M, 6 F, 75.0 ± 2.9 years of age) exhibiting wake times earlier than 6:00 am, and an advance in circadian phase (core body temperature nadir earlier than 4:00 am), received daily exposure to moderate-bright light (4,000 lux) for 14 days in either the morning (9-11 am) or evening (7-9 pm), in a crossover design. Sleep logs and actigraphy were maintained throughout the study. Measures included sleep logs and actigraphic recording, 48 h of core body temperature monitoring, 2 nights PSG, and 2 days of repeated assessment (every 2 h for 12 h) of neuropsychological performance (memory, attention, and mathematical processing) and subjective mood and vigor using VAS scales. These procedures were done at baseline and following 14 days of treatment. There was a 1 month washout period between the 2 treatment phases.

**Results:** Preliminary analysis indicates that exposure to evening light delayed the circadian core body temperature

rhythm (baseline nadir: 1.15 ± 0.36 h, post-treatment nadir: 2.94 ± 0.33, p = 0.03, n = 6). The temperature rhythm was not significantly affected by morning light (baseline nadir: 1.30 ± 0.31 h, post-treatment nadir: 2.17 ± 0.57, n = 6). Both morning and evening light improved subjective measures of global vigor and global mood (p < 0.05). Morning light increased throughput (accuracy/reaction time) throughout the day on 4 of 9 of the neuropsychological performance tests (Sternberg 4, Running Memory, Symbol Copy, Digit Symbol) and improved performance the E-Search task in the afternoon (p = 0.05, Table. 1). In contrast, evening light exposure improved throughput on only 1 of the neuropsychological performance tests (E-search). Actigraphy and PSG data are currently being analyzed.

**Table 1**

Measure	Morning Light	Evening Light
Procedural Memory	0.375	0.730
Sternberg 4	0.043*	0.056
Math Processing	0.466	0.460
Running Memory	0.013*	0.295
Spatial	0.198	0.252
Symbol Copy	0.013*	0.085
Digit Symbol	0.012*	0.832
E Search	0.238 <sup>i</sup>	0.011*
M before C	0.311	0.088
Global Vigor	0.038*	0.025*
Global Mood	0.041*	0.020*

\* p < 0.05, i = significant interaction of treatment and time

**Conclusions:** Exposure to moderate-bright light in the evening normalized circadian phase, and both morning and evening light improved subjective ratings of mood in elderly subjects with advanced circadian and sleep phase. However, exposure to light in the morning resulted in greater improvements in cognitive performance than exposure to light in the evening. Together, these results suggest that in addition to its ability to alter circadian phase, bright light may have direct effects on objective measures of neuropsychological performance and subjective effects on mood.

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Research supported by PO1 AG11412, K01 AG00810

**081.H**

**PLASMA TUMOR NECROSIS FACTOR IS ASSOCIATED WITH IMPAIRED SLEEP IN OLDER ADULTS**

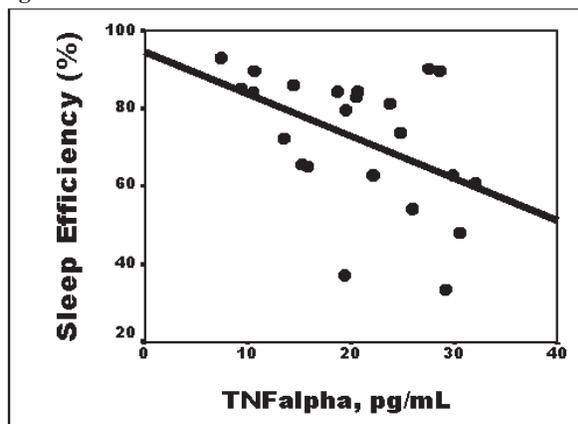
Prinz P,<sup>1,2</sup> Tsuji J,<sup>1,2</sup> Moe KE<sup>1</sup>

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**Introduction:** Sleep impairment in older adults arise from a variety of factors, medical and psychiatric disorders being particularly common factors (1); Recent studies showing that sub-clinical inflammatory processes may accompany age-diseases such as arteriosclerosis, diabetes and Alzheimers Disease (2) raise new questions about the possible role of sub-clinical inflammation in age-related sleep impairment. Plasma TNFa has been used as a marker of inflammatory status. Like other circulating cytokines, it can function as a messenger linking nervous, endocrine and immune systems; it responds to threats to homeostasis (real or perceived). TNFa has a half life of 18 min in blood, where it is partially protected from degradation by its circulating 'binding proteins' or 'receptors', such as TNF Receptor I and II (TNF-RI & TNF-RII). These receptors are also thought to convey TNFa to selected target receptor sites, such as those on immune, endothelial, glial and hepatic cells. This study examined the relationship between sleep and circulating TNFa and its soluble receptors in carefully health-screened older adults.

**Methods:** From a larger study of sleep and diurnal hormones in 'healthy' seniors, we selected 3 groups (men, women using & not using estrogen (ERT & NERT), aged 72+5) for evaluation of plasma cytokine levels. On the 3rd of 3 consecutive day/nights in the CRC sleep lab, iv blood samples were drawn at 20 min intervals. The mid-day (preceeding sleep), mid-sleep and pre-waking samples were selected for immunoassay of TNFa and TNF-RI & RII (using R&D-Quantikine & Biosource kits) in the UW SON immune laboratory. Sleep polysomnograms were scored using Rechtschaffen and Kales criteria. We report here the values for the mid-day samples. Similar results were obtained using the other time points.

**Figure 1**



**Results:** TNFa and TNF-RII levels correlated inversely with sleep quality on the following night in ERT women but not in

the other groups; TNF-RI failed to correlate in this analysis. (Table 1). Similar results were obtained when known correlates of the TNF system (age or AHI) were covaried. The inverse relationships with sleep were consistent; in no instance did TNFa or its receptors correlate positively with measures of good sleep. We next examined whether sleep on the preceding night might predict TNF the next day. A similar pattern of inverse correlations were found between sleep quality and TNF-RI and RII (but not TNFa) for the ERT but not the 2 other groups.

**Table 1**

TNFa & TNF-RII: Partial correlations with sleep (with age covaried) (r/ p).

	TNFalpha		TNF-RII	
	NERT	ERT	NERT	ERT
n	18	24	22	25
SE (%)	ns	-.48/ .02	-.51/ .02	-.58/ .005
S2,3,4*	ns	ns	ns	-.42/ .04
REM*	ns	-.34/ .05	-.34/ .05	-.64/ .005
WASO*	ns	+.58/ .05	ns	ns

\*in minutes

**Conclusions:** These data are suggest that 1) higher levels of circulating TNFa or TNF-RII are associated with poorer sleep & 2) plasma TNF-RI & II may be elevated in ERT women having poorer sleep the preceeding night. This latter finding is congruent with a recent report that plasma TNF-RI was increased following sleep deprivation (3). Although the observed inverse relationships between TNF and sleep may be secondary to disease conditions affecting both, this seems unlikely given the rigorous health screen used here. Further research is needed to evaluate the TNF system in relation to sleep in elderly women, particularly those using estrogen.

Table 1 TNFa & TNF-RII: Partial correlations with sleep (with age covaried) (r/ p).

**References:**

- (1) These data are suggest that 1) higher levels of circulating TNFa or TNF-RII are associated with poorer sleep & 2) plasma TNF-RI & II may be elevated in ERT women having poorer sleep the preceeding night. This latter finding is congruent with a recent report that plasma TNF-RI was increased following
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**Research supported by NR04001, AG12915 & MH33688 & UW CRC & Center for Womens Health Research**

**082.H****OBJECTIVE AND SUBJECTIVE SLEEP QUALITY IN A POPULATION-BASED COHORT OF PER-, PERI-, AND POSTMENOPAUSAL WOMEN**Peterson AG,<sup>1</sup> Young T,<sup>1</sup> Finn LA,<sup>1</sup> Robago D,<sup>1</sup> Austin D<sup>1</sup>

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**Introduction:** Sleep complaints in midlife women are frequently attributed to menopausal changes, but firm evidence in support of an independent role of menopause in diminished sleep quality is lacking. Few data on objectively measured sleep quality by menopausal status are available and findings based on self-reported sleep problems are inconsistent. Determining the extent to which menopause explains diminished sleep quality is of particular importance because sleep problems are often seen by both patients and clinicians as a natural concomitant and primary symptom of menopause and underlying serious sleep disorders may be overlooked.

**Methods:** The association of menopause with objectively and subjectively measured poor sleep quality was investigated in a population-based sample of 539 women, ages 30-60 years, enrolled in the Wisconsin Sleep Cohort Study. Data were obtained from an overnight sleep protocol in a dedicated sleep laboratory. Menopausal status was determined by menstrual and surgical history, use of hormone replacement therapy, and serum FSH. Sleep stage distribution, sleep latency, efficiency, total sleep time and fragmentation were determined with 18-channel polysomnography. Subjective sleep quality was derived from self-reported frequencies of difficulty initiating sleep, difficulty maintaining sleep and hypersomnolence, and usual satisfaction with sleep quality. Differences in sleep quality by menopausal status were expressed with mean values adjusted for age, body mass index, smoking, alcohol, exercise, caffeine, and apnea-hypopnea index using mixed model regression techniques. For categorical data, logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals (CI).

**Results:** Sleep quality measured by PSG was not worse in peri- or postmenopausal women compared with premenopausal women. To the contrary, postmenopausal women, compared with premenopausal women, had more favorable distribution of sleep stages, with more slow wave sleep (17% versus 13%,  $p < 0.04$ ) and significantly longer total sleep time (405 vs. 391 minutes,  $p < 0.001$ ). Objective sleep quality was not better in postmenopausal women who used hormone replacement therapy, relative to those who did not. Menopausal status was moderately related to dissatisfaction with sleep: odds ratios for chronic dissatisfaction with sleep were 2.00 (95% CI=1.1, 3.5) and 2.2 (95% CI=1.2, 4.0) for peri- and postmenopausal women relative to premenopause. However, associations of menopause and specific symptoms of insomnia and hypersomnolence were inconsistent.

**Conclusions:** Menopausal women, relative to premenopausal women, were not more likely to have diminished sleep quality indicated by PSG data. Although menopausal women were more dissatisfied with their sleep in general, menopause was not clearly associated with specific sleep disorder symptoms. Based on these findings, in midlife women, symptoms of sleep disorders should not be routinely treated as primary

menopausal symptoms, and polysomnographic indicators of poor sleep quality should not be attributed to menopause. Signs and symptoms that would normally trigger a full sleep evaluation in premenopausal women should be taken as seriously in postmenopausal women. Furthermore, menopausal women with sleep problems should not dismiss them as a normal part of menopause.

**083.H****GENDER DIFFERENCES IN SUBJECTIVE-OBJECTIVE SLEEP RELATIONSHIPS IN NON-COMPLAINING HEALTHY OLDER ADULTS**Vitiello MV,<sup>1</sup> Larsen LH,<sup>1</sup> Drolet G,<sup>1</sup> Madar EL,<sup>1</sup> Moe KE<sup>1</sup>

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**Introduction:** As many as 40% of older adults complain of significantly disturbed sleep. Recently, it has been suggested that much of this complaint is secondary to medical or psychosocial burden and is not the result of aging, per se (1).

**Methods:** In this context, we examined the baseline subjective (Pittsburgh Sleep Quality Index, PSQI) and objective (polysomnography, second of three nights) sleep of 150 healthy older (67.5±0.5) men (N=55) and women (N=95), from one NIA and two NIMH intervention studies. Subjects did not complain of significant sleep disturbance and were carefully screened to exclude sleep disorders.

**Results:** Despite their non-complaining status, significant proportions of both women (33%) and men (16%) had PSQI scores of > 5, a criterion indicative of significant sleep disturbance. When examined as a function of this criterion, objective sleep was significantly impaired with longer sleep latency (10.4±1.3 vs 22.2±3.6,  $p < .01$ ), less total sleep time (386.1±5.0 vs 367.1±10.6,  $p < .05$ ), and lower sleep efficiency (83.4±0.8 vs 78.8±1.5,  $p < .01$ ) for the PSQI > 5 group. When examined separately by gender, objective sleep was significantly impaired, with longer sleep latency (8.4±1.7 vs 31.7±8.3,  $p < .01$ ), less total sleep time (374.6±7.9 vs 329.9±22.8,  $p < .02$ ), and lower sleep efficiency (82.5±1.3 vs 72.8±3.3,  $p < .02$ ) for PSQI > 5 men, but not for women. A comparison of the 7 component PSQI scores for PSQI > 5 men vs women revealed no significant differences. Finally, when examined separately by estrogen replacement status (38 women on and 57 not on estrogen) this lack of correspondence remained for both groups of women.

**Conclusions:** As we have previously shown, even this large group of healthy, non-complaining older adults manifested significantly disturbed sleep relative to healthy younger subjects (2). This finding is consistent with Foley et al indicating that while aging, per se, results in significant changes in sleep, it does not of necessity result in complaints of insomnia (1). This also agrees with Buysse et al, who suggested that, despite their objectively disturbed sleep, healthy older individuals appear to adapt their perception of what is "acceptable" sleep and therefore do not necessarily complain (3). However, unlike our previous finding where no relationships between subjective and objective sleep were observed, here a strong correspondence was noted for men (power ~ .75) but not for women. This newest finding is provocative and suggests that

what we consider objective measures of good quality sleep may be appropriate for older men but that older women may be evaluating their sleep quality on other criteria.

**References:**

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Research supported by PHS Grants K02-MH01158, MH45186, MH53575, AG15357 and RR37.

**Oral Presentation  
Sleep-Related Movements  
Scientific Basis and Treatment Advance**

**084.N**

**NEUROTOXIC LESION OF THE VENTRAL MESOPONTINE JUNCTION INDUCES HYPERSOMNIA AND MUSCLE HYPERACTIVITY DURING SLEEP – AN ANIMAL MODEL OF PLMD AND RBD**

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**Introduction:** The ventral mesopontine junction (VMPJ) includes the caudoventral mesencephalic reticular formation (MRF), the caudal part of the ventral tegmental area (VTA) and retrorubral nucleus (RR), as well as the rostroventral paramedian tegmental field of the pons. The VMPJ contains dopaminergic, glutamatergic, and GABAergic neurons. Our previous study demonstrated that lesions of the VMPJ induce an increase in phasic muscle activity in the decerebrate cat. We hypothesized that the VMPJ plays an important role in the control of phasic muscle activity during sleep. We assess this hypothesis in the present study using neurotoxic NMDA lesion of the VMPJ in the chronic cat.

**Methods:** Two cats were anesthetized with sodium pentobarbital (35 mg/kg, i.p.) and implanted with electrodes for EEG, EOG, EMG and PGO spikes recordings. After 3-day baseline sleep recording, cats were re-anesthetized and received an injection of 0.5 µl of 0.5 M NMDA in the VMPJ. Recording was resumed on day 2 post-lesion and continued for 4-months.

**Table 1**

Phasic muscle activity (#/min) during sleep in 24 hours recording before and after VMPJ lesion

Cat		C	Post-lesion (days)				
			3	14	30	90	120
LC 11	SWS	0.04	0.24	0.34	0.45	0.59	0.56
	REM	4.21	12.6	24.1	21.9	23.0	23.8
LC 12	SWS	0.03	0.08	0.27	0.39	0.36	NA
	REM	3.87	9.72	16.5	12.9	15.6	NA

Value is the average calculated from the total number of twitches divided by total time in SWS and REM. C: Baseline control, NA: data are not available.

**Results:** The NMDA injection caused neuronal degeneration in the VMPJ. EEG, EOG, and EMG during waking were unaltered after VMPJ lesion. Muscle twitches, which rarely occurred in the intact animal, were seen during slow wave sleep after VMPJ lesion. Muscle twitches occurred regularly once every 5-100 seconds and were present for the entire period of SWS. Phasic muscle activity was also increased during REM sleep after VMPJ lesion. Tonic muscle activity during REM sleep appeared as a combination of atonia and period without atonia after VMPJ lesion. We found that total sleep and SWS time, but not REM sleep time, were increased after VMPJ lesion.

**Conclusions:** The increase in muscle activity during sleep and increase in sleep time strongly resemble aspects of periodic leg movement disorder (PLMD) and REM sleep behavior disorder (RBD) seen in human patients. Our results indicated that the VMPJ 1) plays an important role in the control of sleep and 2) is critical in the regulation of muscle activity during SWS and REM sleep. Our VMPJ lesioned animal may represent a useful animal model of the human sleep motor disorders, PLMD and RBD.

Research supported by HL 41370, HL 60296 and NSC83-0412-B-075A-033.

**085.N**

**A PATTERN OF ALTERNATING LEG MUSCLE ACTIVATION DURING SLEEP**

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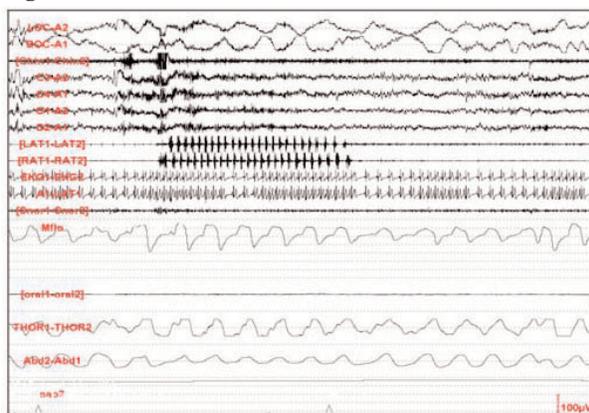
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**Introduction:** The purpose of this report is to describe a sleep-related pattern of alternating leg muscle activation (ALMA) at a rate of about 1 to 2 Hz, during sleep or arousals from sleep. **Methods:** Review of polysomnograms (PSGs) - clinically indicated diagnostic studies or CPAP titrations - that included separate left and right anterior tibialis (AT) surface EMG recordings. Records were scored with standard laboratory parameters for respiratory events and leg movements. A total of 16 index cases with the ALMA pattern came to the authors' attention between 2/00 and 8/01 (among approximately 1,500 PSGs reviewed). A sequence of ALMA was defined as ≥ 4 discrete, brief, alternating muscle activations, each separated by ≤ 2 seconds.

**Results:** Mean age was 41 (± 15 s.d) and 12 (75%) of the patients were male. Twelve patients were referred for sleep apnea, and the others for narcolepsy, periodic leg movements (PLMs), sleepwalking or movements during sleep. Twelve patients were taking antidepressant medication at the time of the index PSG. All except 3 had more than 5 apneas or hypopneas per hour of sleep; ten had 5 or more PLMs per hour of sleep in their index studies; and only 2 patients had no scored PLMs. The number of ALMA sequences during sleep in each recording ranged from 1 to 40 (mean 13 ± 12 s.d.). Each sequence of ALMA during sleep lasted for 1.4 to 22.2 seconds, and each was composed of alternating AT activations of about 0.1 to 0.5 seconds in length. These sequences sometimes

began with one to several lengthy activations (1 to 2 sec) in one or both legs. The rate of leg activation was usually between 1 and 2 Hz, but ranged from 0.5 to 3.0 Hz. Some patients showed similar activity in one leg, at times, rather than two. In 12 patients ALMA closely preceded or followed an arousal or awakening, and gradually petered out as the patient returned to sleep. In 4 subjects ALMA was seen without association with arousals. ALMA was noted to arise from all sleep stages. A subset of 9 patients had a second PSG (3 had subsequent CPAP titrations, 6 had had previous diagnostic baselines) and review of those studies showed ALMA in 8. The mean number of ALMA sequences was no different between baseline and titration studies, and among patients with repeat studies the tendency for ALMA to precede ( $n = 1$ ) or follow ( $n = 5$ ) arousals was replicated in each case.

Figure 1



**Conclusions:** This report describes a previously unreported pattern of ALMA during sleep or arousals from sleep. Antidepressant medication, and perhaps associated increases in serotonergic transmission, may promote ALMA. The rate of ALMA approximates that of leg movements during locomotion, and we speculate that ALMA could represent transient facilitation of a spinal central pattern generator for locomotion.<sup>1</sup>

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**086.N**

**HEART RATE VARIABILITY IN RELATION TO PERIODIC LIMB MOVEMENT (PLM) DISORDER AND CYCLIC ALTERNATING PATTERN (CAP).**

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**Introduction:** Periodic limb movement (PLM) disorder is a very common intrinsic sleep disorder. The rhythm of PLM follows the periodic oscillations that simultaneously involves the

EEG, the heart rate (HR), the blood pressure and the breathing activity. The periodicity of the PLM recalls the physiological EEG arousal rhythm during NREM sleep, described as the cyclic alternating pattern (CAP) (1). Interestingly, in healthy subjects it has been recently found that the sympathovagal balance is unbalanced, during CAP, towards a sympathetic activation (2). The aims of this study were to evaluate: a) the autonomic changes during the CAP condition in the presence or absence of PLM, and b) the coupling among PLM, HR variability, respiratory and EEG signals.

**Methods:** Eight patients (3 men and 5 women; mean age= 50 years; range 46 to 62 years), diagnosed with PLM disorder according to ICSD criteria and without OSA, were included in the study. Polysomnographic recordings showed a mean PLM index of 38.3 (range 28 to 59). All the periods of sleep stage 2 non-REM without artifacts (with and without PLM) were selected for the analysis. CAP was scored according to Terzano et al. criteria (1). The EEG, respiration, ECG and EMG-leg signals were considered for the analysis. The HR variability signal (t) was obtained from the ECG as the sequence of the RR time intervals as function of the beat number (interval tachogram). The respirogram synchronous with the tachogram was obtained from the nasal airflow by subsampling the signal in correspondence of each R wave (r). The EEG signal was rectified by calculating the modulus and its mean value was evaluated in time windows corresponding to RR time intervals. The above procedure allowed to obtain an EEG variability signal (e) on a beat-to-beat basis. The EMG variability signal (m) was derived from the EMG with the same procedure. The coupling relationships between pairs of variability signals was quantified by means of an autoregressive (AR) spectral analysis in the bivariate form.

**Results:** By means of a time domain analysis we observed a synchronization of respiration and tachycardia preceding PLM (autonomic sympathetic pre-activation) in correspondence of the EEG activation. A significantly increase of synchronization between t and r ( $p < 0.001$ ) was found in the passage from stage 2 non-REM CAP (2 CAP) without PLM to 2 CAP with PLM, on the basis of the percentage value of the coherent power between the signals (CPtr%). This indicates an increased coupling between the signals and could be interpreted as an increased vagal activation: however, this result is unexpected on the basis of the literature data. During 2 CAP with PLM, m, e, t and r signals were characterized by high synchronization with a significant ( $p < 0.05$ ) increasing trend of percentage coherent power in the passage from 2 NCAP to 2 CAP, to 2 CAP with PLM.

**Conclusions:** The relationship between PLM and cardiac autonomic activity may not be correctly interpreted on the basis of the traditional parameters used for quantifying the sympatho-vagal balance, both in time and in frequency domains. Our results in patients with PLM show the possibility of a "common central oscillator" triggering the different systems evaluated. Our data suggest that all the cyclic variations with a wave length of about 30-40 seconds may be part of a common endogenous rhythm: PLM seems to be an epiphenomenon of this central mechanism, without a direct responsibility on autonomic activation.

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in the dynamic organisation of sleep. EEG Clin Neurophysiol 1988; 69: 437-447.

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### 087.N

#### MRI MEASURES OF BRAIN IRON AND ITS RELATION TO RLS SYMPTOMS FOLLOWING IV IRON TREATMENT.

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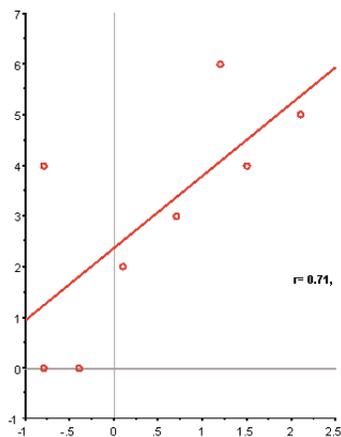
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**Introduction:** About 50 years ago Nordlander reported that treatment with incremental, intravenous (IV) doses of iron can produce long lasting symptomatic relief in RLS patients who were not iron deficient {Nordlander, 1953 #613}. We have found similar results using a single IV infusion of 1000 mg of iron {Earley, 2001 #1903}. In a separate study we have also reported that the iron content in the substantia nigra (SN), as determined by MRI, correlated with the severity of RLS symptoms {Allen, 2001 #1627}. In this study we examine the effects of IV iron treatment on both clinical symptoms and brain iron content in the SN as determined by MRI.

**Methods:** All consenting subjects were screened for the diagnosis of idiopathic RLS and safety for IV iron. Brain MRI measures of iron were obtained baseline and 2 weeks after IV iron treatment following our previously described procedures {Allen, 2001 #1627}. A 1000mg dose of iron in the form of iron dextran was infused over approximately 6 hours. The clinical symptoms were evaluated based on the patient's subjective report of RLS symptoms. All patients were off RLS medications for at least 5 days prior to the study. The time from initial treatment to the time (1) that subject reported symptoms occurring for more than one hour in any day and (2) that subjects requested restarting their RLS medications, were used as our outcome measures. The clinical reports and MRI evaluations were made independently following blinded procedures.

**Table 1**

Months with no RLS Sx after IV iron treatment vs change in R2' MRI measure of iron in the substantia nigra with IV iron treatment (post - pre treatment)



**Results:** Eight patients (ages 51-74; 3 females) were studied. Two failed to show any significant benefit from IV iron and returned to taking their RLS medication 2 weeks after treatment. The remaining 6 showed complete remission from all RLS symptoms which lasted from 2 to 6 months (average: 4 months). They had sufficient reduction in RLS symptoms that a return to RLS medications did not occur for 2 to 20 months (average = 8.5). The MRI showed increases in R2' for the SN in 5 of the 6 patients responding to iron treatment and not in either of the patients who failed to respond. The degree of change (difference between baseline and 2-week, post-treatment measurements) in the R2' correlated significantly ( $r=0.71$ ,  $p<0.05$ ) with the number of months the patient was free of symptoms (see figure) and also the time before restarting RLS medications, measured in ( months +1) ( $r=0.50$ ,  $p=0.10$ ).

**Conclusions:** These data are consistent with our hypothesis that idiopathic RLS follows as a consequence of an iron-deficient state in the brain. The findings also suggest high-dose, IV iron treatment provides relief from RLS symptoms to the degree that it increases the brain iron concentration in the SN. However not all RLS subjects respond to this treatment. Further work is necessary to better define which subpopulation of RLS subjects are likely to respond to IV iron therapy.

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### 088.N

#### A GENETIC LOCUS FOR RLS MAPS TO CHROMOSOME 12Q

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**Introduction:** Restless legs syndrome (RLS) is a relatively common sensori-motor disorder characterized by an imperative urge to move the limb associated with paresthesia. There is a significant worsening of the symptomatology in the evening or during the night, which often interferes with nocturnal sleep, resulting in daytime somnolence and chronic sleep deprivation. Numerous studies have suggested a substantial genetic contribution in the etiology of RLS. Familial aggregation has been repeatedly reported with more than 40% of the idiopathic cases showing a positive family history. A recent twin study observed a high concordance rates of RLS in monozygotic twins(1), suggesting that a significant portion of the familial aggregation may be due to genetic factors. Thus far, few molecular genetic studies have been undertaken

attempting to identify genes that may predispose to this condition and no significant finding has been reported. In order to map and identify the genes that predispose to RLS, we performed a linkage analysis of microsatellite markers spanning the entire genome on a well-characterized French-Canadian family.

**Methods:** A genomewide scan was carried out on a large French Canadian family from which 25 individuals were sampled. All subjects were personally interviewed at two different times during a 10-years follow-up interval. The screening set consisted of a panel of 378 polymorphic fluorescently labeled markers (Whitehead Institute), covering the entire genome with an average intermarker distance of 10cM. Genotyping was conducted using a modified MultiProbe-I (Packard) and two ABI 377 DNA sequencers. Two-point LOD score was calculated using the MLINK routine of the FASTLINK software package whereas location-score analysis and haplotyping were computed by the SIMWLAK2 program. Since the mode of inheritance of RLS is unknown, pairwise LOD scores were maximized over three major models.

**Results:** Parametric analysis revealed maximum two-point LOD score ( $Z_{max}$ ) >1.0 at 12 loci on 3 different chromosomes (i.e. chromosomes 5q, 10q and 12q). All significant and suggestive results were observed under the autosomal recessive mode of inheritance with a high disease-predisposing allele frequency. The strongest evidence of linkage was detected with 8 adjacent microsatellite markers genotyped between D12S398 and D12S78 on chromosome 12q13-23, with a maximum LOD score for D12S1044 ( $Z_{max} = 3.42$  at  $\theta = 0.05$ ;  $P = 6 \times 10^{-4}$ ). Multipoint analysis provided additional support for the localization of RLS-predisposing loci to chromosome 12q, yielding a maximum multipoint LOD score of 3.59 at 13.93cM centromeric from marker D12S1300. Haplotype analysis within the critical region placed the disease-causing gene telomeric to D12S1044 and centromeric to D12S78, defining a 14.71cM interval within chromosome 12q.

**Conclusions:** These findings represent the first mapping of a locus conferring susceptibility to RLS. We are currently carrying out follow-up studies toward identification of the RLS gene through recruitment and investigation of additional families in order to validate this result and to further refine the candidate region.

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## 089.N

### EFFECTS OF IMMOBILITY ON SENSORY AND MOTOR SYMPTOMS OF RESTLESS LEGS SYNDROME

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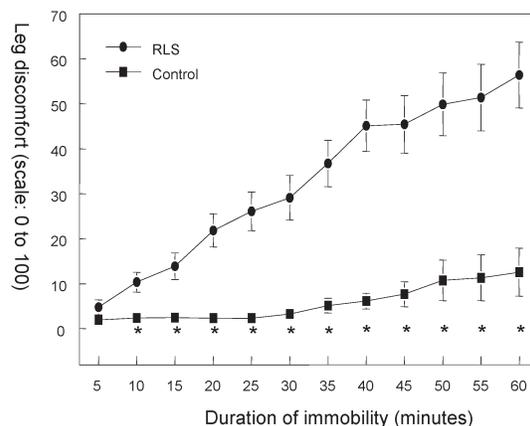
**Introduction:** Restless legs syndrome (RLS) is characterized by a desire to move the legs usually associated with paresthesias or dysesthesias. Two additional features are essential for its diagnosis, namely 1) worsening of symptoms at rest with temporary relief by activity and 2) worsening of symptoms during the evening and/or during the night. A test named the "Suggested Immobilization Test" (SIT) has been developed to evaluate the presence of these features. This test allows leg movements and leg discomfort to be quantified during a one-hour period of immobility prior to bedtime. The aim of the present study was to use the SIT to evaluate the effects of immobility on leg discomfort and leg movements experienced by patients with RLS and healthy control subjects.

**Methods:** Nineteen patients with idiopathic RLS (12 men, 7 women; mean age, SD:  $51.5 \pm 11.8$  years) and nineteen age-matched control subjects (10 men, 9 women; mean age, SD:  $48.3 \pm 8.4$ ) participated in this study. The SIT was administered prior to the nocturnal polysomnographic recording and started at 21h15 ( $\pm 15$  minutes) for all subjects. Surface EMG from right and left anterior tibialis muscles were used to quantify periodic leg movements (PLM) according to criteria described elsewhere(1). Leg discomfort was measured during the SIT by a visual analogue scale connected to an electronic device. This apparatus gave an auditory signal every five minutes, at which time the patient was required to estimate his leg discomfort on a 100-millimeter horizontal bar.

Figure 1

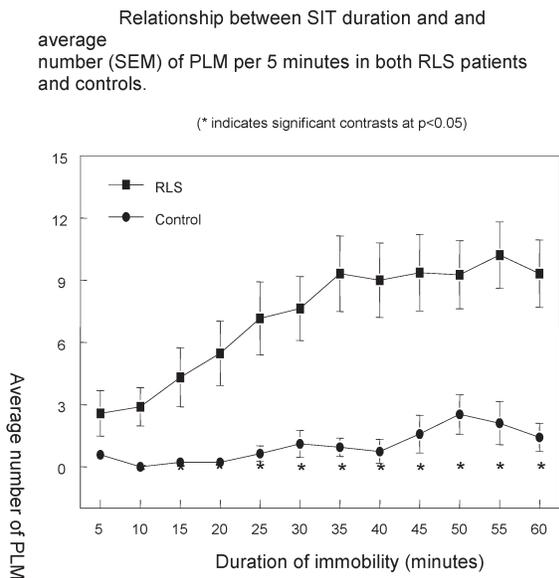
Relationship between SIT duration and mean (SEM) leg discomfort scores in both RLS patients and healthy

(\* indicates significant contrasts at  $p < 0.05$ )



**Results:** Figures 1 and 2 show that immobility significantly worsened both leg discomfort and PLM in patients with RLS but not in controls. Patients with RLS showed a higher leg discomfort score ( $32.6 \pm 15.1$  mm vs.  $5.7 \pm 7.9$  mm;  $p < 0.00001$ ), a greater maximum leg discomfort value ( $63.4 \pm 27.4$  mm vs.  $13.7 \pm 23.0$  mm;  $p < 0.00001$ ) and a greater PLM index ( $88.4 \pm 62.6$  vs.  $10.4 \pm 20.6$ ;  $p < 0.00004$ ) than control subjects.

**Figure 2**



**Conclusions:** These results further validate the use of the SIT as a diagnostic and research tool for RLS and confirm the contention of the International RLS Study Group that RLS symptoms worsen at rest(2).

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Research supported by the Canadian Institutes of Health Research

**090.N**

**TREATMENT OF RESTLESS LEGS SYNDROME WITH GABAPENTIN: A DOUBLE BLIND, CROSS-OVER STUDY WITH POLYSOMNOGRAPHIC CONTROL ON 24 PATIENTS**

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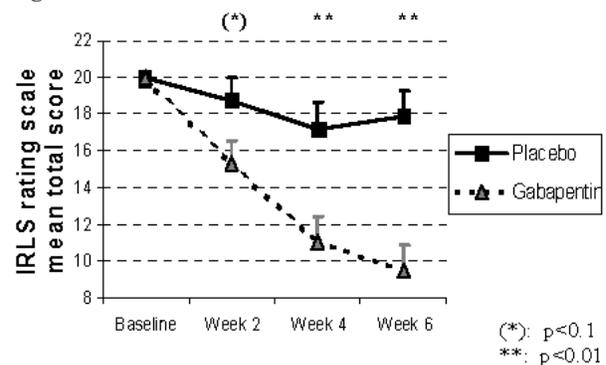
**Introduction:** Gabapentin (GBP) is a structural analogue of

GABA that has been used successfully in several neurological conditions such as epilepsy, essential tremor, trigeminal and postherpetic neuralgia, or diabetic neuropathy (1). So far, several open studies have suggested a therapeutic efficacy of GBP in patients with Idiopathic Restless Legs Syndrome (RLS)(2). Objectives: The objective of this study was to assess under double blind conditions: a. the therapeutic efficacy and tolerability of GBP in RLSb. whether GBP improves both sensorial and motor symptoms in RLSc. the effective dose range of GBP in RLS

**Methods:** 24 consecutive patients diagnosed with Restless Legs Syndrome according to the criteria of the International Rating Scale RLS Study Group(3) were included in the study. Following a two-week washout period and a randomization for the order of treatment, patients underwent a six-week treatment period with either GBP or placebo (PLB). At the end of each treatment condition, a one-week washout period took place before patients were crossed over to the alternative treatment for an additional 6-week period. The starting dose of GBP was 600 mg/d. Every week, the treating physician had the opportunity to increase, decrease or maintain the dosage by a further 600 mg, up to a maximum dose of 2400 mg/d. A PSG was performed on all patients at the end of each treatment period. In addition, patients were rated at baseline and every two weeks by means of IRLSSG-rating scale, Clinical Global Impression (CGI) and Pittsburgh Sleep Questionnaire (PSQI).

**Results:** a) The mean values for the IRLSSG-rating scale are shown in the attached Figure. Furthermore, treatment with GBP caused a reduction in the mean values of PSQI, and a higher change on the CGI (all  $p < 0.01$ ). b) GBP caused a reduction in Periodic Leg Movements of Sleep-Index (PLMS-I) ( $p = 0.05$ ). c) An increase in Total Sleep Time ( $p = 0.01$ ), Sleep Efficiency ( $p < 0.001$ ), and Stage 3 sleep ( $p = 0.05$ ) along with a reduction in Stage 1 sleep ( $p < 0.05$ ) were observed during treatment with GBP. No changes were seen in sleep latency, REM Sleep parameters, arousal index or apnea-hypopnea index. d) The mean effective dose of GBP was 1855 mg/d.

**Figure 1**



**Conclusions:** a) GBP is an effective treatment for RLS. b) The therapeutic efficacy of GBP was not limited to sensorial symptoms, as an improvement of PLMS-index could also be observed. c) A normalization of sleep could be observed following treatment with GBP. However, these changes were caused by improvement of PLMS-index rather than by direct sleep induction. d) The effective dosage of GBP was higher

than shown in previous reports. It is therefore possible, that treatment of PLMs require a higher treatment dosage of GBP than sensorial symptoms do.

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Research supported by Pfizer-Spain.

**091.N**

**EFFECTS OF MODAFINIL ON PLMD-ASSOCIATED DAYTIME SLEEPINESS**

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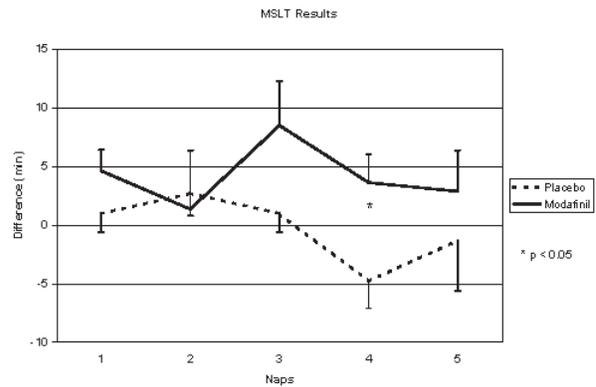
**Introduction:** The aim of this study was to assess the efficacy of modafinil (Provigil) in treating the excessive daytime sleepiness (EDS) associated with Periodic Limb Movement Disorder (PLMD). Modafinil is a wakefulness-promoting medication that has been successfully used to treat the EDS associated with other sleep disorders. We conducted a randomized, double blinded, placebo-controlled trial to explore the effects of treatment with modafinil on objective and subjective measures of PLMD-associated daytime sleepiness.

**Methods:** Ten subjects were recruited from our sleep disorders clinic to participate in the study; informed consent was obtained as per our institutional review board. Subjects were enrolled as participants in the study if they were 18-65 years of age; reported that they suffered from EDS; and were diagnosed with PLMD by clinical evaluation and polysomnography, not treated for their condition, free of serious medical or other sleep disorders, and not taking stimulant, soporific or sedating medications. The subjects had 2 consecutive baseline polysomnograms (PSGs), and a Multiple Sleep Latency Test (MSLT) following the second PSG to objectively measure their level of daytime sleepiness. Subjects then self-administered either modafinil or a placebo (depending on their random group assignment) in the morning for 21 consecutive days. If they were randomized to the modafinil group, they took 100 mg for the first 3 days, and then 200 mg for the remaining 18 days. They returned to the laboratory for an additional 2 consecutive PSGs on the 19th and 20th nights and an MSLT on day 21 following the second PSG. The subjects completed Epworth Sleepiness Scales (ESS) during all baseline and experimental days, and completed Stanford Sleepiness Scales (SSS) prior to each nap of the MSLT. The MSLT, ESS, and SSS comprised the primary outcome measures for this study.

**Results:** There were five subjects (3 men, 2 women, 41.0 ± 9.14 years) randomized to the modafinil group and five sub-

jects (3 men, 2 women, 36.2 ± 3.70 years) randomized to the placebo group. One subject in the modafinil group was dropped due to noncompliance to the medication regimen. The major preliminary results of the study are depicted in the table. All three primary outcome measures revealed trends toward reduction of daytime sleepiness for the modafinil compared to the placebo group, with the ESS revealing the largest effect size. For the MSLT, the figure depicts the difference in sleep latency (experimental-baseline) for the modafinil vs. placebo groups across each nap of the MSLT. The trend for the reduction in daytime sleepiness for the modafinil group compared to both the baseline levels and to that of the placebo group was greatest after nap 3, corresponding to the afternoon-early evening time of day.

**Figure 1**



**Table 1**

Measure	Baseline	Diff from Baseline		Effect Size
		Modafinil	Placebo	
MSLT (min)	9.8 (3.95)	4.2 (2.41)	-0.3 (2.86)	1.56
ESS (score)	11.0 (5.51)	-5.4 (6.34)	-0.3 (1.10)	4.63
SSS (score)	3.0 (0.93)	-0.4 (1.18)	0.3 (1.11)	0.57

Effect Size = modafinil - placebo difference scores from baseline divided by the standard deviation of the placebo post-treatment values

**Conclusions:** Modafinil has been used to treat EDS associated with disorders such as narcolepsy, sleep apnea, and myotonic dystrophy, as well as a countermeasure for the effects of sleep deprivation. The preliminary results from the first systematic study to test modafinil on patients with PLMD revealed that this medication has potential as treatment for the EDS associated with this condition.

Research supported by Cephalon, Inc.

**Oral Presentation  
Treatment of Insomnia**

**092.L**

**THREE-MONTH NON-NIGHTLY USE OF ZOLPIDEM FOR THE TREATMENT OF PRIMARY INSOMNIA**

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**Introduction:** For patients with chronic insomnia, less than nightly usage of hypnotic medication is often recommended,(1) presumably because of concerns about potential tolerance and/or abuse. Yet, only one placebo-controlled, double-blind study of non-nightly use of hypnotic medication for the treatment of chronic insomnia has been carried out.(2) This study compared zolpidem 10 mg (Z10) and placebo dosed 3-5 nights/week, on nights selected by the patients, for a period of eight weeks. They found this Z10 regimen to be efficacious and safe without rebound insomnia, or evidence of tolerance. The present investigation extends these results to a three month period of study, in a new, larger group of patients with chronic primary insomnia.

**Methods:** DSM-IV primary insomniacs were randomly assigned to Z10 (N=95) or Placebo (N=97) in a double-blind, parallel group design. After one week of baseline (with no pill), patients were randomized to either Z10 or Placebo for 12 weeks. They were instructed to take their medication "as needed" with the restriction that they must take it 3 to 5 nights per week. Subjective sleep data were collected for 14 consecutive weeks using daily morning questionnaires. Patient global impression (PGI) and investigator global impression (CGI) measures were completed after every two weeks of randomized treatment. Continuous and categorical variables were analyzed with ANOVA and the Cochran-Mantel-Haenzel Test, respectively.

**Table 1**

Patients' Ratings of the Effects of Treatment on Their Sleep Problem and Associated Daytime Distress After 12 Weeks of Treatment

	Patient Sleep Problems		Patient Daytime Distress	
	Placebo	Zolpidem	Placebo	Zolpidem
Did not improve	57%	12%	60%	18%
Slightly improved	25%	26%	21%	31%
Moderately improved	14%	39%	16%	35%
Greatly improved	4%	23%	4%	16%

Both Sleep Problems and Daytime Distress ratings differed between Placebo and Zolpidem (p<0.001)

**Results:** Z10 was superior to Placebo on all primary measures of treatment efficacy. Significantly greater efficacy was evident on all 7 items of the PGI at all outcome time-points

(p<0.001). As an example of the effects observed, a summary of the PGI ratings of whether "intermittent use of the study medication improved my sleep problem" and "intermittent use of the study medication improved my daytime distress from not sleeping" at the end of the 12-week treatment period appear in Table 1. Similarly, greater efficacy with Z10 was evident in both CGI severity and therapeutic effect ratings at all time-points (p<0.001). A therapeutic advantage for Z10 was also evident in the morning questionnaire data. Averages over all nights of each 2-week treatment period indicated significantly greater efficacy for Z10 at all time-points for: sleep onset latency, ease of falling asleep, total sleep time, sleep quality, morning sleepiness, ability to concentrate in the morning, and feeling refreshed in the morning. Total sleep time data appear in Table 2. In addition, there was no evidence for rebound insomnia on nights when patients elected not to take Z10 nor was there evidence for the development of tolerance to the therapeutic effects of Z10.

**Table 2**

Mean Morning Questionnaire Total Sleep Time Ratings

	Base-line	Wks 1-2	Wks 3-4	Wks 5-6	Wks 7-8	Wks 9-10	Wks 11-12
Pbo	325.9	345.5	353.3	353.5	357.7	351.3	359.3
Z10	316.5	369.5	378.1	392.5	390.6	392.0	394.7

-Differences between Placebo and Z10 were significant at all time-points except baseline (p<0.0001)

-Pbo = Placebo; Z10= Zolpidem 10 mg; Wks=Weeks

**Conclusions:** The treatment of chronic primary insomnia with non-nightly dosing of zolpidem appears to be effective over a 3 month period without leading to tolerance or rebound insomnia.

**References:**

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**Research supported by Lorex Pharmaceutical Corporation**

**093.L**

**ESOPICLONE, A NOVEL NON-BENZODIAZEPINE SEDATIVE-HYPNOTIC: EFFICACY AND SAFETY IN A MODEL OF TRANSIENT INSOMNIA**

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**Introduction:** Esopiclone (ESO) is a novel, isomerically pure, non-benzodiazepine, cyclopyrrolone agent that rapidly induces sleep and improves total sleep time with an absence of residual morning effects.

**Methods:** This randomized, double-blind, placebo (PBO)-controlled study of 436 healthy subjects evaluated the efficacy

and safety of ESO (1.0, 2.0, 3.0, 3.5 mg) in a model of transient insomnia (First Night Effect Model). Subjects analyzed here received either a single nighttime dose of PBO or ESO 2.0 mg or 3.0 mg (N=293). Efficacy was evaluated objectively via polysomnography and subjectively via a morning questionnaire.

**Results:** Relative to PBO, ESO produced significant improvements in all objective and subjective efficacy endpoints (table). Both doses of ESO significantly shortened the latency to persistent sleep and improved the duration and quality of sleep. ESO also provided next day benefit by reducing subjective morning sleepiness (3.0 mg,  $p<0.05$ ). No clinically significant difference in Digit Symbol Substitution Test (DSST) results was observed between PBO (64.6) and ESO 2.0 mg (63.0;  $p=NS$ ) or 3.0 mg (60.8;  $p<0.05$ ) at post-dose measurements taken the following morning. The most common adverse event in the placebo and esopiclone groups was unpleasant taste (7.1%-21.6%), probably attributable to the liquid formulation and mostly noted during ingestion.

**Table 1**

Endpoint	PBO n=98	ESO 2.0 mg n=97	ESO 3.0 mg n=98
<b>Objective Measures</b>			
Latency to Persistent Sleep (min)	17.9	10.1*	9.1*
Sleep Efficiency (%)	87.9	91.7*	93.0*
# of Awakenings	6.0	5.4	4.8*
<b>Subjective Measures</b>			
Total Sleep Time (min)	439.1	458.6*	462.2*
# of Awakenings	2.5	2.0*	1.6*
Quality of Sleep (% "excellent")	5.1*	19.6*	21.4*
Morning Sleepiness <sup>a</sup> (mm)	65.6	70.1	72.5*
* $p<0.05$ vs. placebo. All values represent group means. a: measured by a visual analogue scale where 0 mm = "very sleepy" and 100 mm = "not at all sleepy".			

**Conclusions:** In a model of transient insomnia, ESO demonstrated improvements in the onset and quality of sleep, a reduction in awakenings, an increase in total sleep time, and a reduction in morning sleepiness.

Research supported by Sepracor Inc., Marlborough, MA

**094.L**

**SEQUENTIAL USE OF MEDICATION AND BEHAVIORAL THERAPIES FOR CHRONIC INSOMNIA**

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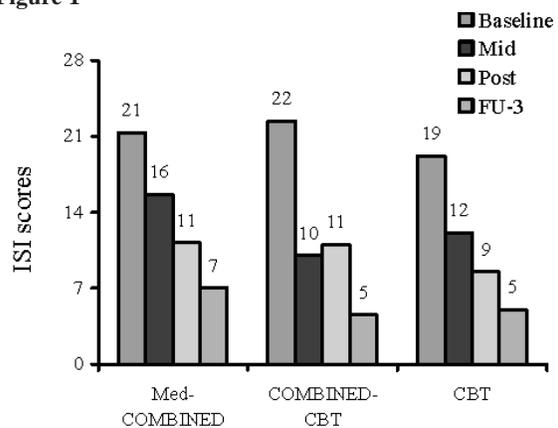
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**Introduction:** Studies of the efficacy of combined behavioural and pharmacological therapies have yielded mixed results as to whether they produce superior outcome to cognitive-behavioural treatment (CBT) alone. The few studies examining this issue have always implemented treatments in a con-

current fashion. A pilot study(1) explored if a sequential implementation would yield superior outcome to concurrent one. Results showed that even if sleep efficiency increased from baseline to posttreatment for all participants, total sleep time increased only for participants who received both treatments in the initial weeks. The present study extends these findings.

**Methods:** The sample included 17 participants (10 women, mean age of 41.6 years, SD = 5.65) meeting diagnostic criteria for chronic primary insomnia. Participants completed the Insomnia Severity Index (ISI) at each assessment period, and daily sleep diaries from baseline to posttreatment as well as during two weeks at the 3-month follow-up. A multiple baseline across subjects design was used. Participants were randomly assigned to one of three baseline durations (3, 5, or 7 weeks), then to one of the following treatment sequences (10 weeks duration): (a) medication (zopiclone) used alone for the first five weeks, followed by combined CBT + medication for five more weeks (Medication - Combined; medication withdrawal after the ninth week); (b) combined treatment for the first five weeks, followed by CBT alone for an additional five weeks (Combined - CBT; medication withdrawal after the sixth week); or (c) CBT alone. Sleep efficiency, Sleep Onset Latency (SOL), Total Wake Time (TWT) and Total Sleep Time (TST) were derived from the sleep diary and were examined with auto-regression analysis. One participant dropped out in the second week.

**Figure 1**



ISI scores at each assessment phase.

**Results:** Each sequence led to significant improvement, but these changes were observed at different points in time. For the Medication - Combined sequence, SOL decreased during the first phase of treatment and TST remained stable. Most improvements in TWT was obtained after the introduction of CBT, but TST also decreased during this period. For the Combined - CBT sequence, most variables improved rapidly during the first phase while TST remained stable up to posttreatment. All participants in CBT alone improved significantly on all sleep variables during the first phase of treatment except for three who experienced a decrease in TST. In the second phase, all variables remained stable. At 3-month follow-up, sleep continuity measures remained improved for 9 partici-

pants and the initial decreases in TST observed during treatment were significantly improved. The ISI shows a tendency for participants receiving CBT alone or combined in the first phase of treatment, to improve more than those receiving medication alone. ISI scores were equivalent at posttreatment and follow-up (figure 1).

**Conclusions:** These results suggest that a sequential treatment is effective. They also suggest that a sequence beginning with combined CBT + medication may be optimal in improving sleep efficiency while minimizing decrease in TST.

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Research supported by FRSQ-FCAR-santé

**095.L**  
**PSYCHOLOGICAL TREATMENT OF HYPNOTIC DEPENDENT INSOMNIA**

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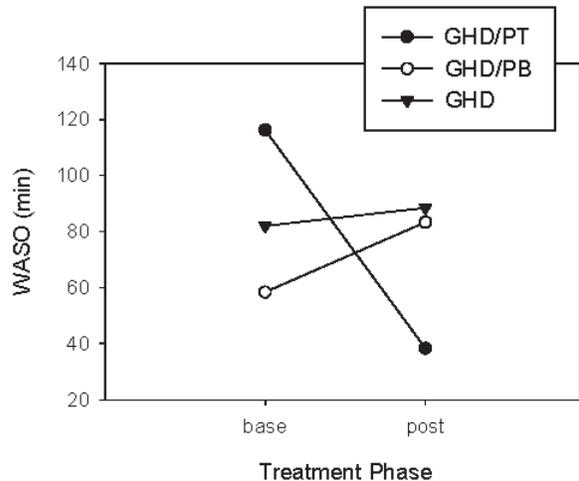
**Introduction:** Chronic use of prescription hypnotics often leads to a new disorder, hypnotic-dependent insomnia, characterized by return of insomnia and sustained hypnotic use. Older adults are disproportionately high users of hypnotics and are particularly vulnerable to hypnotic side-effects including adverse polypharmacy interactions and impaired daytime functioning. The present clinical trial employed psychological interventions and placebo controls to manage and evaluate hypnotic dependence in older adults.

**Methods:** Volunteers were recruited by media announcements. To qualify, volunteers had to meet the following criteria: age 50 or older, current insomnia, dependence on prescription hypnotics for at least 6 months, and free of sleep-active medical or psychiatric disorders or substances (other than the designated hypnotic). We now report on 23 subjects. By meeting time, we will have data on at least twice as many subjects and will present a wider range of self-report and PSG variables than are included herein. The present sample is composed of 16 women and 7 men. They ranged in age from 54 to 86 years (M = 65.9, SD = 7.6), they have been taking hypnotics between 0.5 and 20 years (M = 4.2, SD = 4.3), and they have experienced insomnia between 0.5 and 30 years (M = 7.9, SD = 8.7). About half the subjects were using benzodiazepines and about half other prescription hypnotics. Subjects were randomized to scheduled gradual hypnotic withdrawal (GHD) supplemented by eight sessions of psychological treatment (PT, relaxation, stimulus control, & sleep hygiene)[this group is designated GHD/PT], hypnotic withdrawal supplemented by placebo EEG biofeedback (GHD/PB), or hypnotic withdrawal only (GHD).

**Results:** Among a wide range of dependent measures, we now report only baseline to post withdrawal wake time after sleep

onset (WASO) documented by 2-weeks of sleep diaries and self-reported hypnotic consumption (mean number of daily units of a medication's lowest recommended dose, LRD). Subjects in the GHD/PT group improved in WASO while the other two groups worsened by a small or large margin, interaction F (2, 20) = 3.80, p < .05 (see Figure). Given our small n, a significant interaction is remarkable. For medication consumption, significant findings occurred only for the main effect of time, F (1, 19) = 52.03, p < .01. For the three groups considered jointly, medication use went from 1.6 LRD at baseline to 0.2 LRD post withdrawal, an 86% reduction.

Figure 1



**Conclusions:** Older adults who are chronic users of prescription hypnotic medication are highly receptive to gradual medication withdrawal and attained substantial medication reduction. However, sleep is likely to stay the same or worsen post withdrawal, unless withdrawal is supplemented by psychological treatment for insomnia. In this latter case, sleep can be expected to improve substantially even after dramatic hypnotic reduction.

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**096.L**  
**AN ABBREVIATED COGNITIVE-BEHAVIORAL INSOMNIA THERAPY DESIGNED FOR PRIMARY CARE SETTINGS**

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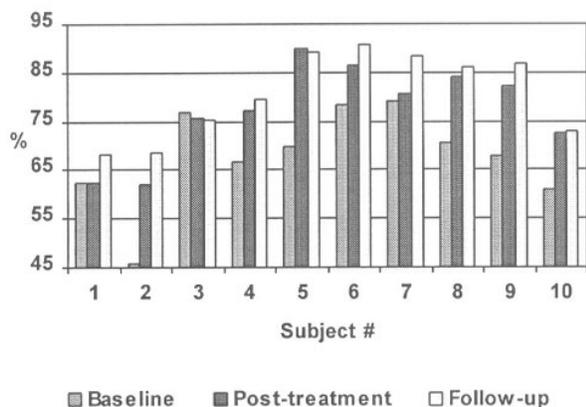
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**Introduction:** Cognitive-behavioral insomnia therapy (CBT) has proven to be a highly effective intervention for chronic insomnia sufferers. Unfortunately most treatment-seeking insomnia patients are encountered in primary care settings where busy practitioners are unable to implement the time-consuming 6 to 8 session CBT protocols previously described in the literature.<sup>1,2</sup> Clearly briefer, primary care-friendly models of CBT are needed if this intervention is to become more commonplace in frontline insomnia treatment. The current

study was conducted to test an abridged CBT (ACBT) insomnia intervention designed specially to fit the needs of the primary care practitioner.

**Methods:** Based on structured interviews, consenting patients were selected for inclusion in this single-blind, randomized, parallel-group trial if they: (1) were enrolled as patients at the V A Medical Center wherein this study was conducted; (2) met DSM-IV criteria for primary insomnia; and (3) were not taking or were willing to withdraw from hypnotic medications at the time of their study enrollment. Of the 32 physician- and 7 self-referred patients considered, 20 (18 men) met entry criteria and were randomized to treatments. Ten male patients ( $M_{sAgeS} = 53.5$  yrs.) were assigned to a brief ACBT intervention whereas the remaining 10 (8 men) patients ( $M_{sAgeS} = 48.4$  yrs.) were assigned to a similarly brief sleep hygiene control (SHC) intervention. Each participant met with the study therapist (WS) for two, 25-minute individual treatment sessions scheduled two weeks apart. Those assigned to ACBT received face-to-face instruction designed to correct dysfunctional sleep-related beliefs and to introduce them to the basic tenants of stimulus control and sleep restriction strategies. Those assigned to SHC were provided a brief description of sleep architecture and were instructed to limit caffeine and alcohol intake, engage in moderate exercise, try a light snack before bed, and keep their bedrooms dark and at comfortable temperatures. In addition, all participants were given printed and tape-recorded information reiterating their respective treatment instructions for their home use. Treatment effects were ascertained from sleep logs and questionnaires completed both prior to and immediately after treatment as well as at a 3-month, post-treatment follow-up.

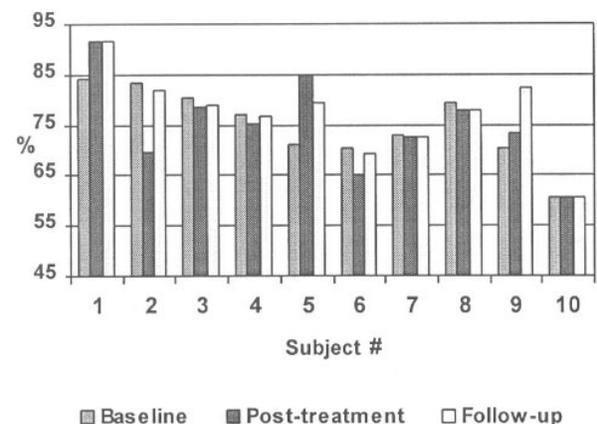
**Figure 1**  
Changes in Sleep Efficiency for ACBT Patients



**Results:** A series of 2 (ACBT vs. SHC) x 2 (post-treatment vs. follow-up) analyses of covariance were conducted in order to compare the two interventions. All analyses used baseline values of respective dependent measures as covariates and employed a conservative 'intention-to-treat' method in which patients' end-point data served as estimates of missing values. Analyses showed significant overall treatment group differences (i.e., main effects) favoring ACBT over SHC for key

outcome measures including total wake time ( $F = 8.24, p = .01$ ), sleep efficiency ( $F = 7.36, p = .01$ ), global sleep quality ratings ( $F = 5.56, p = .03$ ), and the summary score on a 13-item Insomnia Symptom Questionnaire ( $F = 20.41, p = .0004$ ). Figure I, which displays sleep efficiency changes for individual patients, shows that ACBT was more consistently effective across patients than was SHC. Despite its inclusion of sleep restriction instructions, ACBT produced a 12.3% ( $M = 36.0$  min.;  $SD = 33.8$  min.) increase in sleep time along with a 42.3% ( $M = 70.7$  min.;  $SD = 46.7$  min.) decrease in total wake time on average by the follow-up time point. Those receiving SHC realized only a 3.1% ( $M = 10.1$  min.;  $SD = 29.5$  min.) increase in sleep time and an 8.3% ( $M = 9.1$  min.;  $SD = 24.9$  min.) reduction in total wake time by follow-up.

**Figure 2**  
Changes in Sleep Efficiency for SHC Patients



**Conclusions:** Despite its brevity, our ACBT intervention proved relatively effective for treating the sleep disturbances of those enrolled in this study. Results are encouraging since the time required to administer this ACBT seems to fit well within the time constraints imposed on busy primary care physicians. Furthermore, these results were obtained with a sample largely composed of physician-referred real-world patients who are reasonably representative of those treated in primary care settings.

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- (1) Morin, CM, Colecchi C, Stone I, Sood R, Brink D: Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA, 1999; 281 :991-1035.
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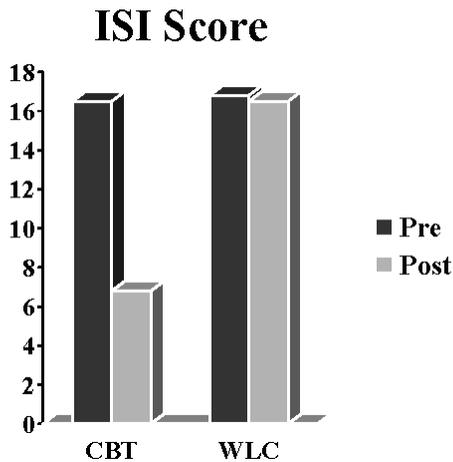
**COGNITIVE-BEHAVIORAL THERAPY FOR INSOMNIA SECONDARY TO BREAST CANCER**

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**Introduction:** Sleep difficulties are highly prevalent in cancer patients (1), particularly in women with breast cancer (2). It has been estimated that 19% of breast cancer survivors meet diagnostic criteria for an insomnia disorder, a problem that is chronic in 95% of the cases and constitutes a clear indication for treatment (3). Although the efficacy of cognitive-behavioral therapy (CBT) for primary insomnia is well documented, no controlled study has yet been conducted to assess its efficacy for insomnia secondary to cancer. The goal of this controlled study was to assess the efficacy of CBT for insomnia in breast cancer survivors.

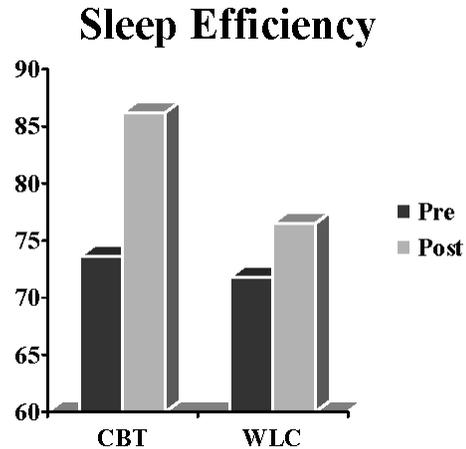
**Methods:** Twenty-five women meeting diagnostic criteria for chronic insomnia secondary to breast cancer (stages I-II) were randomized either to CBT (n = 13) or to a waiting list control condition (WLC; n = 12). Treatment consisted of 8 weekly sessions of CBT administered in a group format, which combined stimulus control, sleep restriction, cognitive restructuring, and sleep hygiene education. Patients assigned to the WLC had to wait 8 weeks before receiving CBT. Participants completed the Insomnia Severity Index (ISI) and a daily sleep diary for a period of 2 weeks at pre- and post-treatment (post-waiting for the WLC group). The main dependent variables were the total ISI score and sleep efficiency derived from the diary data.

Figure 1



**Results:** Two 2 (group) X 2 (time) repeated measures univariate analyses of variance were conducted. They revealed significant Group X Time interactions on the ISI score,  $F(1, 23) = 16.27, p < .001$ , as well as on subjective sleep efficiency,  $F(1, 23) = 7.69, p < .01$ . These results indicate that CBT is associated with a greater reduction of insomnia severity and a greater increase of sleep efficiency at post-treatment than the WLC.

Figure 2



**Conclusions:** Preliminary results of this ongoing randomized trial support the efficacy of CBT for insomnia secondary to breast cancer. Future analyses will allow to confirm this conclusion with stronger statistical power and objective sleep measures (i.e., polysomnography) and evaluate the effect of this treatment on other variables (i.e., psychological distress, quality of life, and immune functioning).

**References:**

- (1) Savard J, Morin, CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19:895-908.
- (2) Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. *Soc Sci Med* in press.
- (3) Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep* 2001;24:583-590.

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098.L

**DEVELOPMENT AND VALIDATION OF THE GLASGOW INTRUSIVE THOUGHTS INVENTORY: A NEW MEASURE FOR THE ASSESSMENT OF PRE-SLEEP COGNITIVE INTRUSIONS**

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**Introduction:** Pre-sleep mental activity has for long been implicated in the development and maintenance of insomnia (1). However, there is no recognised instrument to reliably quantify the content and severity of these thoughts. This study is an extension of recent work using recordings of pre-sleep intrusions (2), and describes the psychometric development of a self-report measure (the Glasgow Intrusive Thoughts Inventory - GITI) to aid the assessment of pre-sleep cognitive intrusions in adults with sleep-onset insomnia.

**Methods:** Over 3 consecutive nights, 12 insomniacs provided "live" recordings of pre-sleep cognitive intrusions on voice-activated recorders, which were used to generate an item pool. Results were compared with the content and categorical structure of pre-sleep cognitive intrusions identified by Wicklow

and Espie (2), and commonalities in thought content used to generate a draft scale. Following further piloting, a 25-item scale was developed and administered to 2 groups (29 insomniacs and 29 good sleepers; mean age 25 yr. for both groups), along with other self-report measures, objective (actigraphic recordings), and subjective (diary) sleep indices, and results analysed to evaluate the psychometric properties of the scale.

**Results:** The GITI demonstrated evidence of construct validity, successfully discriminated between insomniacs and good sleepers, and was significantly correlated with existing, global measures of sleep disturbance such as the Dysfunctional Beliefs and Attitudes about Sleep Scale ( $r = .732$ ). A GITI total score of 43 yielded a sensitivity of 93.1% and specificity of 82.8% to discriminate insomniacs from good sleepers. The GITI demonstrated good test-retest reliability ( $r = .879$ ) and satisfactory internal consistency ( $\alpha = .870$ ). Principal components analysis identified 3 subscales (63% explained variance) that also yielded acceptable internal consistency, with insomniacs scoring significantly higher than good sleepers on all three subscales (all  $p < .001$ ).

**Conclusions:** The GITI is a valid and reliable instrument for use with adults presenting with sleep-onset insomnia.

#### References:

- (1) Lichstein KL, Rosenthal: Insomniacs' perception of cognitive versus somatic determinants of sleep disturbance. *Journal of Abnormal Psychology*, 1980, 89, 105-107
- (2) Wicklow A, Espie CA: Intrusive thoughts and their relationship to actigraphic measurement of sleep: towards a cognitive model of insomnia. *Behaviour Research and Therapy*, 2000, 38, 1-15

### Oral Presentation Narcolepsy, Hypocretin/Orexin, Hypersomnolence

#### 099.K

#### A RAT MODEL OF NARCOLEPSY: GENETIC ABLATION OF OREXIN NEURONS

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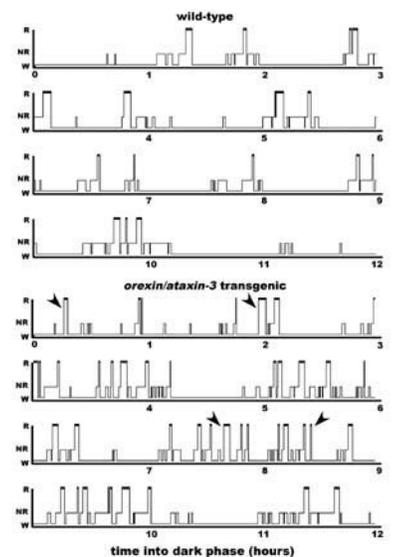
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**Introduction:** Human narcolepsy is likely to be caused by a degeneration of orexin- (hypocretin-) expressing neurons in the lateral hypothalamus (LH). Mice in which the neurotoxic ataxin-3 fragment is expressed under control of the human *prepro-orexin promoter* (*orexin/ataxin-3* transgenic mice) selectively and completely lose their orexin neurons during adolescence, resulting in unequivocal expression of narcolepsy<sup>1</sup>. Because the rat is the species used most widely in sleep research, and because more sophisticated physiologic methodologies are currently available in the rat, we set out to generate *orexin/ataxin-3* transgenic rats. Here we report the initial histological and polysomnographic characterization of *orex-*

*in/ataxin-3* transgenic rats.

**Methods:** Several lines of *orexin/ataxin-3* transgenic rats (Sprague-Dawley) were created by standard procedures using the transgenic construct described previously<sup>1</sup>. Rats were housed under LD 12:12 light cycle conditions. In one selected line, brains of male littermates were histologically examined for the presence of immunoreactivities for orexin, melanin-concentrating hormone (MCH), and transgene c-Myc tag at 17 weeks of age. Using a novel screwless ultra-light weight implant system, which is minimally restraining, we recorded EEG/EMG signals in male hemizygous transgenic rats and male wildtype littermates at the same age, and characterized their vigilance states (currently  $n=2$  per group). Simultaneously, we monitored the behavior of the animals by infrared videophotography during the dark period.

Figure 1



Representative dark phase hypnograms of wild-type and *orexin/ataxin-3* transgenic rats. Transgenic animals often show direct transitions from wakefulness (W) to REM sleep (R) (arrowheads) or transitions with little preceding non-REM sleep (NR). Furthermore, the duration of REM sleep is increased and vigilance states are more fragmented.

**Results:** The *orexin/ataxin-3* transgene immunoreactivity (c-Myc tag) colocalized correctly within orexin neurons in the LH; no ectopic expression was found. At 17 weeks of age, no orexin immunoreactivity could be detected in brains of transgenic animals, whereas it could be readily found in wildtype littermate controls. Transgenic rats showed the same distribution of MCH immunoreactive neurons as wildtype controls, indicating a selective elimination of orexin-expressing neurons. Polysomnographic recordings from transgenic rats showed multiple occurrences of direct transitions from wakefulness to REM sleep (Fig.1) and indications of cataplexy (episodes of sudden muscle atonia during wakefulness without a change in the awake EEG pattern concomitant with a postural collapse). Neither of these abnormalities were seen in wildtype littermate controls. Furthermore, during the dark period, transgenic rats had a reduced REM sleep latency, an increased amount of REM sleep, a higher frequency of REM sleep episodes, and a shortened non-REM sleep episode dura-

tion (Table 1). No differences between the genotypes were apparent during the light period.

**Table 1**  
Vigilance state parameters for male *orexin/ataxin-3* hemizygous (Tg/+) and wild-type (WT) control littermate rats for the 12-h dark period.

	Tg/+	WT
<b>REM sleep</b>		
Total time (min)	58.9 ± 6.5*	31.8 ± 3.1
Episode duration (sec)	94.9 ± 2.8	92.1 ± 14.8
Latency (min)	2.7 ± 0.1*	4.8 ± 0.1
Frequency (min)	25.3 ± 2.9*	42.1 ± 3.5
<b>Non-REM Sleep</b>		
Total time (min)	162 ± 14	181 ± 19
Episode duration (sec)	95.7 ± 3.3*	153 ± 3
<b>Awake</b>		
Total time (min)	498 ± 19	506 ± 17
Episode duration (sec)	298 ± 37	451 ± 52

Values are expressed as mean±SEM. Significant differences ( $p < 0.05$ ) between Tg/+ and WT rats are indicated with asterisks.

**Conclusions:** Transgenic expression of a neurotoxic ataxin-3 polypeptide in rats selectively and completely eliminates orexin neurons. This genetic ablation leads to a phenotype that closely resembles human narcolepsy. *Orexin/ataxin-3* transgenic rats will therefore be a valuable addition to the existing canine and murine models of narcolepsy.

#### References:

(1) Hara J, Beuckmann CT, Nambu T et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia and obesity. *Neuron* 2001;30:345-354.

Research supported by CTB is an Associate, REH is a Senior Associate, and MY is an Investigator of HHMI.

### 100.K

#### ECTOPIC EXPRESSION OF OREXIN TRANSGENE RESCUES NARCOLEPSY IN OREXIN NEURON-ABLATED MICE

Willie JT,<sup>1</sup> Sakurai T,<sup>1</sup> Hara J,<sup>4</sup> Takahira H,<sup>4</sup> Yun Z,<sup>4</sup> Beuckmann CT,<sup>4</sup> Sinton CM,<sup>1,2</sup> Yanagisawa M<sup>3</sup>

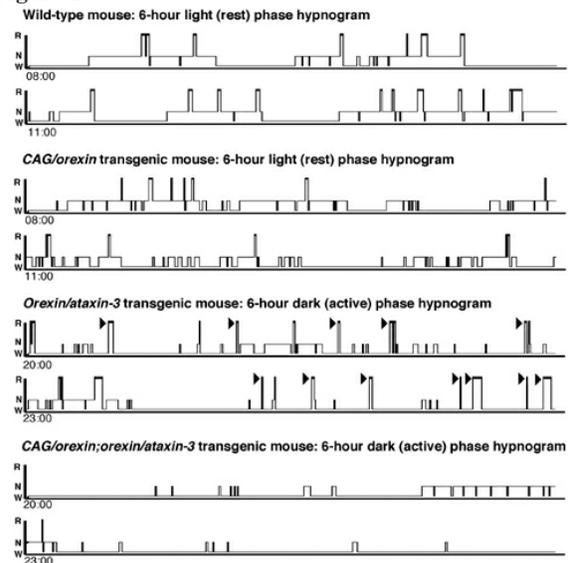
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**Introduction:** Deficiency in orexin (hypocretin) neuropeptides is associated with narcolepsy<sup>1,2</sup>. Mice expressing the neurotoxic *ataxin-3* fragment under control of a *prepro-orexin* promoter (*orexin/ataxin-3* transgenic mice) develop ablation of endogenous orexinergic neurons, and exhibit behavioral and polysomnographic features of narcolepsy<sup>2</sup>. To determine the effects of ectopic overexpression of orexin on vigilance,

we produced mouse strains expressing orexins ubiquitously (*CAG/orexin* transgenic mice). We also bred mice carrying both *CAG/orexin* and *orexin/ataxin-3* transgenes to examine the effects of ectopic orexin expression on narcolepsy in orexin neuron-ablated mice.

**Methods:** We constructed a transgene consisting of the CAG promoter and rat *prepro-orexin* cDNA. Expression of the transgene in *CAG/orexin* mice was confirmed by Northern blot analysis and orexin radio-immunoassay of whole brain extracts. *Orexin/ataxin-3* transgenic and *CAG/orexin; orexin/ataxin-3* double transgenic littermates (10-20 weeks of age, C57Bl6/J:DBA1 mixed background, n=3 per group) were screened for narcoleptic behavioral arrests during the dark phase using infrared videophotography<sup>1</sup>. Wild-type (n=7), *CAG/orexin* (n=8), *orexin/ataxin-3* (n=2), and *CAG/orexin; orexin/ataxin-3* double transgenic (n=2) mice were implanted with EEG and nuchal EMG electrodes<sup>1</sup> and recorded at 14-15 weeks of age. Vigilance states were classified according to standard criteria.

**Figure 1**



**Results:** *CAG/orexin* mice ectopically overexpress *prepro-orexin* mRNA, and brains from *CAG/orexin* mice have increased levels of orexin peptides. Although *CAG/orexin* mice display no overt behavioral abnormalities, polysomnography reveals abnormally frequent nuchal muscle activities during sleep, disruption of REM-related muscle atonia, and associated arousals. Hypnograms of *CAG/orexin* mice are characterized by poorly consolidated sleep with increased cycling among vigilance states compared to wild-type littermates, especially during the normal light (rest) phase (Figure). Over 24 hours, mean episode durations of REM, non-REM, and waking are significantly reduced compared to wild-type littermates (Table). Although REM latency was significantly reduced, no direct transitions from wake to REM were observed. *Orexin/ataxin-3* transgenic mice exhibit a narcoleptic phenotype with behavioral arrests resembling cataplexy and direct transitions from wake to REM, especially during the dark (active) phase (Figure). In contrast, we observed neither

narcoleptic behavioral arrests nor direct transitions to REM in *CAG/orexin;orexin/ataxin-3* double transgenic mice. Indeed, dark phase hypnograms are relatively normal compared to narcoleptic *orexin/ataxin-3* littermates (Figure).

**Table 1**

**Vigilance state parameters recorded from *CAG/orexin* transgenic and wild-type control mice.**

	REM sleep	
	<i>CAG/orexin</i>	Wild-type
Total time (min)	41.5 ± 3.49	50.5 ± 2.86
Episode duration (sec)	43.0 ± 2.28 <sup>‡</sup>	64.8 ± 1.60
REM latency (min)	6.51 ± 0.47 <sup>‡</sup>	9.66 ± 0.56
REM interval (min)	25.6 ± 1.85	31.4 ± 2.09
	Non-REM sleep	
	<i>CAG/orexin</i>	Wild-type
Total time (min)	571.5 ± 43.9	597.3 ± 33.5
Episode duration (sec)	190.7 ± 14.6 <sup>‡</sup>	264.3 ± 16.1
	Awake	
	<i>CAG/orexin</i>	Wild-type
Total time (min)	824.4 ± 44.2	789.6 ± 35.7
Episode duration (sec)	309.2 ± 27.2 <sup>†</sup>	453.4 ± 55.5

Data are means ± SEM over 24 hr. Significant differences demonstrated by one-way ANOVA ( $p \leq 0.05^{\dagger}$ ,  $p \leq 0.005^{\ddagger}$ )

**Conclusions:** Orexin overexpression alters both baseline and narcoleptic sleep/wake patterns. Our results support a specific role for orexins in regulating vigilance and muscle tone. Abnormal muscle activity observed in *CAG/orexin* transgenic mice may relate pathophysiologically to restless leg syndrome or REM sleep behavior disorder. The disruption of sleep states we observed in *CAG/orexin* mice during the light phase is in contrast with that observed in narcoleptic orexin-deficient mice, which exhibit increased sleep and sleep fragmentation only during the dark phase<sup>1,2</sup>. *CAG/orexin;orexin/ataxin-3* double transgenic mice demonstrate a genetic rescue of the narcoleptic phenotype by ectopic orexin expression even in the absence of endogenous orexin neurons. This suggests that ectopic orexin production or administration may be effective in treating narcolepsy caused by orexinergic deficiency.

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- (2) Hara J, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron* 2001;30:345-54.

**Research supported by funds from the WM Keck and Perot Family Foundations. JTW is a joint fellow of the Department of Cell and Molecular Biology and the Medical Scientist Training Program of UTSW. CMS is the recipient of an MSTP award. CTB is an associate, and MY is an Investigator of HHMI**

## 101.K

### EARLY DEVELOPMENTAL CHANGES IN HYPOCRETIN-1 (OREXIN-A) AND CATAPLEXY IN NARCOLEPTIC DOBERMANS

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**Introduction:** Narcolepsy is a disabling disorder characterized by cataplexy, excessive daytime sleepiness, and other sleep abnormalities. Cataplexy onset occurs at 1-4 months of age in canine narcoleptics. Our earlier study found that axonal degeneration in the amygdala and other forebrain region at 1-4 months of age in narcoleptic dogs (Siegel et al. 1999). Recent studies have shown that disruption of the hypocretin (Hcrt) system is linked to human and canine narcolepsy. This study was undertaken to investigate the temporal relation between developmental changes in cerebrospinal fluid (CSF) Hcrt-1 level and cataplexy in narcoleptic dogs.

**Methods:** Thirty-four genetically narcoleptic Dobermans and seven normal Dobermans were used in this study. Under isoflurane anesthesia, CSF was collected from the cisterna magna of the eighteen narcoleptic Doberman puppies (10 M, 8 F) at 4 days and 2, 4, 6, 8, 10, 14, 18, 26 and 32 weeks after birth. The development of cataplexy was monitored starting from three weeks after birth (n=8). One normal Doberman puppy was used as control and CSF was collected at the same time points as in the narcoleptic puppies. CSF was also collected from 22 adults, 16 narcoleptic (10 F, 6M) and 6 normal (3M, 3F). Hcrt-1 was extracted from 0.5-1 ml samples with a reversed phase SEP-PAK C18 column. An iodine-125 Hcrt-1 radioimmunoassay was used to measure concentration in reconstituted aliquots (Phoenix Pharmaceuticals, Mountain View, CA).

**Results:** In narcoleptic dogs, Hcrt-1 concentration at different stages of development shows a large fluctuation ( $F=3.64, df=9, 153; p<0.0005$ ). Relative to adult levels, a significant elevation of Hcrt level was seen at 4 days ( $p<0.01$ , Bonferroni t-test), and 6-8 weeks ( $p<0.01$ , Bonferroni t-test), after birth. From 10 weeks onwards Hcrt was at the adult level. Cataplexy onset was at about 4 weeks after birth in this group of puppies (n=8) and the severity of cataplexy increased with age with cataplexy symptom reaching a plateau by 10-14 weeks. The time course of changes in Hcrt level and development of cataplexy were compared in the same group of eight narcoleptic puppies. The onset and increase in severity of cataplexy coincides with significant variation of Hcrt seen within eight weeks after birth. The trend of changes in Hcrt-1 during development in male and female narcoleptic dogs was similar. The onset or severity of cataplexy also showed no difference between male and female dogs. But unlike the narcoleptic puppies, CSF collected from a normal Doberman puppy during same period as in narcoleptic puppies, did not show any fluctuation of Hcrt-1 level at any stage of development. The Hcrt-1 concentration in adult normal and narcoleptic Dobermans did not show any significant difference.

**Conclusions:** An elevated concentration of Hcrt-1 was seen at 4 days of age and at six to eight weeks of age, the later point

coinciding with the period of cataplexy onset. The elevated Hcrt levels seen during the development in narcoleptic dogs may be due to the absence of functional Hcrt-2 receptors affecting a feedback loop that regulates Hcrt release. The coincidence of onset of cataplexy and variation in Hcrt-1 suggests that the altered concentrations of Hcrt-1 during development may be linked to the development of narcoleptic symptoms.

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(1) Siegel JM, Nienhuis R, Gulyani S, Ouyang S, Wu MF et al., Neuronal degeneration in canine narcolepsy. *J Neurosci*. 1999 19:248-57

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## 102.K

### VOXEL-BASED MORPHOMETRY IN HYPOCRETIN-DEFICIENT NARCOLEPSY

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**Introduction:** Most human narcoleptic patients lack hypocretin-1 in the cerebrospinal fluid (CSF) (see (1)). Furthermore, post-mortem studies in a few patients showed that hypothalamic hypocretin mRNA was undetectable and immunoreactive hypocretins were greatly diminished. These findings, together with the association between narcolepsy and HLA subtype DQB1\*0602, suggest that an autoimmune mediated degeneration of hypocretin neurons is responsible for the disease. We investigated whether degeneration of hypocretin neurons in the hypothalamus or their projection areas is associated with structural change that can be visualised using voxel-based morphometry (VBM).

**Methods:** Fifteen narcoleptic patients (8 females, mean age: 44.7±14.3 years) and fifteen healthy controls (8 females, mean age: 44.5±14.2 years) were included after written informed consent. All patients lacked CSF hypocretin-1. Imaging was performed on a 1.5T MR system using a 3-dimensional T1-weighted gradient-echo pulse sequence. Image parameters were chosen to optimise grey-white matter contrast. VBM is based on a sophisticated whole brain technique which registers images from groups of subjects into a common stereotactic space, in order to detect local differences in grey (or white) matter density on a voxel-by-voxel basis (2). Data were analysed with statistical parametric mapping (SPM99) using the General Linear Model.

**Results:** There was no difference between global grey matter volume ( $F(1,28)<1$ ) or white matter volume ( $F(1,28)<1$ ) between patients and controls. VBM detected no significant regional differences in grey or white matter between patients and controls. Even when we lowered thresholds and applied a small-volume correction, no differences between the groups were found.

**Conclusions:** Recent research points to possible degeneration

of hypocretin neurons in the hypothalamus of narcoleptic patients. We used VBM, a highly sensitive, unbiased MRI morphometric method (2), to detect structural changes in the brain. The absence of detectable structural changes in the brain of narcoleptic patients is either due to a relative insensitivity of VBM to detect subtle hypothalamic changes, or challenges the hypothesis that a degenerative process is involved. To consider the first scenario; the hypothalamus lacks optimal contrast resolution, owing to its intrinsic anatomy, with embedded nuclei and adjacent white matter connections. However, VBM would still be sensitive to a systematic difference in the anatomy. If the hypocretin producing cells are destroyed indeed, this would be a remarkably selective process. Our results may also indicate that the affected hypocretin neurons remain intact. The two available post mortem studies could not formally prove cell loss, because an independent marker for hypocretin neurons was not available (see (1)). Various mechanisms other than neuronal degeneration could be responsible for the hypocretin deficiency in narcolepsy (3). Genetic factors could play a role, including mutations in transcription factors required for hypocretin transcription, or alterations in proteins crucial for proper splicing of hypocretin mRNA.

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## 103.K

### CLINICAL OVERLAPS OF THE NARCOLEPSY AND HYPOCRETIN/OREXIN DEFICIENCY SYNDROMES

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**Introduction:** Narcolepsy is a disorder characterized by sleepiness and abnormal Rapid Eye Movement (REM) sleep. The most specific symptom is cataplexy, a sudden loss of muscle tone triggered by emotions. It affects 1 in 2,000 individuals. Narcolepsy-cataplexy is linked with Human Leukocyte Antigen (HLA) DQB1\*0602 and is associated with decreased brain hypocretin/orexin levels. We analyzed patients with various sleep disorders to delineate the clinical spectrum of the hypocretin deficiency syndrome.

**Methods:** Clinical data, HLA-DQ typing, Multiple Sleep Latency Tests (MSLT) and cerebrospinal fluid (CSF) hypocretin-1 (direct assay and after extraction) were studied in 275

patients with various sleep disorders (Narcolepsy, Idiopathic Hypersomnia, Obstructive Sleep Apnea Syndrome, Restless Leg Syndrome and Insomnia). Atypical hypersomnia cases such as familial cases, narcolepsy without cataplexy, narcolepsy-cataplexy without HLA-DQB1\*0602, recurrent hypersomnias and symptomatic cases with hypersomnia or narcolepsy (e.g., Parkinson's disease, depression, Prader-Willi syndrome, Niemann-Pick Type type C and others) were also included, together with 295 controls (67 healthy and 228 with various neurological disorders). Signal detection analysis was used to determine CSF hypocretin-1 levels best predictive for narcolepsy.

**Results:** DQB1\*0602 frequency was increased in narcolepsy with typical cataplexy (93% vs 17% in controls), narcolepsy without cataplexy (56%) and idiopathic hypersomnia (52%). Low hypocretin-1 values (direct assay \*110 pg/ml) were diagnostic for narcolepsy. Values above 200 pg/ml were considered in the normal range for healthy subjects. Almost all patients with low hypocretin-1 levels were HLA-DQB1\*0602 positive subjects with narcolepsy-cataplexy. These subjects had moderately increased Body Mass Index, normal CSF leptin levels but did not always have abnormal MSLT diagnostic sleep tests. Rare narcolepsy subjects without cataplexy, without HLA-DQB1\*0602 and/or with secondary narcolepsy had low hypocretin-1 levels. Ten subjects with hypersomnia had intermediate levels, 7 of whom were narcolepsy cases (often HLA negative, of secondary nature and/or with atypical or no cataplexy), and one of whom was a periodic hypersomnia case (one of 3 total, during an episode). Normal controls and subjects with sleep disorders other than hypersomnia/narcolepsy were all in the normal range. Subjects with neurological disorders very rarely had low levels (one comatose subject with myxedema and 3 subjects with Guillain-Barre syndrome). More frequently (n=30) intermediate levels were observed with various acute pathologies such as head trauma and encephalitis, though most subjects (n=194) with neurological disorders had normal levels.

**Conclusions:** Narcolepsy-cataplexy with hypocretin deficiency is a genuine disease entity. Measuring CSF hypocretin-1 levels is the definitive diagnostic test, providing it is interpreted within the clinical context. It may be most useful in cases where the MSLT is difficult to interpret; for example in subjects already treated with psychoactive drugs and/or with other concurrent sleep disorders such as sleep apnea syndrome.

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## 104.K

### SLEEP AND HLA IN FIRST-DEGREE RELATIVES FROM A CASE SERIES OF PATIENTS WITH NARCOLEPSY

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**Introduction:** We are studying narcolepsy genetics using a case series model of ascertainment. We previously reported on the first 32 narcoleptic probands showing that only 68% had both the HLA-DRB1\*1501 and HLA-DQB1\*0602 markers.(1) We now present data on first-degree relatives.

**Methods:** Each patient (proband) in the series had: 1) excessive daytime somnolence (EDS); (2) cataplexy or hypnagogic hallucinations; (3) mean Multiple Sleep Latency Test (MSLT) <7.9 minutes; (4) >2 two REM sleep periods on the MSLT; (5) no sleep apnea (RDI<10). Evaluations of first-degree relatives comprised medical examination, polysomnography, and HLA typing.

**Results:** Fifty-two probands and 53 first-degree relatives from 20 probands have been evaluated. Remaining relatives will be evaluated as they become available. There were 17 parents, 19 siblings and 17 offspring. Age ranges were: 31-92, 19-75 and 10-52, respectively. Evaluations revealed 7 subjects with narcolepsy (13.2%; 2 parents, 4 siblings, 1 offspring), 4 subjects with obstructive sleep apnea syndrome (OSA) (7.5%; 2 parents, 1 siblings, 1 offspring), 1 subject with periodic leg movements in sleep syndrome (PLMS) (1.9%, 1 parent) and 41 subjects without primary sleep disorders (WPSD) (77.4%; 12 parents, 14 siblings, 15 offspring). Table 1 presents nighttime polysomnographic and MSLT data and Table 2 presents the percentages of the relevant HLA haplotypes according to these diagnostic categories. To our knowledge, these are the first systematic data on first-degree relatives in randomly selected narcoleptic probands, as approximated by case series. The 13.2% diagnosis of narcolepsy is unexpectedly high and is due to multiple narcoleptic relatives in three families, one family with, and two families without, the HLA markers typical of narcolepsy. Of the narcolepsy group, 57.1% had both DR and DQ markers, which is comparable to the 68% rate we reported for narcoleptic probands. About 50% of the OSA group had both, and 49% had no HLA markers for narcolepsy. There was no statistically significant difference in the polysomnographic results among the three WPSD subgroups, indicating that the HLA markers may not influence sleep/wake patterns in this population. There was a trend for the subgroup with DQB1\*0602/other haplotypes to have low MSLT SLs - consistent with the Stanford group's data on the importance of DQB1\*0602 in expression of narcolepsy and EDS.(2) However, the subgroup with both DRB1\*1501/DQB1\*0602 had the highest MSLT SLs.

**Table 1**  
PSG and MSLT Data by Diagnostic Category

	SL (min)	TST (min)	SE (%)	REM (%)	MSLT (min)	REMs (#)
Narcolepsy:	11.2	418	83	22	6.9	2.90
OSA:	6.6	462	89	24	8.3	1.50
PLMS:	43.5	408	85	20	9.6	1.00
WPSD:	17.4	429	83	19	10.5	0.08
HLA a:	15.7	449	90	20	12.3	0.13
HLA b:	12.6	406	79	19	8.6	0.11
HLA c:	20.3	430	82	18	10.6	0.05

**Table 2**  
HLA typing codes by Diagnostic Category

Narcolepsy:	a. DRB1*1501/ DQB1*0602	- 57.1%
	c. Other HLA haplotypes	- 42.9%
	a. DRB1*1501/ DQB1*0602	- 50.0%
OSA:	b. DQB1*0602/others	- 25.0%
	c. Other HLA haplotypes	- 25.0%
	c. Other HLA haplotypes	- 100%
PLMS:	a. DRB1*1501/DQB1*0602	- 26.8%
WPSD:	b. DQB1*0602/others	- 24.4%
	c. Other HLA haplotypes	- 48.8%

**Conclusions:** Narcolepsy appears in 13% of first-degree relatives of narcoleptic probands; OSA, in 7.5%; and PLMS in 1.9%. The first-degree relatives with narcolepsy showed 57.1% association with the HLA markers. The WPSD relatives showed only 26.8% association with both HLA markers and 24.4% association with DQB1\*0602. Finally, relatives with only the DQB1\*0602 marker tended to have the lowest MSLT sleep latencies.

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**105.K**

**WHAT ARE THE PREVALENCES OF HYPNAGOGIC HALLUCINATIONS AND SLEEP PARALYSIS IN NON-AFFLICTED FAMILY MEMBERS OF NARCOLEPSY PATIENTS?**

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**Introduction:** The prevalence of both hypnagogic hallucinations and sleep paralysis in the general population is approxi-

mately 30%. The purpose of this project was to address the following question. Is the prevalence of hypnagogic hallucinations (HH) or sleep paralysis (SP) higher in non-afflicted relatives of narcolepsy patients than in the general population?

**Methods:** This study employed a group of 17 community controls and a group of 28 relatives of a single narcolepsy proband. Several members of this large, African-American kindred have been diagnosed with narcolepsy/cataplexy. However, these family members were excluded in order to examine the prevalence of HH and SP in non-afflicted individuals. HH and SP as well as the participant's Epworth Sleepiness Scale (ESS) score and whether the participant had disturbed sleep (DS) were obtained using the Stanford Center for Narcolepsy Sleep Inventory.

**Results:** Descriptive statistics for age and gender across each group as well as the results for each of the variables examined can be found in the table below. Family members were significantly more likely to experience HH than non-family members. As has been previously reported, family members were also significantly sleepier than non-family members. However, they were not more likely to experience SP or DS.

**Table 1**

	Family Member		t	$\chi^2$
	Yes (n = 28)	No (n = 17)		
<u>Age</u>	27.5 ± 12.3	35.9 ± 14.7	2.08*	
<u>Male</u>	43%	35%		0.25
<u>ESS</u>	13.1 ± 5.7	9.1 ± 5.0	2.41*	
<u>HH</u>	61%	29%		4.15*
<u>SP</u>	32%	35%		0.05
<u>DS</u>	38%	25%		0.81

\*  $p < .05$ ; ESS = Epworth Sleepiness Scale; HH = Hypnagogic Hallucinations; SP = Sleep Paralysis; DS = Disturbed Sleep

**Conclusions:** The prevalence of sleepiness and HH but not SP and DS may be higher in non-afflicted blood relatives of narcolepsy patients than in the general population. Since sleepiness and HH can be inferred to be more common in blood relatives than in the general population, the cause of these symptoms may have a strong genetic influence. On the other hand, since this was not the case for SP or DS, the cause of these symptoms may have a strong environmental influence. Indeed, previous research has demonstrated a similar finding. Using the Ullanlinna Narcolepsy Scale in the Finnish Twin Cohort, Kapiro and colleagues found that while genetics accounted for approximately 37% of the variance in the scale overall, this value decreased for the cataplexy items (1). Since SP is physiologically similar to cataplexy, the DS and muscle paralysis-related symptoms of narcolepsy may have more of an environmental influence than the sleepiness and hallucinations associated with narcolepsy. However, since the present data

were collected from a single family, the results may not generalize to other narcolepsy families or to sporadic cases of narcolepsy.

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### 106.K

#### BODY WEIGHT AND -COMPOSITION IN PATIENTS WITH NARCOLEPSY VERSUS IDIOPATHIC HYPER-SOMNIA

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**Introduction:** The implication of the hypocretin system in the pathophysiology of narcolepsy has revamped the interest in other parts of the narcoleptic phenotype, besides the sleep symptoms (see (1)). The influence of hypocretin deficiency on the body weight of narcoleptic patients is one of them. It has been known for a long time that narcoleptics have a higher body weight than controls. There has been debate however, whether this finding is directly due to the pathophysiologic process involved, or secondary because of a decreased activity due to excessive sleepiness throughout the day. In this study we compared the body weight and -composition between patients with narcolepsy (who are hypocretin deficient) and patients with idiopathic hypersomnia (IH, who presumably sleep a comparable amount of time per day, but have normal hypocretin levels).

**Methods:** We examined 64 male patients with narcolepsy and 21 male patients with IH. Diagnoses were made using the ICSD criteria, together with hypocretin measurements in part of the subjects. The following measurements were performed in all subjects: body weight and length (using standardized and calibrated scales), waist circumference, and percentage body fat (%bodyfat, using bioimpedance analysis). Primary outcome parameter was the body mass index (BMI), defined as subject mass (in kg) divided by the square of subject body length (in m). Comparisons were made using the Student's t-test, c2 test and analysis of covariance (ANCOVA) where appropriate.

**Results:** Narcoleptic patients had a significantly higher BMI, waist circumference and %bodyfat when compared with IH (table 1). After correction for differences in disease duration or the use of medication, the differences in outcome parameters between the two groups remained. Within diagnostic groups, use of medication did not influence BMI, waist circumference or %bodyfat either.

Table 1

	Narcolepsy	IH	p
n	64	21	
age (years)	45.6 ± 15.7	42.5 ± 8.7	.4 <sup>1</sup>
dis.dur. (years)	23.7 ± 15.9	17 ± 9.7	.1 <sup>1</sup>
stimulants n(%)	23 (36)	8 (38)	.86 <sup>2</sup>
antidepressants n(%)	16 (25)	0 (0)	.01 <sup>2</sup>
BMI	29 ± 4.5	25.4 ± 2.5	0.02 <sup>3</sup>
waist (cm)	100.4 ± 12.5	92.6 ± 9.5	0.01 <sup>3</sup>
body fat (%)	26.5 ± 6.9	20.3 ± 6.0	0.041 <sup>3</sup>

data are mean±SD; dis.dur.: disease duration; <sup>1</sup>: Student's t-test; <sup>2</sup>:  $\chi^2$  test; <sup>3</sup>: ANCOVA, with age as covariate (age and BMI for %bodyfat)

**Conclusions:** An increase in body weight seems to be an integral part of the narcoleptic phenotype (1;2). In this study we found a markedly increased BMI in narcolepsy when compared with IH patients. Furthermore, two other indicators of obesity, namely waist circumference and percentage body fat, were similarly increased in narcoleptics. Our results confirm the notion that obesity in narcolepsy is due to the hypocretin deficiency itself, and not secondary to inactivity accompanying daytime sleepiness. The use of medication in our sample did not influence the body weight and -composition either. Since earlier studies showed that narcoleptics do not have a higher food intake (3), differences in metabolic rate are the most likely explanation for the obesity found in narcolepsy.

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### 107.J

#### ADMINISTRATION OF A NOVEL ANTI-OXIDANT (PNU-101033F) ATTENUATES INTERMITTENT HYPOXIA-INDUCED SPATIAL LEARNING DEFICITS IN THE RAT.

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**Introduction:** Exposure to intermittent hypoxia (IH), such as occurs in obstructive sleep apnea (OSA), is associated with

increased apoptosis in the hippocampus and cortex and neurobehavioral impairments in the adult rat [1]. Oxidative stress has been implicated in the neurodegenerative changes seen in various CNS disorders, including exposure to low oxygen states [2]. We hypothesized that exposure to IH will induce oxidative stress to vulnerable neural regions, and that protection from such oxidative stress by administration of an electron-trapping agent, will prevent the neurobehavioral impairments seen with IH.

**Methods:** 36 young adult male rats (175-200g) were exposed to Room Air (RA, n=18) or IH (10% O<sub>2</sub> alternating with RA every 90 sec; n=18) for 8 days. Each group was further subdivided and received a twice daily injection of either the electron trapping agent PNU-101033F (3mg/kg ; n=9) or vehicle (n=9). Behavioral testing consisted of a standard place-training reference memory task in the Morris water maze. Rats were trained to locate a submerged platform using spatial cues. On each trial, the rat was placed into the pool from quasirandom start points and allowed a maximum of 90 seconds to escape to the platform, where it was allowed to remain for 15 seconds. Training consisted of a 8-trial training session, followed by a 4-trial retention session 24 hours later. To assess performance during place training, mean escape latencies, swim distances, and swim speeds were analyzed by a two-way (hypoxic condition x treatment) repeated measures ANOVA. A p value <0.05 was considered statistically significant.

**Results:** Vehicle-injected rats exposed to IH were found to require significantly longer times (latency) and distances (pathlength) to locate the hidden platform. PNU-101033F injected rats were not significantly different from RA. No significant differences were found between groups in regards to swim speeds or on the latency and pathlength to locate a cued platform, indicating that group differences were not due to sensorimotor impairments.

**Conclusions:** PNU-101033F prevented the spatial learning impairments associated with IH exposures. We speculate that protection from oxidative stress by systemic administration of anti-oxidants may be a potentially useful intervention to reduce the neurobehavioral deficits of patients with OSA.

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### 108.J

#### POST-NATAL EXPOSURE TO CHRONIC INTERMITTENT HYPOXIA IMPAIRS SPATIAL LEARNING IN RATS.

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**Introduction:** Exposure to intermittent hypoxia (IH), such as

occurs in obstructive sleep apnea (OSA), is associated with neurodegenerative changes in the hippocampus and cortex and neurobehavioral impairments in the adult rat [1]. The post-natal rat brain displays marked increases in susceptibility to IH during a critical developmental window (10-25 days of age), suggesting that exposure to IH during this period may result in significant functional impairments [2].

**Methods:** 24 rat pups were exposed to 14 days of either Room Air (RA, n=12) or IH (10% O<sub>2</sub> alternating with RA every 90 sec; n=12) starting at post-natal (PN) day 10. Pups were weaned at PN day 21, and group housed with their littermates. Behavioral testing began at PN day 23, and consisted of a standard place-training reference memory task in the Morris water maze. Pups were trained to locate a hidden, submerged platform using only distal, spatial cues. Each animal received one training session per day, consisting of four trials, separated by a 4-minute inter-trial interval (ITI). On each trial, the rat was placed into the pool from quasirandom start points and allowed a maximum of 90 seconds to escape to the platform, where it was allowed to remain for 15 seconds. The position of the platform remained constant across trials. To assess performance during place training, mean escape latencies, swim distances, and swim speeds were analyzed by a one-way repeated measures ANOVA. A p value <0.05 was considered statistically significant.

**Results:** Pups exposed to IH required longer times (latency) and distances (pathlength) to locate the hidden platform. In contrast, both groups had similar swim speeds, and latencies and pathlengths to locate a cued platform, indicating that the group differences were not due to sensorimotor impairments.

**Conclusions:** Exposure to IH during a critical developmental period results in substantial neurobehavioral impairments in the young rat. We speculate that these adverse effects may persist into adulthood.

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### 109.J

#### CORRELATES OF OBSTRUCTIVE SLEEP APNEA IN 6-12 YEAR OLD CHILDREN—THE TUCSON CHILDREN ASSESSMENT OF SLEEP APNEA STUDY (TUCASA)

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**Introduction:** Sleep disordered breathing (SDB) in children can be associated with excessive daytime sleepiness (EDS), loud snoring, neurocognitive deficit, behavioral problems, and

attention deficit hyperactivity disorder (ADHD)<sup>(1,2)</sup>. However, these findings are derived from parental report, small samples, clinic patients, or have used limited polysomnography (PSG). General population data using full PSG is lacking. The TuCASA study utilizes home PSG to determine the relationship between SDB in children and symptoms, physiologic/anatomic risk factors, and performance on neurobehavioral measures. This is a report of our findings in the first 211 children enrolled.

**Methods:** Parents of all children in 8 Tucson elementary schools were asked to complete a 15-item survey inquiring about symptoms attributable to SDB. Parents of children who met the study criteria were asked if their child would permit an overnight, unattended recording of their sleep. Polysomnograms were obtained with the Compumedics PS-2 system and were scored according to recently published criteria<sup>(3)</sup>. On the survey, parents were asked whether or not their child stopped breathing or struggled to breathe during sleep, turned “blue” while sleeping, snored loudly, was sleepy during the daytime, fell asleep at school or while watching television, whether they ever awakened their child because they stopped breathing, or if their child had learning problems (LP). EDS was defined as being sleepy in the daytime, falling asleep at school or while watching television either “frequently” or “almost always”. Witnessed apnea (WA) was defined as stopping breathing or struggling to breathe during sleep, turning blue while sleeping or waking the child because of stopping breathing “occasionally”, “frequently” or “almost always”. Snoring (SN) was considered present if it occurred more often than “occasionally” and DIMS was present if the child currently experienced trouble falling asleep, staying asleep, or waking too early. Obesity was defined as a body mass index (BMI) in the 90th percentile of the child’s age/gender category.

**Results:** Of the 211 subjects, 52.1% were males and 47.9% were females with a mean age of 8.7 years (range 6-12). Ethnic distribution was 54% Caucasian and 46% Hispanic. The mean RDI was 6.1 (range .8-72.3). The log transformed RDI as a continuous variable and the student’s t test were used to show a significant association between RDI and obesity ( $p<.004$ ), EDS ( $p<.02$ ), and LP ( $p<.004$ ). No significant association was shown between RDI and race, gender, snoring, or WA. To examine what level of RDI might be clinically significant, cutpoints of 3, 5, 6, 7, 8, 9, and 10 events per hour were analyzed in contingency tables to show that at a level of 7 events per hour, obesity ( $p<.001$ ), EDS ( $p<.002$ ), DIMS ( $p<.04$ ), and LP ( $p<.006$ ) all became significant, while gender, race, and snoring were not significant at this level.

**Conclusions:** In this population based sample of children ages 6-12 years, an RDI of  $> 7$  events per hour is associated with obesity, EDS, DIMS, and LP. Gender, race (Hispanic or Caucasian), and snoring are not significantly associated with RDI.

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## 110.J

### SLEEPINESS, HYPERACTIVITY, AND RDI IN A COMMUNITY SAMPLE OF SCHOOL CHILDREN

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**Introduction:** The present study sought to examine the co-existence of sleepiness, hyperactive behavior, and possible sleep disordered breathing (SDB) in a community sample of school children. Excessive daytime sleepiness (EDS) is frequently documented in adults with sleep apnea. EDS has been empirically documented in children, but hyperactivity has also been widely hypothesized as a sign of pediatric apnea. Relationships between these two seemingly incongruent behaviors have not been well documented in this population.

**Methods:** A prospective cohort study of 149 children from public schools each underwent unattended in-home overnight polysomnography as part of the Tucson Children Assessment of Sleep Apnea Study (TuCasa). Parents filled out questionnaires about their child’s sleep habits on the TuCasa Sleep Habits Questionnaire and their behavior on the Conners’ Parent Rating Scale – Revised.

**Results:** Of the entire sample, 10 children (6.7%) were rated as frequently or almost always having problems with sleepiness during the daytime by their parent and 23 children (15.4%) were rated as moderately to markedly hyperactive (Score of 66 or above) on the Conners Hyperactivity Index. Of 37 subjects with an RDI in the upper quartile (Median RDI 9.71) only 3 were rated as sleepy. These 3 subjects constituted 33% of all sleepy subjects and 8.1% of high RDI subjects. Of this upper quartile of the RDI distribution 8 subjects were rated as hyperactive (constituting 34.8% of hyperactive subjects and 21.6% of high RDI subjects). Two subjects overall were perceived as both sleepy and hyperactive, but no subjects in the upper part of the RDI distribution were rated as both sleepy and hyperactive. A subject was more likely to be rated as hyperactive if their RDI was in the upper quartile of the distribution (odds ratio: 1.76, CI .673-4.59). Children who were rated as hyperactive also had significantly more problems falling asleep during the day than those rated as not hyperactive ( $t=7.86$ ,  $p=.006$ ,  $df 1,137$ ). Finally, the correlations between hyperactivity and sleepiness were non-significant in the general sample ( $r =.001$ ) and non-significant for those in the upper quartile of RDI ( $r =.019$ ).

**Conclusions:** Children with high RDIs were not perceived as both excessively sleepy and hyperactive. The hyperactive subjects actually had more difficulty falling asleep during the day, none were rated as having problems with sleepiness by a parent, and sleepiness and hyperactivity were not significantly

correlated. When a child had an RDI in the upper quartile of the distribution, they were more likely to be rated as hyperactive. Prevalence estimates of ADHD in the childhood population range from 3-5% (1). These data provide tentative support for the hypothesis that hyperactivity may be more commonly associated with SDB than sleepiness in children. However, there are various causes of hyperactive behavior and sleepiness. The relationships between SDB, sleepiness, and hyperactivity merit additional attention in longitudinal prospective research, particularly as they relate to age and severity of SDB.

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Research supported by HL62373

### 111.J

#### ACTIGRAPHIC MEASUREMENTS OF SLEEP AND ACTIVITY DURING SLEEP IN CHILDREN WITH SLEEP DISORDERED BREATHING

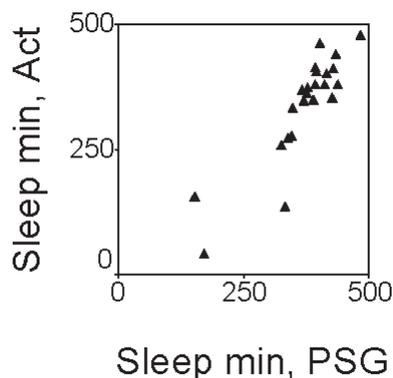
Suratt PM,<sup>1</sup> Nikova M,<sup>1</sup> D'Andrea L<sup>1</sup>

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**Introduction:** Actigraphy (ACT) accurately measures sleep time in normal children but its accuracy in sleep disordered breathing (SDB) is unknown. It is also not known whether ACT indices of movement during the sleep period correlate with the degree of SDB. We therefore compared ACT measurements to polysomnographic (PSG) measurements in children with suspected SDB.

**Methods:** Twenty four children suspected of having sleep apnea, ages 6-12, had simultaneous polysomnography and ACT. We used a Mini Motionlogger actigraph (Ambulatory Monitoring Inc.) with 1-minute recording bins, zero crossing mode and amplifier setting of 18. PSG was performed with standard methods including EEG, EOG and EMG, nasal flow with nasal pressure, chest and abdominal plethysmography and oximetry. Statistical analysis was performed with non-parametric tests.

Figure 1



**Results:** There was a significant correlation between PSG and Act sleep time ( $r = 0.78$ ,  $p < 0.001$ ). PSG sleep time was higher than ACT sleep time (mean difference = 47 min + 80 SD,  $p < 0.01$ ). ACT mean activity/min, % of epochs with activity  $> 1$ , and mean duration of wake episodes were weakly correlated with AHI in all subjects ( $r = 0.34$ ,  $p < 0.02$ ,  $r = 0.30$ ,  $p < 0.05$  and  $r = 0.30$ ,  $p < 0.05$ ).

**Conclusions:** In children with SDB, actigraphy is a simple method of approximating sleep time though it tends to underestimate it. Actigraphic measures of activity during sleep are too variable to detect SDB in individual subjects.

Research supported by HL62401

### 112.J

#### PHYSICAL EXAM FINDINGS IN CHILDREN SCHEDULED FOR ADENOTONSILLECTOMY COMPARED TO CONTROLS AND THEIR RELATIONSHIP TO THE PRESENCE OF SLEEP-DISORDERED BREATHING

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**Introduction:** Adenotonsillectomy (AT) is frequently performed in children to treat obstructive breathing symptoms, including sleep-disordered breathing (SDB). (1) The presence of certain physical exam characteristics is one of the factors used to determine the likelihood any given patient has SDB, thus supporting surgical intervention. SDB in children has been associated specifically with enlarged tonsils as well as several other craniofacial features. An improved understanding of the relationship between preoperative exam findings and the presence and degree of SDB would help identify those patients most at risk for the disorder.

**Methods:** Sixty nine (69) children aged 5 to 12 years scheduled for adenotonsillectomy (AT, n=60) or other non-airway procedures (non-AT, n=9) entered our protocol. These children were examined preoperatively for the presence or absence of several head and neck exam findings including long face, open bite deformity, overbite, overjet, enlarged tongue, high arched hard palate, long soft palate, hyponasalality, Body Mass Index, and allergy. In addition, tonsil size was graded on a 1-4 scale, and the patients were examined for an abnormal Mallampati score (1-3 scale). All patients underwent preoperative polysomnography (PSG) with the following outcome variables being calculated: pediatric obstructive apnea index (pedoai), pediatric respiratory disturbance index (pedrdi - a combined measure of obstructive apneas, hypopneas, and respiratory event-related arousals all scored by pediatric criteria), minimum oxygen saturation (minO2), ASDA-defined arousal index (eega), and periodic leg movement index (plm).

**Results:** The AT group differed from the non-AT group with respect to four of the twelve traits (Table 1). Three of these four measures comparing the AT vs. non-AT groups reached statistical significance using the two-tailed Fisher's exact test (Table 2). Linear regression models were then constructed to explain the variability in PSG outcome measures as determined by eight of the preop findings. The results of the multivariate analysis showed that the two most robust models are as

follows: (1.)  $\text{minO}_2 = 95.5 - 2.36(\text{tonsil}) + 5.54(\text{overbite})$ . SE(1.12,2.08) and  $p(0.04,0.01)$  respectively (2.)  $\ln(\text{pedrdi}) = 1.27 + 0.82(\text{tonsil})$ . SE=0.68 and  $p=0.07$

**Table 1**

Clinical characteristics in each group

Finding	AT subjects		non-AT subjects	
	n/total	%	n/total	%
long face	1/60	2%	0/9	0%
open bite	6/55	11%	1/9	11%
overbite	32/50	64%	4/7	57%
overjet	30/50	60%	5/7	71%
large tongue	0/60	0%	0/9	0%
high hard palate*	18/60	30%	0/9	0%
long soft palate	0/60	0%	0/9	0%
Hyponasality*	40/60	67%	8/9	0%
Allergy	24/60	40%	4/9	44%
enlarged tonsils*	56/60	93%	1/9	11%
Abnormal Mallampati score*	15/60	25%	8/9	89%

\* denotes difference between groups ( $\alpha \leq 0.10$ )

**Table 2**

P-values for significant findings in AT group vs. non-AT group

Finding	Two-tailed Fisher's Exact Test
high hard palate	0.099
hyponasality	1.77E-04
enlarged tonsils	5.02E-07
abnormal Mallampati score	4.12E-04

**Conclusions:** Tonsillar size is the best physical correlate of the frequency of apneic events among children scheduled for AT or unrelated procedures. Surprisingly, overbite correlated with less severe oxygen desaturation, after controlling for tonsillar size. This raises the possibility that craniofacial changes in children with adenotonsillar enlargement may be adaptive and helpful, rather than harmful. In any case, these types of correlations may be helpful clinically in determining the possible presence of SDB in children with adenotonsillar enlargement. These data may be an important step in the hypothesis that the extent of SDB in children with adenotonsillar enlargement can be identified clinically, and would thus be one criterion with which to base decisions regarding treatment (adenotonsillectomy).

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**113.J**

**SCHOOL PERFORMANCE, RACE, AND SYMPTOMS OF SLEEP-DISORDERED BREATHING**

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**Introduction:** Sleep-disordered breathing (SDB) in children may impair cognition and school performance.<sup>1</sup> Both SDB and poor performance are more common among African-American (AA) children than among their peers. However, the extent to which an increased prevalence of SDB might account for poor performance among AA children is unknown, and potential confounding factors, such as socio-economic status (SES), have not been well studied.

**Methods:** We surveyed parents of 2nd and 5th grade students at the six elementary schools of an urban public school district (Ypsilanti, MI). Student performance was assessed by teachers' Likert-scale ratings and by year-end district-wide reading and math assessments. Risk for SDB was assessed with the validated parental Pediatric Sleep Questionnaire,<sup>3</sup> and socio-economic status (SES) was assessed by qualification for a school lunch assistance program.

**Results:** A total of 146 completed surveys represented an 18% yield, which was excellent in comparison to previous surveys in this highly urbanized environment. Key variables are summarized in Table 1. The variables AA race, low SES, and SDB risk were each strongly associated with each other ( $p < 0.01$ ). Regression models showed that AA race and low SES were associated with poor assessment scores and teacher-rated performance ( $p < 0.01$ ); risk for SDB was associated with poor teacher-rated performance ( $p < 0.01$ , Table 2). In multiple regression models, low SES and AA race, but not SDB risk, were independently associated with poor assessment scores ( $p < 0.01$ ). Only low SES was independently associated with poor teacher-rated performance ( $p < 0.01$ ).

**Table 1**

Subject demographics

	All subjects (n = 146)
Age	9.3 ± 1.6
No. (%) Male	58 (40)
No. (%) AA	61 (42)
No. (%) Low SES	63 (43)
No. (%) Low Perf	25 (17)
Benchmark Score	63 ± 19

**Table 2**

Logistic regressions of poor teacher-rated performance on African-American (AA) race, sleep-related breathing disorder (SDB) symptom score (normalized), and low socioeconomic status (lunch assistance): beta coefficients, standard errors, tests of significance, and odds ratios are shown. \*

	Beta	s.e.	p-value	OR
AA race	1.28	0.48	0.0081	3.58
SDB score	0.56	0.20	0.0048	1.75
Low SES	2.94	0.68	≤ 0.0001	18.95

\* All models adjusted for grade level

**Conclusions:** The SDB symptoms, AA race, and low SES all vary with poor school performance, but the only variable independently associated with both assessment scores and teacher-rated performance is SES. Increased SDB is therefore unlikely to account directly for the relatively poor school performance in AA children. Limitations of this study included the survey return rate, but this would affect individual variables more than associations between them. Future studies of SDB and performance should account for SES.

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## 114.J

### DECLINE IN HEALTH-RELATED FUNCTIONAL STATUS WITH SLEEP-DISORDERED BREATHING IN CHILDREN

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(1) Case Western Reserve University,

**Introduction:** In adults, sleep-disordered breathing (SDB) is associated with impaired quality of life, especially decreases in vitality and physical functioning as measured by a health-related quality of life tool, the SF-36 (1). Similar assessments have not been performed in large samples of children. In this study, we assessed whether mild SDB, including snoring or an elevated apnea hypopnea index (AHI), would be associated with decreases in health-related functional status in a population-based non-clinical sample of children.

**Methods:** Participants (n=758; ages 8-11 years) in the Children's Sleep and Health Study (CSHS) were selected from a stratified random sample of term and preterm children born in Cleveland between 1988-1993. SDB was assessed with overnight in-home cardiorespiratory monitoring with meas-

ures of pulse oximetry, estimated tidal volume, thoracic and abdominal excursions, ECG, and body position (SensorMedics). The AHI included obstructive apneas regardless of associated desaturation and hypopneas with 3% desaturations. Respiratory events ≥ 8 seconds long were scored, representing two missed respiratory cycles for an average respiratory rate of 16 breaths/min in this age group. Children who reported loud snoring more than once a week were considered habitual snorers. Snoring children or children with AHI ≥ 5 events/hour were considered to have SDB. Measures of health-related functional status were derived from standardized inventories, including the Connors Parent Rating Scale (CPRS), Child Behavior Checklist (CBCL) and parent version of the 50 item Child Health Questionnaire (CHQ). Data are reported as adjusted least square means, adjusting for age, sex, ethnicity, prematurity, and asthma.

**Results:** The mean age was 8.9 ± .8 yrs, with 50% female, 48% former preterm, and 36% minority children. Twenty children (3%) had an AHI ≥ 5, while 110 children (15%) snored habitually with an AHI < 5. Compared to children without SDB, children with any SDB (snoring or elevated AHI), had reduced scores in the overall Physical Health Summary of the CHQ (adjusted means, 51.0 vs. 53.3, p = .001) and in the General Health domain of the CHQ (67.2 vs. 71.9, p = .003), and elevated problem scores on the Somatic scale (complaints of dizziness, tiredness and other physical problems with no known medical cause) of the CBCL (1.9 vs. 1.3, p = .0015), and on the Psychosomatic Scale (stomachache, aches and pains, headaches, and the appearance of tiredness) on the CPRS (adjusted means, 2.4 vs. 1.9, p = .0226).

**Conclusions:** In this community sample, small but significant differences in overall physical health, general health, and physical complaints were observed in children with generally mild levels of SDB (snorers or those with AHI ≥ 5). Whether snoring and mild SDB are causally related to these effects requires further study. More work is needed to assess the impact of SDB on functional outcomes in more severely affected children.

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**Poster Symposium  
Sleep Deprivation:  
Behavioral Effects and Their Predictors**

**115.I****DISSOCIATION OF TRAIT-DEPENDENT SUBJECTIVE AND OBJECTIVE ALERTNESS DURING EXTENDED WAKEFULNESS**

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**Introduction:** The similarity of the temporal pattern of alterations in subjective and objective alertness during extended wakefulness has led to the implicit assumption that their respective degrees of impairment are quantitatively correlated and that individuals who feel subjectively more sleepy are also more cognitively impaired. The reproducibility for a given subject of decrements of subjective and objective alertness across a night of sleep deprivation has never been evaluated yet and the relationship between the subjective report of increased sleepiness and the objective deficit in performance has not been examined. Therefore, this study investigates the individual reproducibility of alterations of subjective, objective and EEG measures of alertness during 27 hours of continuous wakefulness and analyzes their interrelationships.

**Methods:** Eight subjects were each studied on two occasions, separated by several weeks, under the same conditions involving constant bedrest, light intensity and caloric intake under the form of an intravenous glucose infusion. Computerized performance tasks and a paper and pencil scale were administered at hourly intervals to define temporal changes in objective and subjective alertness. Recordings of the EEGs were performed every two hours, 2 minutes with eyes open and 2 minutes with eyes closed. Plasma glucose and melatonin levels were measured to estimate brain glucose utilization and individual circadian phase, respectively.

**Results:** Decrements of subjective alertness and deficits of cognitive performance were found to be highly reproducible for a given individual. The minimum score of alertness and the longest response times on the first night of sleep deprivation predicted with high accuracy the level of subjective and objective impairment on a second night awake several weeks later. Remarkably, there was no relationship between the impairments of subjective and objective alertness and some subjects reported extreme levels of subjective sleepiness despite minimal impairment of performance. With increased duration of wakefulness, EEG activity with eyes closed increased in the delta range and decreased in the alpha range but the magnitudes of these changes were also unrelated.

**Conclusions:** These findings indicate that sleep deprivation has highly reproducible, but independent, effects on brain mechanisms controlling subjective and objective alertness.

**116.I****TOPOGRAPHICAL DIFFERENCES IN SWA REBOUND AFTER ACUTE SLEEP DEPRIVATION IN THE MIDDLE YEARS OF LIFE**

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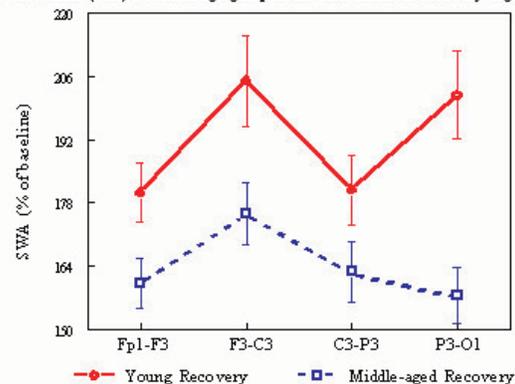
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**Introduction:** We have recently shown that compared to the young, middle-aged subjects show a reduced rebound of slow-wave activity (SWA: spectral power between 0.5 Hz and 4.5 Hz in N-REM sleep) in C3 following acute sleep deprivation(1). Studies have reported that the effects of a 40-hour sleep deprivation on SWA varies along the antero-posterior axis, predominantly in frontal regions of the brain (2). In addition, compared to the middle-aged, young subjects show more SWA particularly in anterior derivations of the brain in the first two N-REM periods of the night (3). The aim of this study was to evaluate age-related modifications in SWA rebound along the antero-posterior axis during recovery sleep following a 25-hour sleep deprivation. We hypothesised that the difference between young and middle-aged subjects in SWA rebound following sleep deprivation would be greater in the more anterior derivations of the brain.

**Methods:** Thirty-nine subjects were studied. They were separated into two groups according to their age: young (17 subjects, 25-39 y, 9W, 8M) and middle-aged (22 subjects, 40-60 y, 6 pre-menopausal W, 7 post-menopausal W, 9M). All subjects came to the sleep laboratory for 4 consecutive nights and 2 days. Baseline sleep was recorded on the third night. Following the third night, subjects were put in a mini-constant routine for 25 hours. The recuperative sleep episode started the morning after the 25 hours of sleep deprivation. EEG power spectra from Fp1-F3, F3-C3, C3-P3 and P3-O1 bipolar derivations were computed. A two-way factorial ANOVA on the pourcentage of baseline SWA activity of the average first three N-REM periods of recovery night, with one group factor (age) and one repeated factor (4 derivations), was used to analyze the effect of age group, sleep deprivation, and derivation on SWA (Huynh-Feldt correction was used). Contrast analyses were used to decompose the interaction effects.

**Figure 1**

SWA means (sem) for each age group in all derivations at recovery night



**Results:** The results revealed a significant interaction between age group, and derivation ( $p=0.018$ ). Figure 1 illustrates mean SWA (% of baseline) for all derivations in both groups of subjects. Contrast analysis showed that compared to the young, middle-aged subjects showed a reduced rebound of SWA in Fp1-F3 ( $p=0.025$ ), F3-C3 ( $p=0.017$ ) and P3-O1 ( $p=0.0003$ ). The rebound of SWA in C3-P3 did not differ between the two age groups.

**Conclusions:** To our knowledge, this is the first demonstration that there are topographical differences in the response of SWA to acute sleep deprivation with increasing age. As predicted, compared to the young, the rebound of SWA following sleep deprivation was less pronounced in the middle-aged subjects in the most anterior derivations of the brain. Unexpectedly, young and middle-aged subjects also showed an important difference in SWA rebound in the most posterior derivation. These results suggest that the response of SWA to an increase in the number of hours of wakefulness is attenuated in older subjects in anterior and posterior regions of the brain.

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**117.I HIGH SCHOOL START TIMES AND TEEN AUTO ACCIDENTS**

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**Introduction:** Driving while drowsy is a serious traffic safety problem, especially among young drivers (1,2). It is also clear that early school start times contribute to the endemic sleepiness of adolescents. Therefore, it is possible that a delay in high school start times might result in a reduction in auto accident rates for teen drivers. The following is a test of this hypothesis in one large county-wide school district. In the Fall of 1998, this district changed high school start times from 7:30 AM to 8:30 AM. In the year following this change, students averaged up to 50 minutes more sleep per weekday night (3). If one can presume that this additional sleep promoted daytime alertness, then this benefit might show up in auto accident statistics.

**Methods:** The state of Kentucky keeps detailed auto collision statistics, by age and residence of driver. By combining this data with auto license records, it was possible to compute crash rates per 1000 licensed drivers for drivers aged 16, 17, and 18. Separate rates were computed for the county that changed high school start times and for the state as a whole (with the county data excluded). Crash rates were computed

for the two years prior to the school start change (1996 and 1997) and the two years following (1999 and 2000). Results are presented with 16 year olds included and excluded because Kentucky instituted a graduated drivers license program in 1996 that severely restricts 16 year olds' driving privileges. For their first six months, 16 year olds may not drive after midnight and must have a licensed adult in the car with them at all times. These restrictions have resulted in a considerable decrease in crashes among 16 year olds but have not influenced crash rates for older drivers.

**Results:** 1.In the county, crash rates dropped for ages 16 (22.1%), 17 (7.6%) and 18 (23%).2.In the rest of the state, crash rates dropped for age 16 (13.8%) but increased for ages 17 (6.2%) and 18 (12%).3.Considering only 17 and 18 year old drivers with unrestricted privileges, the county crash rates dropped 15.6% while the rest of the state increased by 8.9%.

Figure 1

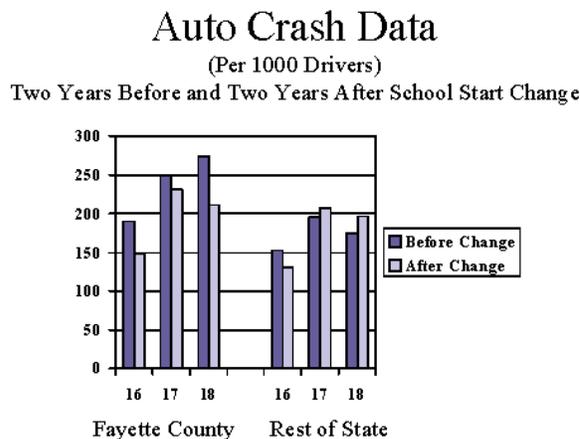
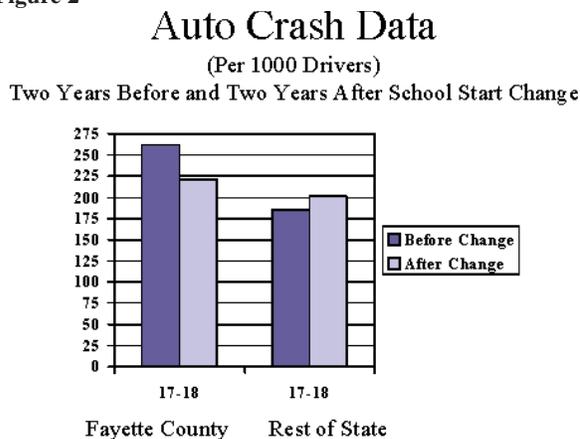


Figure 2



**Conclusions:** Moving the high school start time one hour later in a single county was associated with a drop in auto collision rates for high school aged drivers in that county while crash rates increased in the rest of the state during the same time period. While one cannot make any cause and effect statements with a simple association, these data are consistent with the idea that allowing adolescents to sleep more has a measurable effect on their safety.

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**118.U**

**NAPPING IN THE WORKPLACE: WHAT ARE THE IMPLICATIONS FOR SLEEP LENGTH AND STRUCTURE?**

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**Introduction:** Laboratory studies have provided information suggesting that short (~1 hour) naps during the night shift are effective in maintaining or improving the alertness and performance of individuals [1,2]. However, the effectiveness of a nap depends on the quantity and quality of sleep individuals obtain. A workplace nap is taken under very different conditions from sleep in laboratory studies, which could result in significantly different sleep structure and duration. From a work-based study of air traffic controllers (ATCs), findings are presented here on the length and structure of sleep obtained during napping opportunities provided on night shifts.

**Methods:** Twenty-eight operational ATCs (mean age = 35.5 years, 19 males and 9 females) wore an ambulatory Embla device that recorded polysomnographic data during 2 night shifts. At either 0030 or 0230 participants were provided with a 40-minute napping opportunity. Two experienced sleep scorers viewed the polysomnographic data from the nap opportunity and scored it according to standard criteria [3]. Differences in sleep outcomes according to the timing of the napping opportunity were examined using mixed model analyses. These models controlled for length of prior wakefulness, level of acute sleep debt (both estimated from actigraphy and sleep logs) and the order of the napping condition.

**Results:** The total amount of nap sleep obtained by participants varied widely from 0 minutes through to 47 minutes, with a mean of 17.7 minutes (SD = 12.2, N = 54). Five individuals on five separate occasions did not sleep at all. Amongst those who did sleep, the mean latency to the first minute of sleep was 19.4 minutes (SD = 10.5, Range = 2 - 46.8, N = 48). This resulted in a mean sleep efficiency (across the total time allowed for the nap) of 41% (SD = 27.3, Range = 0 - 94.9, N = 54). Table 1 presents details on the duration and percentage of the nap occupied by the sleep stages 1-3 and Figure 1 shows a histogram of the structure of a typical sleep seen during the study. The only sleep variable that differed with the timing of the nap was the occurrence of stage 3 sleep,

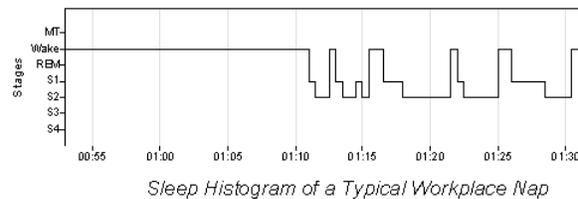
which was more likely to be seen during the later naps,  $F(1,37.5) = 7.35, p = .010$ .

**Table 1**

*Average Time Spent in Sleep Stages 1-3 During Nap.*

Sleep stage	Average duration (minutes)	
	Across all nap opportunities	Across naps which include sleep stage
1	5 (2.9)	
2	12.8 (8.5)	14.6 (7.4, N = 43)
3	1.4 (3.7)	3.5 (5.2, N = 20)

**Figure 1**



**Conclusions:** The findings of this study indicate that individuals napping at work take much longer to fall asleep, obtain less sleep and only occasionally enter the deeper stages of sleep compared to laboratory based studies of sleep opportunities of a similar duration [1,2]. Without further research to determine whether short, light and relatively poor quality sleep improves performance and alertness, care needs to be taken when applying laboratory findings on napping to workplace situations.

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TUESDAY, JUNE 11, 2002

119.I

**VISUAL NEGLECT IN SLEEP DEPRIVED AIR FORCE PILOTS IN A SIMULATED 12-HOUR FLIGHT**

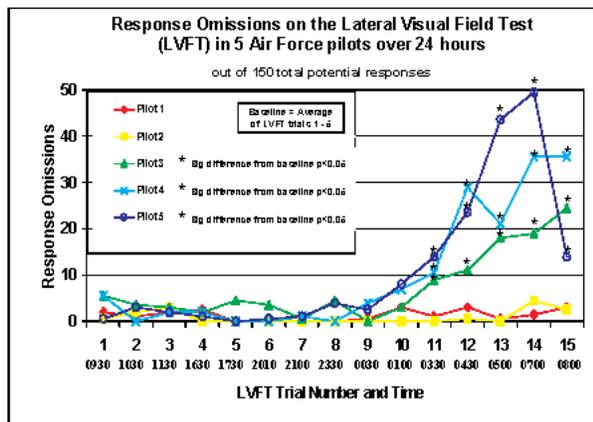
Russo MB,<sup>1</sup> Escolas S,<sup>1</sup> Santiago S,<sup>1</sup> Thomas ML,<sup>3</sup> Sing HC,<sup>1</sup> Thorne DR,<sup>1</sup> Holland D,<sup>1</sup> Johnson DE,<sup>2</sup> Redmond DP,<sup>1</sup> Hall SW

(1) Walter Reed Army Institute for Research, (2) U.S. Air Force Office of Scientific Research, (3) L-3 Com Flight Simulators Division,

**Introduction:** In two earlier sleep deprivation studies, we reported finding impairments in a visual divided attention task (Thorne et al, 1999). Based upon fdg-PET studies showing cerebral glucose hypometabolism at 24 hours of sleep deprivation (Thomas et al, 2000) we hypothesized that these impairments of visual awareness could occur prior to 24 hours and could represent a sleep deprivation-induced transient metabolic equivalent of Balint's syndrome (Russo et al, 1999). Subsequently, we conducted a sleep deprivation study to assess characteristic features of Balint's syndrome. We implemented a visual field task (LVFT) designed to assess awareness of visual stimuli during cognitive loading, and tested U.S. Air Force pilots in an Air Re-fueling Partial Task Trainer (ARPTT - C141 cargo jet) simulator. In this abstract we report preliminary findings of the LVFT in 24 hours of continuous sleep deprivation.

**Methods:** Five male pilots between the ages of 25 and 50 were studied, two were instructor pilots, all were pre-certified on the ARPTT. On study Day 1 the subjects trained on the LVFT, and received 6 hours of time-in-bed overnight. On Day 2 subjects remained active throughout a 12-hour day then simulated a 12-hour overnight flight. The 20 minute LVFT presented 150 sequential single or double light stimuli, each 0.5 second duration at semi-random intervals while the pilot maintained a position approximately 50 feet behind and below the fuel-containing tanker jet. Stimuli spanned 75-degrees left through 75-degrees right of center at 15-degree intervals just below the simulated horizon and against a black background. Responses by the pilot to the stimuli were verbal. 15 LVFT sessions were conducted during Day 2.

Figure 1



**Results:** When compared to baseline (LVFT #1-5, averaged), the combined performance (five pilots) on the LVFT showed significant response omissions to stimuli beginning in LVFT #14, at approximately 25 hours of sleep deprivation (paired t-test, p<.05) and persisting. Three pilots accounted for all of the significant changes, which began at LVFT #11, after approximately 21.5 hours of sleep deprivation (paired t-test, p<0.05), while the two instructor pilots showed no significant changes, possibly reflecting their increased familiarity with the ARPTT. Several types of errors were combined for analysis.

**Conclusions:** Impairments in responses to LVFT visual stimuli presented along the horizontal meridian began after about 21.5 hours of sleep deprivation in three pilots, and at 25 hours in five pilots. These preliminary findings support our hypothesis that transient visual performance impairments similar to those seen in Balint's syndrome may occur with less than 24 hours of sleep deprivation and are exacerbated by circadian effects.

**References:**

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**Research supported by U.S. Army Medical Research and Materiel Command and U.S. Air Force - Special thanks to Greg Lounsberry, Walter Reed Army Institute of Research**

120.I

**EFFECTS OF COGNITIVE DEMANDS ON CEREBRAL RESPONSE TO TOTAL SLEEP DEPRIVATION**

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**Introduction:** We recently reported the brain can adapt during cognitive performance of certain tasks following total sleep deprivation (TSD)[1]. Adaptation manifested as recruitment of additional brain regions during task performance following TSD that were not involved (or as involved) after normal sleep, particularly regions within the bilateral fronto-parietal working memory system. This pattern was seen during verbal learning and a divided attention task containing a verbal learning component, but not arithmetic[2]. One potential explanation for this task-specific difference is that the brain's ability to adapt depends on the cognitive demands placed on the brain[2]. It may be that language-processing tasks more readily elicit adaptation than working memory tasks. Here we test this hypothesis by examining the effects of sleep deprivation on brain function during language-processing and arithmetic working memory tasks.

**Methods:** Baddeley's Logical Reasoning (LR) and serial subtraction (MATH) were examined. Each task contained 4 conditions: resting baseline and 3 levels of task difficulty (2, 3, & 4 letter sentences and -1,-3,-7, respectively). Seven adults (4M, age: 32.3 ±6.2 years, education 15.1 ±2.2 years) performed each task twice: after normal sleep and following a mean of 35.5hrs TSD, each while undergoing fMRI (TR=2.5s, 28 axial slices, 4mm resolution, 171 repetitions, run time=427.5s). A block design alternated among three 20-sec rest periods and 12 30-sec activation periods. Analysis consisted of motion coregistration, cross-correlation with a shifted reference function, and 4mm Gaussian spatial smoothing. Significant activation was determined with cluster thresholding. Analyses identified regions responding to increasing difficulty in task demands and examined within- and between-night effects. One subject fell asleep during one TSD scan and was removed from analyses involving that night.

**Table 1**

Logical Reasoning	
Condition	Region of Activation
Normal Sleep	B. Premotor Area (BA6)
	B. Superior Parietal Lobes (BA7)
	R. Inferior Parietal Lobe (BA40)
	B. Visual Association Cortex (BA18/19)
TSD	L. Middle Frontal Gyrus (BA10)
	R. Middle/Superior Frontal Gyri (BA6/8)
	B. Medial/Middle/Superior Frontal Gyri (BA 6/8/9/32)
	L. Anterior Cingulate (BA24/32)
	B. Basal Ganglia/Thalamus
	L. Superior/Middle Temporal Gyri (BA21/22)
	R. Middle/Inferior Temporal Gyri (BA37)
	B. Superior/Inferior Parietal Lobes (BA7/39/40)
	B. Visual Association Cortex (BA18/19)

B=bilateral; L=left; R=right; BA=Brodmann's Area

**Table 2**

Arithmetic	
Condition	Region of Activation
Normal Sleep	B. Inferior Frontal Gyrus (BA47)
	L. Middle/Inferior Frontal Gyri (BA46/45)
	L. Anterior Cingulate/Medial Frontal Gyri (BA32/6)
	L. Premotor Area (BA6)
	L. Thalamus/Caudate/Lenticular Nucleus
	L. Inferior Temporal Gyrus (BA37)
	B. Inferior Parietal Lobes (BA40)
	L. Precuneus (BA7)
	L. Lingual Gyrus (BA18)
	TSD
B. Anterior Cingulate/Medial Frontal Gyri (BA32/6)	
L. Middle Frontal Gyrus (BA8/9)	
B. Premotor Area (BA6)	
L. Middle/Inferior Temporal Gyri (BA21/37)	
L. Inferior Parietal Lobe (BA40)	
L. Superior Parietal/Middle Occipital Gyri (BA7/19)	
R. Superior/Inferior Parietal Lobes (BA7/40)	

**Results:** On LR, 4-ltr sentences produced the worst performance within each night and declined after TSD vs. normal sleep. MATH showed expected differences within nights, but accuracy on -7 actually increased after TSD. Tables show brain responses elicited by each task on each night. After normal sleep, increasing difficulty on the LR task activated spatial working memory and visual association regions. Following TSD, LR activated these regions plus bilateral prefrontal cortex (PFC), striatal-thalamic, and temporal regions. Regions responding to LR task demands to a significantly greater degree after TSD included left PFC, bilateral language processing areas, and right parietal cortex. For MATH, brain responses to task demands were similar after both normal sleep and TSD.

**Conclusions:** LR elicited an adaptive response following TSD that is largely consistent with that previously reported[1,2]. That is, bilateral fronto-parietal regions showed increased response following TSD compared to normal sleep. MATH, on the other hand, elicited essentially identical responses under both conditions. This is contrary to our previous report of deactivation during MATH following TSD[3] and may relate to increased performance seen here with TSD. Overall the results are preliminarily consistent with the cognitive-demand specific hypothesis of cerebral adaptation[2] in that language processing elicited cerebral adaptation while working memory did not.

**References:**

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**Research supported by SMERF #01-01-01 (SPAD); T32 MH18399; M01 RR00827**

**121.I**

**REPEATED EXPOSURE TO TOTAL SLEEP DEPRIVATION: SUBSTANTIAL TRAIT DIFFERENCES IN PERFORMANCE IMPAIRMENT AMONG SUBJECTS**

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**Introduction:** Neurobehavioral performance deficits during total sleep deprivation (TSD) differ considerably among subjects. These inter-individual differences have generally been treated as stochastic error variance, but their apparent consistency suggests that trait-like variability may be involved [1]. We designed a study to quantify the trait component of inter-individual differences in vulnerability to performance impairment from sleep loss.

**Methods:** As part of a larger, ongoing study, n=10 normal, healthy subjects (ages 23-38; 4 females) each completed two laboratory-based TSD sessions, at intervals of 2-4 weeks. The study protocols for the two sessions were identical, and involved 36 hours (from 10:00 until 22:00 the next day) of behaviorally monitored TSD in a controlled, isolated laboratory environment with fixed ambient temperature (21°C) and

light (<50lux). Every 4 hours, subjects received a standardized meal. Every 2 hours, they were tested on a 1-hour neurobehavioral performance battery, which included a 20-minute psychomotor vigilance task (PVT). On the 7 days preceding each of the two TSD sessions, subjects were scheduled to sleep 12 hours (time in bed 22:00-10:00) in order to satiate the need for sleep before TSD, and they were not allowed to use any alcohol, caffeine, tobacco or drugs. Compliance was verified by means of actigraphy and a diary, and subjects called the laboratory to report their bedtimes. The last of the 12-hour sleep periods preceding TSD was spent inside the laboratory and was recorded polysomnographically. Each of the two TSD sessions was followed by a 12-hour recovery sleep opportunity. Two weeks prior to the actual experiment, subjects adapted to the experimental procedures in a 29-hour adaptation session in the laboratory.

**Results:** The number of PVT performance lapses ( $RT > 500ms$ ) during sleep loss, averaged over the night (22:00-08:00) as well as over the subsequent day (10:00-20:00), was subjected to random-effects analysis of variance (ANOVA) to separate between-subjects variance from within-subjects variance (maximum likelihood estimates). The intra-class correlation (ICC) was then computed to quantify the trait variance (as a fraction of total variance) of vulnerability to performance impairment from sleep loss. We found  $ICC = 0.42$  for the night, and this increased to  $ICC = 0.70$  for the subsequent day ( $F[9,9] = 7.96$ ;  $P = 0.003$ ). When average PVT lapses were expressed as percentage of baseline average (10:00-20:00 at the beginning of TSD), the ICC values remained essentially the same (0.45 and 0.72 for night and day, respectively).

**Conclusions:** Up to 70% of the variance in psychomotor vigilance performance deficits during laboratory-controlled TSD resulted from substantial, trait-like inter-individual differences in vulnerability. The increase of the ICC from the nighttime to the subsequent daytime period of sleep loss suggested that TSD progressively exposed the trait-like inter-individual differences in vulnerability, and/or that there was a circadian modulation of these inter-individual differences. The trait component of vulnerability will be further quantified at the completion of the study, involving 14 additional subjects and many more neurobehavioral performance measures to be analyzed.

#### References:

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Research supported by NASA grant NAG9-1161 and NIH grant RR00040

### 122.I

#### EFFECT OF PARADOXICAL SLEEP DEPRIVATION DURING EARLY PREGNANCY ON PUP'S ANXIETY STATE: A PILOT STUDY.

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**Introduction:** It is known that prenatal stress induces high

anxiety like behaviour in offspring (1). It is also known that the small platform technique used to deprive animals from paradoxical sleep (PS) is stressful. We evaluated whether PS deprivation (PSD) in pregnant female rats was associated with measures of trait and state anxiety in offspring. In order to clarify whether anxiety measures were due to the stressful technique or to PSD itself, we also measured anxiety using a larger, equally stressful, platform size.

**Methods:** We studied 14 rats (7 males, 7 females) born from two PSD mothers and eight rats (4 males, 4 females) born from a control mother. The PSD platform was 10 cm<sup>2</sup>/100 g body weight while the surface of the control platform was 100cm<sup>2</sup>/100g (2). Mothers were exposed to their respective platform for four hours a day, upon the first 10 days of pregnancy, starting at the beginning of the light period (8h00), after which they were returned to their individual home cage. Half the offspring was tested on postnatal day 34 in either one of two anxiety tasks : the emergence or the elevated-plus maze test. The first consists of a small dark box positioned in a large lighted open field; the dependant measure is the time needed by animal to exit the dark box. The other test consist of a pair of orthogonal alleys, one with walls and one without. The time spent in each was measured. Results were compared using Mann-Whitney U-tests.

Figure 1

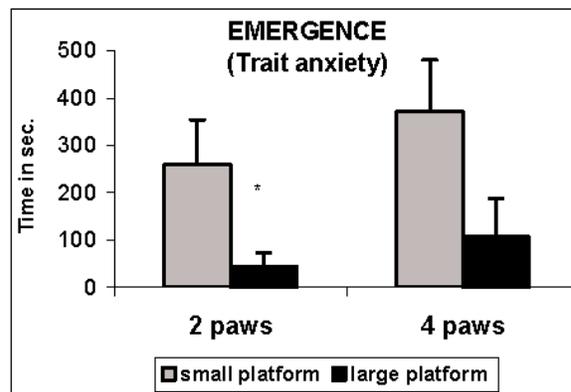
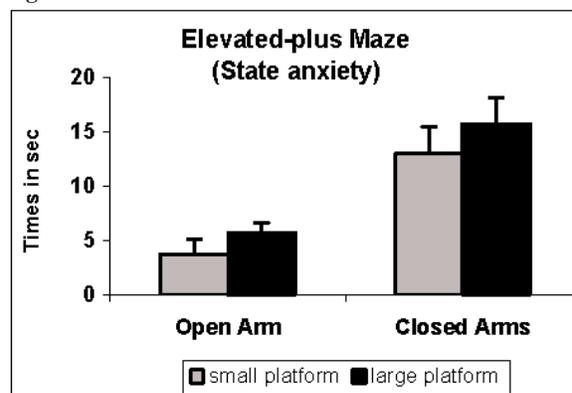


Figure 2



**Results:** Rats from PSD mothers took more time than controls to exit from the dark box (latency) using for the two paws cri-

terion ( $259.9 \pm 94.0$  vs  $45.3 \pm 27.9$ ,  $p < .05$ ) as well as the 4 paws criterion ( $372.1 \pm 107.3$  vs  $106.5 \pm 81.4$ ,  $p < .05$ ). There was no significant difference between groups in the elevated-plus maze.

**Conclusions:** Offspring from PSD mothers showed increased trait anxiety measures but were not different from controls on state anxiety. Whether this difference is associated to CNS alterations induced at the fetal stage or to altered maternal care needs to be determined.

**References:**

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### 123.I

#### NEUROBEHAVIORAL PERFORMANCE DEFICITS DURING TOTAL SLEEP DEPRIVATION: EFFECTS OF SLEEP/WAKE HISTORY AND PRIOR EXPOSURE TO TOTAL SLEEP DEPRIVATION

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**Introduction:** An experiment was designed to determine the influence of recent sleep/wake history on the magnitude of neurobehavioral performance impairment during total sleep deprivation (TSD).

**Methods:** As part of an ongoing study to be completed on 24 subjects,  $n=9$  healthy subjects (ages  $29.4 \pm 5.5$ ; 4 females) participated in three laboratory-based TSD sessions, at intervals of 2 weeks, after having first completed a laboratory-based adaptation session. The study protocols for the three experimental sessions were identical, and involved 36h (from 10:00 until 22:00 the next day) of behaviorally monitored TSD in a controlled, isolated laboratory environment where standardized meals were provided every 4h. Subjects were tested every 2h on a 60min neurobehavioral performance battery, which included a 20min psychomotor vigilance task (PVT). Sleep/wake history was manipulated on the 7 days preceding each of the three TSD sessions: Subjects were given either 6h TIB (04:00-10:00) or 12h TIB (22:00-10:00). They were not allowed to use any alcohol, caffeine, tobacco or drugs. Compliance was verified by means of actigraphy and a diary, and subjects called the laboratory to report their bedtimes. The last of the 6h or 12h TIB periods preceding TSD was spent inside the laboratory and recorded with PSG. Each subject underwent the 6h sleep history condition once and the 12h sleep history condition twice. The order of conditions was randomized across the three experimental sessions such that a third of the subjects had the 6h-12h-12h order; a third had the 12h-6h-12h

order; and a third had the 12h-12h-6h order.

**Results:** The number of performance lapses ( $RT > 500$ ms) on the PVT, administered every 2h across the 36h TSD, was averaged for each subsequent 12h wakefulness interval. Next, the 6h sleep history condition was compared with the first of the two 12h sleep history conditions using repeated-measures analysis of variance (ANOVA) for wakefulness interval (3 levels) by condition (2 levels: 6h vs. 12h sleep history), with order of conditions as between-subjects factor. A main effect of wakefulness interval was found ( $F[2,12]=44.7$ ;  $P < 0.001$ ), indicating that performance degraded significantly as TSD progressed. A significant sleep history condition by order interaction was observed ( $F[2,6]=8.3$ ;  $P=0.019$ ), revealing that neurobehavioral performance impairment during TSD increased over subsequent exposures to TSD, with a relatively small non-linear influence of sleep/wake history. Finally, there was a trend for a main effect of condition ( $F[1,6]=5.6$ ;  $P=0.056$ ), suggesting that performance during TSD was more impaired after the 6h than after the 12h sleep history condition.

**Conclusions:** The preliminary result of increasing levels of neurobehavioral performance deficits across repeated exposures to TSD suggests that prior exposure to TSD (at least within two weeks) can sensitize subjects to subsequent TSD regardless of sleep/wake history. The influence of sleep/wake history (6h vs. 12h TIB for 7 days) on neurobehavioral performance during TSD was comparatively small, but this effect may increase as more subjects are studied.

**Research supported by NASA grant NAG9-1161 and NIH grant RR00040**

### 124.I

#### EPIDEMIOLOGY AND MORBIDITY OF EXCESSIVE DAYTIME SLEEPINESS

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**Introduction:** Although the National Commission on Sleep Disorders Research has identified excessive daytime sleepiness (EDS) as a major public health problem (1), little representative, population-based information regarding the prevalence, consequences, and risk factors for EDS exists. Due to the imprecise nature of self-reported daytime sleepiness (2), research investigating these questions requires combining the rigorous sampling, field assessment, and recruitment methods of epidemiological research with the standardization of controlled laboratory procedures. Therefore, the present study assessed physiological sleep tendency on the Multiple Sleep Latency Test (MSLT) in a representative sample of the U.S. population and examined the relationship between EDS and major behavioral and health-related morbidity.

**Methods:** Thus far, 1648 individuals randomly selected from the general population have been assessed for general sleep habits and excessive daytime sleepiness (Epworth sleepiness scale; ESS). Response rate = 68%. Prevalence of EDS was determined in the laboratory from a randomly selected subsample ( $n = 157$ ). In addition, all subjectively sleepy individuals were recruited for laboratory participation ( $n = 114$ ) in

order to increase the sample size for the study of causes and consequences of EDS. The 24-hr laboratory protocol included an overnight polysomnogram (8.5-hr PSG), daytime MSLT, and a variety of performance measures (Psychomotor Vigilance Task, divided attention, auditory vigilance). In addition, self-report data on motor vehicle accidents was concomitantly collected. The total sample (N = 271) was divided into "EDS"(MSLT<6), "borderline"(MSLT6-10), and "alert"(MSLT>10) groups based on data from previous studies. Performance measures were divided into quartiles. Data were analyzed using parametric (ANOVA) and non-parametric (Kruskal-Wallis) methods where appropriate.

Figure 1

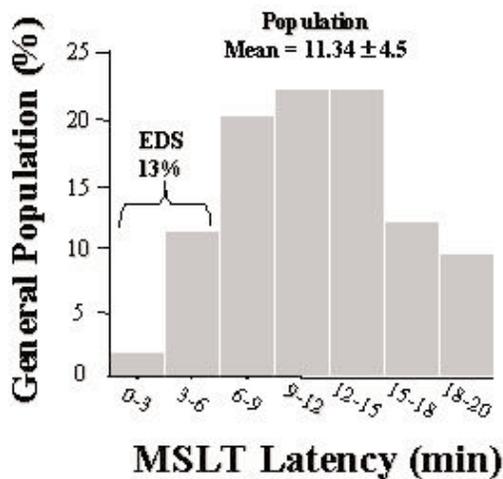


Table 1

PSG	MSLT < 6	MSLT 6-10	MSLT >10
Sleep Eff.*	90.37 ± 6.30	87.57 ± 9.20	83.24 ± 11.42
Latency*	11.74 ± 22.97	12.28 ± 13.03	19.95 ± 21.57
Stage 1 %	11.46 ± 5.45	11.53 ± 7.67	12.99 ± 10.69
Stage 2 %	58.34 ± 8.16	58.37 ± 7.97	58.45 ± 9.47
SWS %	8.51 ± 7.75	11.21 ± 7.67	11.87 ± 7.64
REM %*	21.67 ± 8.22	18.83 ± 6.23	16.63 ± 6.03
MSLT*	4.05 ± 1.29	8.45 ± 1.48	14.78 ± 2.62
Epworth*	9.58 ± 4.44	10.28 ± 4.52	8.46 ± 4.18
TST(diary)*	7.42 ± 1.12	7.58 ± 1.12	7.98 ± 1.12

\* p < .05

**Results:** The prevalence of EDS (MSLT <6) was 13.4% in the randomly selected laboratory sample (Figure). EDS subjects had significantly higher sleep efficiencies on the laboratory PSG  $F(2,247) = 9.88, p = .001$ , and shorter nightly self-reported time-in-bed (Table, 2-week diary)  $F(2,254) = 5.44, p = .005$ , in comparison to alert individuals (Table). Borderline sleepy individuals were midway between the other groups on these measures. In terms of morbidity measures, participants with EDS reported a greater prevalence of "dozing off while driving" (49%) compared with the alert group (35%) (K-W,  $p = .01$ ). When performance quartiles were assessed, poor performance on the PVT (lapses) and divided attention (lapses) was associated with lower MSLT latency  $F(3, 260) = 4.58, p = .004$ ;  $F(3, 264) = 2.94, p = .03$ , respectively.

**Conclusions:** EDS (13%) appears to be substantial in the gen-

eral population. Moreover, the higher PSG sleep efficiency and lower habitual time-in-bed in individuals with EDS suggest that much of this sleepiness can be traced to voluntary curtailment of sleep. Moreover, the association of poor performance with decreased alertness as well as the higher prevalence of "driving while sleepy" in EDS subjects, suggests that EDS poses a potential hazard for motor vehicle and other sleepiness-related accidents in a substantial percentage of the general population. In future analyses, state-reported motor vehicle accidents will be compared as additional data are collected in this epidemiological/laboratory sample.

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**125.I**

**SLEEP PHYSIOLOGY FOLLOWING 88H TOTAL SLEEP DEPRIVATION: EFFECTS OF RECOVERY SLEEP DURATION**

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**Introduction:** Following one or more nights of total sleep deprivation (TSD), selective enhancement of REM and slow-wave sleep (SWS) has been reported during recovery sleep (1). However, few studies have examined sleep physiology across multiple recovery nights and with different durations. This study examined the first 7h of sleep physiology across 3 nights of recovery with 7h vs. 14h TIB following 88h TSD.

**Methods:** N=26 healthy males (21-39yr) lived in the sleep laboratory for 10-days. Following 3 baseline nights (8h TIB), subjects remained awake for 88h, followed by 3 recovery nights. From 22 to 88h of waking, subjects were randomized (double-blind) to receive hourly caffeine (0.3mg/kg/hr; n=14) or placebo (n=12). Subjects were further randomized to two 7h TIB recovery nights followed by one night of 14h TIB (n=14) or three 14h TIB recovery nights (n=12). Lights-out for all nights was 2330h. Baseline night (BL) 2 PSG was used for comparison to recovery night PSGs. Data were analyzed using mixed-model ANOVA (drug by recovery sleep duration by day). This abstract focuses on PSGs from the first 7h of each recovery sleep period (R1, R2, R3).

**Results:** Caffeine versus placebo yielded no statistically significant main effects or interactions for sleep latency (SL), latency to stages 3 (S3) and 4 (S4), sleep efficiency (SE), amount of stage 2 (S2), SWS, and WASO. In contrast, days (BL, R1, R2, R3) and recovery TIB (7h vs. 14h) influenced all variables. SL, latency to S3 and S4 were shortened on R1 relative to baseline, and progressively lengthened from R1 to R3 ( $p < 0.05$ ). Amount of stage 1 (S1) was markedly reduced on R1

relative to baseline, and progressively increased from R1 to R3 ( $p=0.008$ ). S2 was shortened on R1 relative to baseline, and remained reduced from R1 to R3 ( $p<0.001$ ). Interactions between recovery TIB and days were found for SE ( $p=0.002$ ), WASO ( $p=0.001$ ), SWS ( $p=0.037$ ), and REM ( $p=0.005$ ). SE was not different between 7h and 14h conditions on R1, but was elevated in the 7h condition on R2 ( $p=0.007$ ) and R3 ( $p=0.012$ ). WASO showed the same profile as SE, but was higher in the 14h condition relative to the 7h condition on R2 ( $p=0.004$ ) and R3 ( $p=0.032$ ). SWS showed a unique interaction profile ( $p=0.037$ ) – a 79% increase on R1 relative to baseline, but significantly more SWS in the first 7h of the 14h condition than the 7h condition on R1 ( $p=0.019$ ). REM sleep was the only variable with a complex 3-way interaction with drug condition, recovery sleep condition and days.

**Conclusions:** 88h TSD was a greater factor in altering recovery sleep physiology than 66h sustained low-dose caffeine. Nearly every PSG variable was affected on R1 and to a lesser extent on R2. Providing 14h TIB relative to 7h TIB recovery resulted in reduced homeostatic drive for sleep being evident in the first 7h of sleep on subsequent nights. However, the 14h TIB condition also produced significantly more SWS on R1. Since only the first 7h TIB on all nights was analyzed, which involved the same times of day, this latter result suggests that knowledge of recovery sleep time markedly influenced SWS in the first 7h TIB. To the best of our knowledge, this is a completely new finding that raises provocative questions regarding a possible role for cognition/expectation in recovery sleep physiology.

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**Oral Presentation**  
**Prevalence of Sleep and Sleep Disorders**

**126.L****PREVALENCE OF INSOMNIA IN THE GENERAL POPULATION OF FINLAND***Ohayon MM,<sup>1</sup> Partinen M<sup>1</sup>*

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**Introduction:** The prevalence of insomnia symptoms has been set between 10% and 40% in the European countries depending on the time frame assessed and the methodology used (1). However, other factors can be responsible of such variations. This study assess the prevalence of insomnia symptoms and insomnia disorders in the general population of Finland.

**Methods:** 982 participants representative of the general population of Finland were interviewed by telephone using the Sleep-EVAL system (2). The minimum age for the participation in the study was set to 18 years old. The sample was drawn according to a two-stage sampling design. The participation rate was 78%. To achieve this participation rate, the initial refusers were called a second time at least three weeks later unless the individuals stressed on the first phone contact that they do not wish to be called again. The questionnaire included the assessment of sleep habits, insomnia symptomatology according to DSM-IV classification, associated and sleep/mental disorders and daytime consequences.

**Results:** Overall, 37.6% of the subjects reported insomnia complaints at least three nights per week. Difficulty initiating sleep (DIS) at least 3 evenings per week were mentioned by 11.9% of the sample, difficulty maintaining sleep (DMS) at least 3 nights per week by 31.6%, early morning awakenings (EMA) at least 3 times per week by 11.0% and non-restorative sleep (NRS) at least three nights per week by 7.9% of the sample. Overall, 43.6% of participants with insomnia symptoms also reported being excessively sleepy during the daytime. Prevalence of any DSM-IV insomnia diagnosis was 11.7% (95% confidence interval: 9.7% to 13.7%). Primary insomnia had a prevalence of 1.6% and insomnia related to another mental disorder was at 2.1% in this sample. Use of sleep promoting medication was reported by 9.4% of the sample.

**Conclusions:** Insomnia is widespread in Finland: close a third of participants reported at least one insomnia symptoms occurring 3 nights per week or more. The prevalence of DSM-IV insomnia diagnosis is higher than the rates observed in other European countries studied with the same methodology (1). The consequences are important: about 40% of individuals with insomnia symptoms had also an excessive daytime sleepiness. Appropriate recognition and treatment of insomnia should be part of an educational program for general practitioners everywhere.

**References:**

(1) Ohayon MM. Epidemiology of Insomnia: What We Know and What We Still Need to Learn. *Sleep Medicine Review*. 2002: In press.

(2) Ohayon MM. Improving decision making processes with the fuzzy logic approach in the epidemiology of sleep disorders. *J Psychosom Res* 1999;47:297-311.

**Research supported by an unrestricted educational grant from Sanofi-Synthelabo Group**

**127.L****INSOMNIA DETERMINANTS IN SOUTH KOREA***Hong CS,<sup>1</sup> Ohayon MM<sup>1</sup>*

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**Introduction:** Insomnia can be caused or maintained by various life habits, physical and mental diseases[1]. Few studies attempted to determine the relative importance of these different factors in relationship to difficulty initiating or maintaining sleep or non-restorative sleep in the general population. This study examines the determinants of insomnia symptoms using a representative sample of South Korea.

**Methods:** A representative sample of the South Korean general population aged 15 years or older(37.4 million inhabitants) composed of 3,719 individuals were interviewed by telephone using the Sleep-EVAL system[2]. The participation rate was 91.4%. Participants were interviewed about their sleep habits and sleep symptomatology. The average duration of interview was 37.07 minutes. Measures in this report included socio-demographic characteristics; consumption of alcohol, tobacco and caffeine; physical activities; physical illnesses, perception of health quality; life stress; sleeping habits; sleep duration and sleep latency

**Results:** 17.0% of the sample reported insomnia symptoms occurring at least 3 nights per week: 4.0% of the sample reported having difficulty initiating sleep(DIS) at least 3 evenings per week; 11.5% had difficulty maintaining sleep(DMS) at last 3 nights per week; 1.8% reported early morning awakenings(EMA) at least 3 times per week and 4.7% of the sample mentioned non-restorative sleep (NRS) at least three nights per week. Most important factors associated with DIS were: being aged between 35 and 44 years(odds ratio: 2.6); having a very stressful life(OR: 2.7); being dissatisfied with his/her social life(OR: 2.9) and having a physical disease(OR: 3.2). Most important factors associated with DMS were being widowed(OR:2.4); having a poor health(OR:3.0); eating before going to sleep(OR:1.6); and having a physical disease(OR:2.9). Most important factors associated with EMA were being older than 55 years of age(OR:14.6); alcohol abuse(OR:2.0); having a poor health(OR:4.5); Finally, most important factors associated with NRS were being a shift worker(OR:2.8); alcohol abuse(OR:2.0); having a very stressful life(OR:3.1); being dissatisfied with his/her social life(OR:2.8) and having a poor health(OR:2.9).

**Conclusions:** This study confirms the high frequency of insomnia symptoms in South Korea that is as important as in North America and European countries. The prevalence of insomnia symptoms had little variation between gender and

age groups. The results clearly show that health and psychological status are two important determinants for insomnia

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- (1) Ohayon MM. Epidemiology of Insomnia: What we know and what we still need to learn. *Sleep Medicine Review*. 2002: In press.
- (2) Ohayon MM. Improving decision making processes with the fuzzy logic approach in the epidemiology of sleep disorders. *J Psychosom Res* 1999;47:297-311

**Research supported by an unrestricted educational grant from Sanofi-Synthelabo Korea**

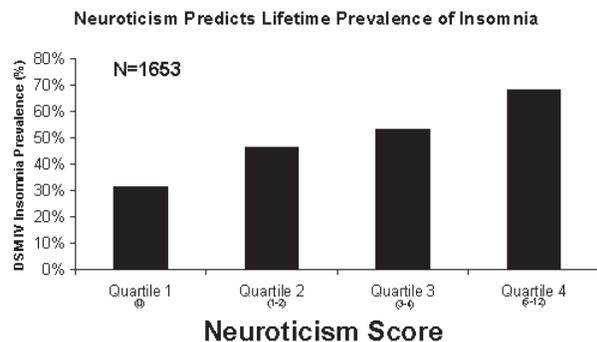
**128.L  
NEUROTICISM PREDICTS LIFETIME PREVALENCE OF INSOMNIA**

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**Introduction:** Previous studies have looked at the relationship between personality and insomnia in clinical samples. However, no studies have examined the extent to which normal personality characteristics relate to insomnia in the general population. Measures of neuroticism are related to individual vulnerability to stress (1). As insomnia is often elicited in response to stress (2), we hypothesized that trait-neuroticism may increase the likelihood of developing insomnia. Thus, the present study assessed the relationship between neuroticism (3) and the prevalence of insomnia in a population-based sample.

**Methods:** A total of 1653 individuals were assessed for neuroticism and lifetime prevalence of DSM-IV defined insomnia. Individuals were randomly selected from the population by random-digit-dialing and were given a phone interview regarding sleep habits and personality. Neuroticism scores were divided into quartiles for the total sample and insomnia prevalence (% positive) was assessed in each quartile using Pearson Chi-Square. The relationship between degree of neuroticism and severity of insomnia in affected individuals was also examined. Finally, in a subset of individuals who were studied in the laboratory (n = 271), the association of neuroticism and nocturnal polysomnographic variables was assessed.

**Figure 1**



**Results:** Individuals who scored higher in neuroticism showed a higher prevalence of insomnia, Chi-Square ( $p < .05$ ) (Figure). Among individuals who endorsed insomnia (N=811), higher neuroticism scores were associated with more severe insomnia  $r = .28, p < .001$ . In the laboratory sample (N = 256), high neuroticism scores were associated with lower sleep efficiency  $r = -.17, p = .006$ , increased latency to persistent sleep  $r = .14, p = .02$ , and higher percentage of stage 1 sleep  $r = .14, p = .02$ .

**Conclusions:** The present results suggest the possibility that particular personality traits, specifically neuroticism, may put individuals at risk for clinically significant insomnia. While significant, the small amount of variance accounted for by neuroticism, suggests it is unlikely to play a major etiological role in the development of insomnia.

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**129.U  
DO SURVEYS PRODUCE ACCURATE DATA REGARDING HIGH SCHOOL STUDENTS' SLEEP PATTERNS?**

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**Introduction:** Large-scale studies reporting adolescent sleep patterns typically rely on survey self-report, and the accuracy of these measures is rarely questioned. Such field measures as actigraphy provide more objective assessment. This study compares high school students' survey descriptions of their usual sleep habits with actigraphically-estimated sleep behavior over a subsequent week.

**Methods:** Grade 9 - 12 students (195 girls and 105 boys, ages 13.8-19.9 yr (M=16.0)), recruited from 5 high schools completed a Sleep Habits Survey (2) about the previous 2 weeks and then wore an actigraph (AMI, Ardsley, NY) for 8 days while keeping a daily sleep diary. Actigraph data were analyzed with sleep diaries to estimate sleep using Action-W software (AMI) and a validated algorithm (1). Survey variables were total sleep time (TST), bedtime (BT), and rise time (RT), and actigraph variables were sleep period (SP = sleep onset to sleep offset), sleep onset (time of first consolidated sleep after bedtime), and sleep offset (time of last consolidated sleep before rise time). Effects of sex and grade level were assessed

using MANOVA. Survey versus actigraph variables were compared using Pearson correlations and difference scores.

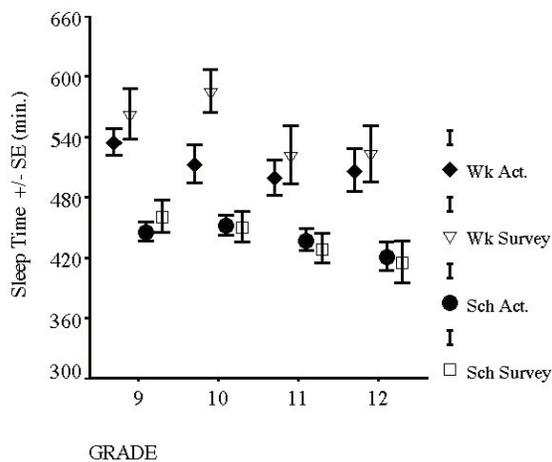
**Results:** Group means for school-night survey and actigraph measures of sleep were similar (Table 1). Also, they were strongly correlated ( $r$ 's  $> .77$ ,  $p$ 's = .000). For weekend-nights, survey reports indicated significantly longer TST and later RT than actigraphy. School-night survey and actigraph variables were affected by grade ( $F$ 's  $\geq 5.38$ ,  $p$ 's  $< .001$ ). Survey TST and actigraph SP decreased from grades 9 – 12 (Figure) by approximately 25 minutes ( $p$ 's  $< .05$ ), BT and sleep onset were about 50 minutes later, and RT and sleep offset about 25 minutes later ( $p$ 's  $< .001$ ). Weekend survey TST and actigraph SP decreased and BT/onset times became later over the 4 years ( $F$ 's  $> 3.25$ ,  $p$ 's  $< .001$ ); weekend RT/offset times did not change. No sex differences were noted for actigraph sleep; however, females reported on the survey rising about 10 min. earlier, and sleeping 20 min. less on school-nights ( $p$ 's  $< .01$ ). We examined difference scores between survey and actigraph variables to evaluate individual differences. 70% of students' survey reports of their school-night TST were within 60 minutes of their SP (BT/onset: 58%, RT/offset: 92%). In contrast, 43% of students reported weekend-night sleep habits to within 60 minutes of actigraphic sleep parameters.

Table 1

	SCHOOL-NT		WEEKEND-NT	
	M	SD	M	SD
Survey Total Sleep (min.)	440	73	549	114
Actig Sleep Period (min.)	440	48	514*	76
Survey Bedtime	22:46	:59	24:17	1:27
Actig Onset Time	22:59	:59	24:11	1:19
Survey Rise Time	6:20	:34	9:40	1:31
Actig Offset Time	6:18	:32	8:43*	1:18

\*  $p < .001$

Figure 1



**Conclusions:** These data support previous surveys showing short school-night sleep in high school students and confirms such survey reports with actigraphy. Larger discrepancies for weekends may reflect greater variability of weekend sleep schedules and the relative unreliability of actigraphy for 2 nights of data. Thus, survey data provide reasonable estimates of sleep patterns for group data; however, actigraphy over several nights gives a more precise estimate of an individual's sleep behavior at one point in time.

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**Oral Presentation**  
**Forebrain Mechanisms of Sleep Regulation**

**130.A**

**THE VENTROLATERAL PREOPTIC AREA: ROLE AND ORIGIN OF CHOLINERGIC AFFERENTS IN THE CONTROL OF WAKEFULNESS AND PENILE ERECTIONS**

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**Introduction:** Sleep active neurons in the ventrolateral preoptic nucleus (VLPO) likely play a role in sleep generation through reciprocal inhibitory interactions with structures involved in generating wakefulness. GABAergic VLPO neurons are inhibited by acetylcholine *in vitro* (1), suggesting that acetylcholine may promote wakefulness by inhibiting sleep active VLPO neurons. Our prior work demonstrates that the lateral preoptic area (LPOA) also is essential for generating penile erections during paradoxical sleep (PS). Recent collaborative work using single unit recording demonstrates the presence of cholinergic neurons in the laterodorsal tegmental nucleus (LDT) that are selectively active during PS-related erections (2). In the following study, carbachol (cholinergic agonist) was iontophoretically administered into the VLPO to test the hypothesis that acetylcholine may promote both wakefulness and penile erections. In addition, the retrograde tracer cholera toxin B-subunit (CT-b) was co-injected, and double staining with choline acetyltransferase (ChAT) was performed to identify the source of all cholinergic inputs to the VLPO.

**Methods:** Carbachol or normal saline was iontophoretically administered for 15 minutes into the VLPO or surrounding preoptic areas from a multibarrel pipette assembly in 6 awake, head-restrained, rats while recording sleep-wake states and penile erections. CT-b was iontophoretically injected from an adjacent barrel of the micropipette assembly at the end of the experiment to identify the injection sites. Cholinergic afferents to the VLPO were identified using CT-b and ChAT double-immunohistochemistry.

WEDNESDAY, JUNE 12, 2002

**Results:** Iontophoretic carbachol administration into the VLPO increased wakefulness 162% relative to saline administration ( $p < 0.001$ ). Carbachol also induced erections with consistently short latencies. During 45 minute bouts, penile erections increased from 1.5 per hour (saline) to over 10 per hour following carbachol ( $p < 0.001$ ). Similar carbachol injections into the medial preoptic area, rostral, caudal, or lateral to the VLPO were not effective in generating erections or wakefulness. Immunohistochemistry revealed CT-b injection sites to be within the VLPO or adjacent LPOA. An analysis of cholinergic afferents to the VLPO demonstrated that double labeled cells (CT-b+ and ChAT+) were only identified in the mesopontine LDT. No double labeled cells were found in basal forebrain cholinergic structures just adjacent to the VLPO.

**Conclusions:** These data suggest that acetylcholine release into the VLPO generates wakefulness and penile erections, and that the mesopontine LDT is the only source for this cholinergic control. Since acetylcholine inhibits VLPO GABAergic neurons *in vitro* (1), acetylcholine may promote wakefulness by inhibiting sleep-active VLPO neurons. A separate set of VLPO neurons are excited by carbachol *in vitro* (1), while LPOA neurons in close proximity to the VLPO increase activity specifically during PS (3). We hypothesize that LPOA PS-on neurons may play a role in generating PS-related erections. We further hypothesize that our finding of increased wakefulness and penile erections following carbachol administration into the VLPO may be secondary to a simultaneous and non-specific interaction of this cholinergic agonist with both cell types.

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### 131.A

#### INFLUENCE OF CONTEXTUAL FEAR ON SLEEP ARCHITECTURE IN MICE: VARIABILITY AMONGST STRAINS

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**Introduction:** We previously demonstrated that a fear-conditioned auditory tone (cue) associated with shock produced alterations in sleep similar to those produced by shock itself (1). In contextual fear, animals display a fearful response when returned to the chamber in which they have received shock (2). Because of the relative non-specificity of the stimulus information associated with the shock context, contextual fear may model chronic anxiety, whereas cued fear, in which shock is linked to a specific stimulus, may better model fearful responses (3). In this study, we examined the effect of re-exposure to a fear-conditioned context on subsequent sleep in mouse strains that are differentially responsive on behavioral tests of anxiety.

**Methods:** Two inbred strains (C57BL/6J (B6), n=8; BALB/cJ (C), n=8) and their F1 hybrid (CB6F1/J (CB6), n=8) were used in this study. The mice were intraperitoneally implanted with

transmitters (DataSciences ETA10-F20) for recording sleep via telemetry. Behavioral state was visually scored based on EEG and activity. After baseline sleep recording sessions, the mice were trained to associate a context (shock chamber) with footshock (15 shocks on 4 consecutive days, conducted between 0800 to 0900 h). Five days after the last shock training session, the animals were returned to shock chamber (no shock given) and allowed to freely explore for 25 min immediately prior to 1100 h. They were then returned to their home cages. Sleep was examined after shock training and after exposure to the shock context alone.

**Results:** Shock training selectively suppressed REM in mice compared to time matched baseline recordings. The suppression of REM was relatively greater in the reactive C and the F1 hybrid strains compared to the less reactive B6 strain. Post-training exposure to the context alone (Table 1) suppressed REM in much the same manner as exposure to the foot shock with the CB6 hybrid mice exhibiting greater alterations in sleep and a greater suppression of REM.

**Table 1**

Sleep parameters during 4 h of baseline and following exposure to fear conditioned context.

	Total NREM	Total REM	REM Episodes
<b>B6</b>			
Baseline	137.0 (3.0)	15.9 (0.7)	11.1 (0.5)
Context	138.5 (4.4)	13.8 (1.1)**	9.0 (0.7)*
<b>C</b>			
Baseline	134.1 (4.9)	11.6 (1.3)	9.1 (0.9)
Context	131.2 (7.9)	8.4 (1.2)**	6.5 (0.1)*
<b>CB6</b>			
Baseline	141.9 (6.0)	18.9 (1.4)	12.5 (0.7)
Context	109.4 (12.3)*	10.7 (1.4)**	7.9 (0.9)**

\*,  $p < .05$ ; \*\*,  $p < .01$

**Conclusions:** Both shock training and re-exposure to the fear-conditioned context produced significant alterations in electrophysiologically defined sleep that varied across mouse strains. As with explicitly cued fear conditioning, the greatest alterations were observed in REM. In addition, shock training and fear-conditioned contexts produced alterations in total sleep and NREM in the hybrid strain, which also showed the greatest alterations in both REM and NREM. These data demonstrate that contextual reminders of footshock can alter subsequent sleep, and that genetic factors are involved in the relative influence of contextual reminders on sleep. Examining differences in the processes involved in the influence of contextual and explicitly cued fear on sleep may contribute to an understanding the influence of anxiety and fear on sleep.

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Research supported by NIH grant MH61716.

### 132.A

#### NREM AND REM SLEEP RELATED NEURONS IN THE CENTRAL NUCLEUS OF THE AMYGDALA AND THEIR MODULATION BY DORSAL RAPHE STIMULATION IN RATS

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**Introduction:** There is ample evidence that the amygdala plays a vital role in the modulation of sleep mechanisms. Neurons with increased firing rate during NREM and REM sleep have been recorded in the amygdala. It has been reported that electrical stimulation of the central nucleus of the amygdala (Ace) during REM increases PGO wave frequency in cats and amplitude in rats<sup>2</sup>, and administration of serotonin directed at Ace induced state changes when injected in REM sleep but not NREM sleep<sup>3</sup>. The amygdala is heavily interconnected with brainstem nuclei involved in REM sleep control, including the serotonergic dorsal raphe nuclei (DRN)<sup>2</sup>. Which NREM and REM-related cells in Ace are modulated by serotonergic DRN neurons is not known. The present study was designed to investigate the role DRN plays in the modulation of NREM and REM-related cells in Ace.

**Methods:** Experiments were performed on male Sprague-Dawley rats (n= 4) weighing between 300-350 gm. Standard electrodes for the chronic recording of sleep and wakefulness, a microdrive holding 32 mm wires for single-cell recording in Ace (P 2.3, L 4.0, V 4.0) and bipolar stimulating electrode in DRN (P 7.8, L 0.0, V 6.2) were implanted aseptically under inhalation anesthesia. Once a well-discriminated, single unit (signal-to-noise ratio at least 3:1) was encountered, it was amplified and displayed on a TDS210 (Tektronix) oscilloscope and recorded through an ADC (CED 1401) interface with a computer. Neuronal firing was correlated with the different EEG states (at least two episodes of REM, NREM and wakefulness) The effect of DRN stimulation (200mA, 200ms, 1 Hz) on neuronal firing rate was ascertained by acquiring 10 overlapping-stimulus-bound responses. In addition, the effect on sleep-wake of this low frequency stimulation of DRN, presented for 1 hour was studied in three rats.

**Results:** A total of 15 neurons were recorded from Ace (confirmed histologically). Out of 15 neurons, 3 were NREM related, 3 were REM related and 9 were unrelated to sleep-wake state. Stimulation (200mA, 200ms, 1 Hz) of DRN inhibited a REM-ON type cell for 65 ms at a latency of 15 ms. Furthermore, continuous, low frequency stimulation of DRN significantly increased REM sleep (P< 0.05) as compared to the one-hour pre-stimulation period.

Table 1

Neurons	Frequency	
	W	NREM
NREM related	W	:- 0.41 (± 0.34)
	NREM	:- 1.3 (± 0.06) $\Psi^*$
	REM	:- 0.21 (± 0.05)
NREM related & REM-OFF type	W	:- 0.47 (± 0.07)
	NREM	:- 1.42 (± 0.08) $\Psi^{**}$
	REM	:- 0.25 (± 0.04) $\$^{**}$
NREM related & REM-OFF type	W	:- 0.26 (± 0.05)
	NREM	:- 1.24 (± 0.08) $\Psi^{**}$
	REM	:- 0.07 (± 0.02) $\$^{**}$
REM-ON type	W	:- 0.49 (± 0.05)
	NREM	:- 1.22 (± 0.08) $\Psi^*$
	REM	:- 1.88 (± 0.05) $\$^{**}$ #
REM-ON type	W	:- 0.09 (± 0.02)
	NREM	:- 0.1 (± 0.01)
	REM	:- 0.33 (± 0.03) $\$^{**}$ #
REM-ON type	W	:- 0.15 (± 0.05)
	NREM	:- 0.23 (± 0.08)
	REM	:- 1.35 (± 0.16) $\$^{**}$ # <sup>**</sup>

The state-related neurons recorded from Ace and their mean firing frequencies  $\pm$  S.E.M. Significance levels \* P< 0.05, \*\* P< 0.001 one way ANOVA are shown as compared to  $\Psi$  = W vs NREM,  $\$$  = W vs REM and # NREM vs REM.

**Conclusions:** These preliminary data confirm the presence of cell types related to behavioural state in Ace of rats. They also reveal that DRN stimulation can affect the REM-ON type of cells in Ace as well as behavioural state. We can not be certain that only serotonergic cells were activated by the DRN stimulation. An unexpected finding was that REM sleep was significantly increased during DRN stimulation with a trend towards a post-stimulation decrease in REM sleep.

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## 133.A

## NEURO-ANATOMICAL, -PHYSIOLOGICAL AND -PHARMACOLOGICAL CHARACTERISTICS OF HISTIDINE-DECARBOXYLASE KNOCKOUT MICE: ROLE OF BRAIN HISTAMINE IN BEHAVIORAL AND CORTICAL AROUSAL IN THE MOUSE

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**Introduction:** The hypothesis that histamine(HA)rgic neurons are involved in brain arousal has been supported by considerable experimental data(1). However, the effects of a selective and long-term abolition of HA neurons on sleep-wake cycle, which are indispensable to determine their functional role, remained unknown. We have, therefore, studied and compared the gene expression of histidine-decarboxylase (HDC, HA synthesizing enzyme) and brain HA immunoreactivity in wild-type (WT) and HDC-knockout (KO) mice as well as their cortical EEG and sleep-wake cycle under baseline condition or following behavioral or pharmacological stimuli.

**Methods:** 15 pairs of male adult WT (129Sv) and KO mice(2) were used in this study with multidisciplinary approaches, including polygraphic sleep-wake recordings and scoring, analysis of cortical EEG-power spectral density, detection of HDC gene with polymerase chain reaction (PCR), immunohistochemistry of HA, pharmacological administrations and behavioral tests, such as test of new environment, which consisted of housing mice from their habitual home cage (transparent barrel) to a new one (opaque rectangular box with open field).

**Results:** We found that KO mice presented an increase in paradoxical sleep (+23%/24h), a decrease in cortical EEG power spectral density at theta rhythm during waking (W) and a reduced ratio of cortical EEG power between slow wave sleep and W. Although no major quantitative change was noted with respect to the daily amount of spontaneous W, these mice presented a deficit of W just before and after lights-off and also clear signs of sedative behavior, as demonstrated by a significant decrease in sleep latencies following various behavioral stimuli. For example, housing KO mice in a new environment elicited no clear response in W as they fell asleep after a few min, while the same environmental change caused W for 2-3h in the WT mice (Fig. 1). Absence of HDC and so that of brain HA are likely to be responsible for the observed effects. Indeed, intraperitoneal injection of alpha-fluoromethylhistidine (50 mg/kg, specific inhibitor of HDC) caused a decrease in W in WT but not in KO mice and that of ciproxifan (1 mg/kg, HA-H3-receptor antagonist), which elicited W in WT mice, had no effect in KO mice. Furthermore, PCR and HA immunohistochemistry revealed absence of HDC gene and brain HA immunoreactive neurons in KO mice (Fig 2).

Figure 1

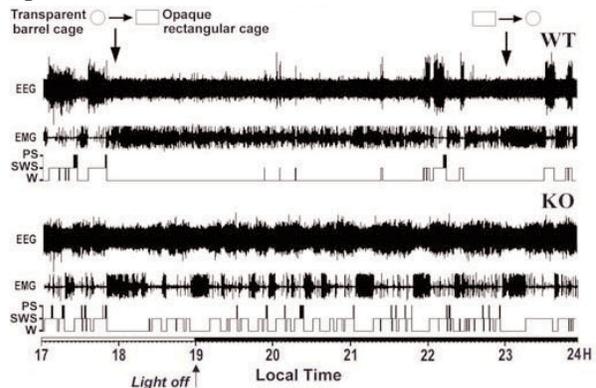
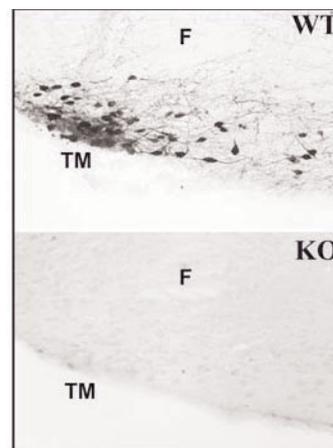


Figure 2



**Conclusions:** These data indicate that, disruption of HA synthesis causes permanent change in cortical EEG and sleep-wake cycle and suggest that at moments when a high vigilance is required, e.g., a lights-off period or environmental change, mice lacking brain HA are unable to maintain awake, a prerequisite condition for responding to behavioral and cognitive challenges. We suggest that, in addition to their importance in arousal under baseline condition(1), HA-neurons could also play a key role in maintaining the brain awake in the presence of behavioral challenges.

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Research supported by INSERM U480

## 134.A

## MANIPULATIONS OF THE NITRIC OXIDE/CGMP SYSTEM IN THE ANTERIOR DIENCEPHALIC REGION OF RATS AFFECTS SLEEP

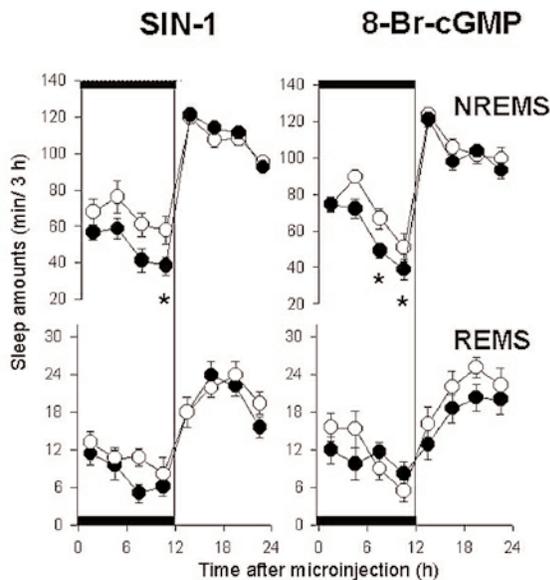
Ribeiro AC,<sup>1</sup> Kapas L<sup>1</sup>

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**Introduction:** The anterior diencephalic region, an area relatively rich in nitric oxide (NO) synthase-positive neurons, plays a role in sleep regulation. Preoptic levels of NO and cGMP exhibit diurnal variations and NOergic mechanisms in this region mediate complex behaviors, such as copulation in male rats. Intracerebroventricular injections of NO donors (1), NO synthase inhibitor (2) and 8-Br-cGMP (3) affect sleep in rats. To test whether the anterior diencephalic region could be a target for the sleep responses to NO, we studied the effects of microinjecting 3-morpholinosydnonimine (SIN-1), a NO donor; Nw-nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor; L-arginine ethyl ester and 8-Br-cGMP in the anterior diencephalic region on sleep in rats.

**Methods:** Male rats (250-300 g) were implanted with EEG and EMG electrodes, and a microinjection cannula targeted at the medial preoptic region. Sleep was recorded on 3 baseline days, on a test day [10 ng (n = 9), 1 ug (n = 9) or 10 ug (n = 8) of SIN-1, 0.4 ug of 8-Br-cGMP (n = 8)], and on 2 recovery days. In addition, 2 doses of L-NAME (n = 7) and L-arginine ethyl ester (n = 8) were tested (0.1 mg and 1.33 mg). All injections were performed at dark onset and the volume was 1 ul. Rapid-eye-movement sleep (REMS) and non-REMS (NREMS) amounts were determined as well as delta activity (0.5-4 Hz) of the EEG during NREMS, an indicator of NREMS intensity, and theta activity (4.5-8 Hz) during REMS.

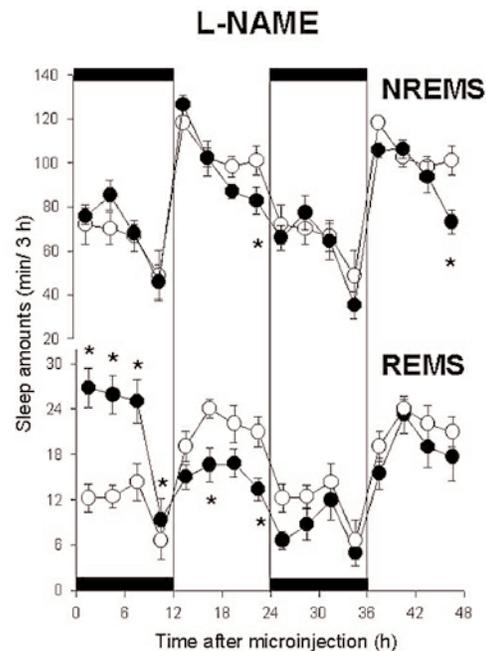
Figure 1



**Results:** The 10 ng dose of SIN-1 increased REMS amounts during the first 3 h on the test day and the first 6 h of the first

recovery day by 87% and 127%, respectively. One ug SIN-1 decreased NREMS amounts by 26% in the 12-h period following its administration. Ten ug SIN-1 did not affect sleep amounts. Intra-diencephalic injection of 8-Br-cGMP decreased NREMS amounts by 17% during the dark period immediately following the injection. L-NAME administration increased REMS by 70% during the dark period, followed by a negative rebound during the light period. L-arginine ethyl ester did not affect sleep amounts or intensities.

Figure 2



**Conclusions:** The present findings suggest that pharmacological manipulations of anterior diencephalic NOergic neurotransmission affect sleep in rats. Furthermore, the similarity of sleep effects observed following SIN-1 and 8-Br-cGMP support the hypothesis that the sleep-modulatory effects of NO in this brain region could be mediated by cGMP.

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**135.A****EFFECTS OF RESTRAINT STRESS ON SLEEP IN MICE LACKING THE H3 RECEPTOR**Laposky AD,<sup>1</sup> Koehl M,<sup>1</sup> Dugovic C,<sup>1</sup> Toyota H,<sup>1</sup> Lovenberg TW,<sup>2</sup> Turek FW<sup>2</sup>

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**Introduction:** Alterations in sleep patterns are associated with a number of conditions that challenge the hypothalamic-pituitary-adrenal (HPA) axis, including sleep deprivation, psychiatric illness and stress. For example, restraint stress in rats and mice is reliably followed by enhanced REM sleep as well as increased plasma levels of ACTH, corticosterone and prolactin. The histaminergic system, which has a demonstrated role in sleep/wake regulation, also influences the HPA-axis response to stress. The histamine (HA) synthesis inhibitor, alpha-fluoro methylhistidine and the H3 agonist, R-alpha methylhistidine (RmHA), reduce the prolactin, corticosterone and beta-endorphin response to restraint stress in rats by 30-80%. Recent data show that mice lacking the H3 receptor (H3<sup>-/-</sup>) have a 50% reduction in basal HA levels (unpublished data). In this study, we performed restraint stress and sleep recordings in H3<sup>-/-</sup> mice to test the hypothesis that the histaminergic system plays a role in sleep changes following restraint stress.

**Methods:** This study was performed on 7 mice (male, 30-35g) that harbor a targeted inactivation of the H3 receptor and 6 litter-mate controls (male, 30-35g) with a C57BL/6J background. Mice were maintained on a 12-h light:dark cycle (lights on 10:00) in temperature controlled (21±1C°) recording chambers. Electrodes for electroencephalography and electromyography were surgically implanted and following 2 weeks of recovery, mice were adapted for 4 days to the recording chamber. Restraint stress was performed for 1 hour (11:00-12:00) by enclosing animals in a plastic tube with a diameter of 3 cm. This procedure was immediately followed by 22-h of sleep-wake recording. In addition to restraint stress, a 1 hour (11:00-12:00) sleep deprivation session was performed using "gentle handling", followed by 22-h of sleep recording, to control for the sleep loss induced during restraint. Recordings were visually scored in 10-sec epochs for wake, NREM and REM and dependent t-tests were run to compare the change in sleep parameters between handling and stress procedure.

**Results:** Following restraint, wild-type mice had a 48% increase in REM%/recording time (t=6.30, p<.001) and 25% increase in REM%/total sleep time (t=7.11, p<.001) during the dark-phase (22:00-1000) compared to the control "gentle handling" procedure. REM percentages did not significantly change in H3<sup>-/-</sup> mice following restraint. In both groups, the number of REM bouts significantly increased during the dark-phase following restraint, whereas the duration of REM bouts increased for wild-type (t=2.70, p<.05) and decreased for H3<sup>-/-</sup> mice (t=-2.28, p<.06, NS). NREM latency increased in wild-type (t=2.81, p<.05) and H3<sup>-/-</sup> (t=3.83, p<.01) mice following restraint, whereas a dramatic increase in REM latency (occurred only in H3<sup>-/-</sup> mice (t=3.71, p<.01).

**Conclusions:** In response to 1-hr of restraint stress, wild-type

mice had significant increases in REM time and REM bout duration that did not occur in mice lacking the H3 receptor. In combination with previous data showing that histaminergic neurotransmission modulates the HPA-axis response to stress, our data indicate that HA may be involved in stress-related changes in sleep. One possibility is that reduced HA levels in H3<sup>-/-</sup> mice prevent corticosterone and prolactin increases following restraint, which may be necessary for increased REM in response to stress.

**References:**

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**Research supported by NIH grants R01-AG-18200 and R01-HL-59598.**

**136.A****THE SELECTIVE MGLU2/3 RECEPTOR AGONIST LY379268 SUPPRESSES REM SLEEP AND FAST EEG IN THE RAT**Feinberg I,<sup>1,2</sup> Campbell IG,<sup>1,2</sup> Schoepp DD<sup>1</sup>

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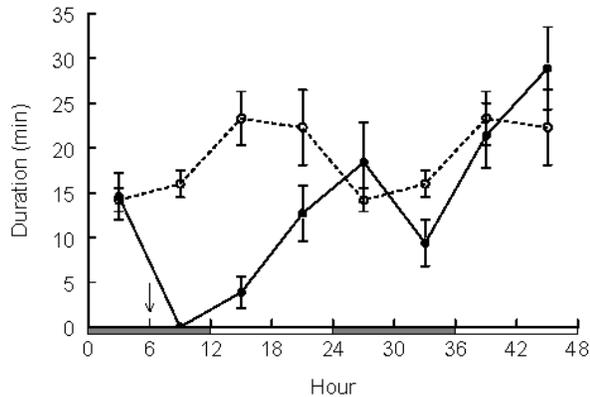
**Introduction:** Evidence for a significant role for glutamate neurotransmission in sleep regulation continues to accumulate. We have previously demonstrated that noncompetitive NMDA antagonists, which increase brain metabolism, produce a massive but delayed increase in NREM delta EEG intensity (1). CPPene, a competitive NMDA antagonist increases NREM but decreases delta intensity (2). Sleep states are relatively protracted. Therefore, it seemed likely that, in addition to the relatively short acting ionotropic glutamate receptors, glutamate receptors that control metabolic processes (mGluRs) might play an important role. It was already known that mGlu2/3 agonists, such as LY379268, have anxiolytic properties (3). We, therefore, tested the effects of LY379268 on sleep.

**Methods:** EEG was recorded continuously for 24 h on saline and drug days in 12 rats implanted with EEG and EMG electrodes. Rats randomly received either 0.25 or 1.0 mg/Kg LY379268 injected s.c. midway through the dark period. EEG was digitized and analyzed with the FFT and period amplitude routines of PASS PLUS (Delta Software, St.Louis). Using a computer display, each 10 sec epoch was scored as NREM, REM or wake. Vigilance state durations and EEG power densities for each vigilance state were determined for 6 hour time blocks.

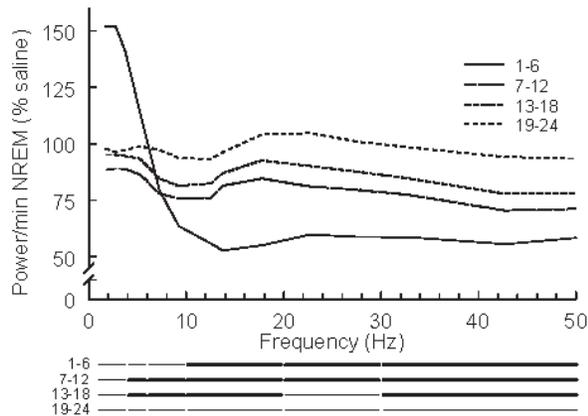
**Results:** LY379268 produced a dose-dependent suppression of REM sleep duration and fast EEG activity during NREM sleep. The 1.0 mg/Kg dose totally suppressed REM sleep in the first 6 h post injection and reduced REM duration by 80%

in the next 6 h. NREM duration was unchanged during the period of REM suppression. 1.0 mg/Kg LY379268 uniformly reduced high frequency (10-50 Hz) NREM EEG power density by nearly 50 % in the first 6 h post injection. These sleep and EEG effects were unaccompanied by motor or behavioral abnormalities.

**Figure 1**—REM sleep duration in 6 hour blocks following saline (o) or drug (●) injections at hour 6 (I) of the dark period. 24 h saline data are double plotted. LY379268 (1.0 mg/Kg s.c.) completely suppressed REM sleep in the first 6 h post drug and greatly reduced REM in the next 6 h.



**Figure 2**—LY379268 suppressed NREM high frequency EEG power. Effect on the NREM power spectrum in 4 successive 6 h periods post drug are plotted as a percent of saline control. Bold bars under the abscissa indicate in which frequency bands power differed significantly from saline at  $p < 0.01$ .



**Conclusions:** We hypothesize that the REM and fast EEG suppression both reflect depression of brain arousal systems by LY379268. The one-stimulus model of NREM-REM interaction predicts that a drug that reduces arousal level would depress REM sleep. It is of further interest that depressing brain arousal by reducing excitatory neurotransmission produces distinctly different sleep and EEG effects from those observed when arousal is depressed by enhancing neural inhibition with GABA-modulating drugs. This alternative method of modifying the excitation/inhibition balance of the brain might produce novel therapeutic effects. There is already evi-

dence that mGluR agonists have antipsychotic and antianxiety effects in animal models and the finding here of powerful REM suppression raises the additional possibility of antidepressant potency.

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Research supported by R01-MH57928 and by the office of R&D, Medical Research Service, Department of Veterans Affairs

### 137.A

#### RELATIONSHIPS BETWEEN NREM SLEEP DELTA EEG SPECTRAL POWER AND MORNING WAKING REGIONAL CEREBRAL GLUCOSE METABOLISM IN ADULT HUMANS: AGE-DEPENDENT AND AGE-INDEPENDENT EFFECTS

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(1) University of Pittsburgh,

**Introduction:** Slow wave sleep represents the intrinsic electrical oscillations of thalamocortical networks in the absence of ascending activation. Intrinsic properties of the thalamus and cortex, as well as the degree to which ascending activation is present may modify the expression of slow wave sleep. Age modifies slow wave sleep, although it is unclear if this effect is mediated by age-related alterations in either cortical function or in the ascending arousal system. The current study assessed regional cerebral metabolism in waking as an indicator of a background cerebral state that may be more or less conducive to the expression of delta sleep. We hypothesize that delta sleep would be directly proportional to function in the prefrontal cortex and inversely proportional to function in ascending activating systems. We also predicted that age-related declines in relative function of prefrontal cortex would account for some of the relationship between waking prefrontal cortex function and delta spectral power during NREM sleep.

**Methods:** Fourteen healthy subjects (age range 21 to 49; 10 women and 4 men) received assessments of delta EEG spectral power during NREM sleep and of regional cerebral glucose metabolism during morning wakefulness using the [18F]-FDG PET method. Brain MR scans provided neuroanatomical localization. Correlations were performed between waking relative metabolism (after correcting for the effects of inter-subject variations in global metabolism) and NREM sleep delta EEG spectral power. Results were controlled for multiple comparisons by reporting as significant only those brain

regions that were components of a larger confluent cluster of voxels that demonstrated significance at the  $p < .05$  level.

**Results:** NREM sleep delta power positively correlated with relative metabolism in prefrontal, parietal, and anterior cingulate cortex, predominantly, although not exclusively right hemispheric. Correction for age greatly reduced the spatial extent of these regions. An interaction analysis showing structures that covaried more positively with delta power than with age showed a very extensive region consisting of frontal, prefrontal, parietal, and anterior cingulate cortex as well as the putamen. NREM sleep delta power negatively correlated with relative metabolism in the temporal and inferior parietal cortex around the lateral sulcus, the ventromedial prefrontal cortex, left amygdala and hippocampus, left parietal-occipital cortex and the right inferior temporal gyrus. Most regions remained significant after corrections for age. Additionally, a region inclusive of the lateral hypothalamus, medial and ventral thalamus became significant.

**Conclusions:** This study shows that delta EEG sleep at night is positively related to relative function in the neocortex and cingulate cortex and negatively related to relative function in a collection of structures implicated in cortical arousal. The relationship between neocortical function and slow wave sleep was largely age-dependent, whereas the effects of activating brain structures on delta sleep were largely age-independent. These findings support the model that slow wave sleep expression is dependent on the functional status of heteromodal association cortex and the anterior cingulate as well as on the functional status of a collection of brainstem, limbic and paralimbic structures that mediate cortical arousal.

Research supported by MH01414, MH61566, MH30915, MH37869, RR00056, MH24652, and MH52247

**Oral Presentation**  
**Physiologic Effects of Sleep Deprivation**

**138.I**

**LETHAL EFFECTS OF "SLEEP" DEPRIVATION IN DROSOPHILA MELANOGASTER**

Shaw PJ<sup>1</sup>

(1) The Neurosciences Institute

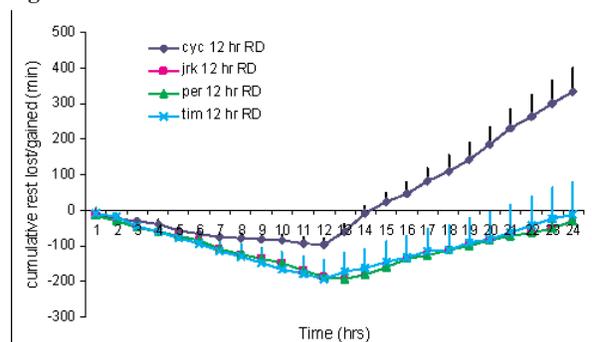
**Introduction:** We have shown that periods of quiescence in *Drosophila melanogaster* share many traits with mammalian sleep. Perhaps the most important of these is that when flies are kept awake they show a large compensatory increase in rest the next day. In mammals, sleep is also regulated by the circadian pacemaker which actively promotes and maintains wakefulness at specific times of the day. To more thoroughly evaluate the relationship between homeostatic and circadian processes on sleep regulation, we have studied homeostasis in the canonical clock mutants *per01*, *tim01*, *Clkjrk* and *cyc01*.

**Methods:** Rest was evaluated in 3 day old female flies maintained at 25 C, under a 12:12hr DD cycle. In order to insure that flies were awake during the rest deprivation procedure, we developed a system that coupled the Trikinetics activity monitors with the deprivation apparatus. The Sleep Nullifying Apparatus (SNAP) asymmetrically tilted -60 to +60 degrees

such that the resting flies were gently displaced during the downward movement.

**Results:** Upon release from 3, 6, 9 and 12 hours of rest deprivation, flies carrying a loss-of-function mutation in the clock gene *cyc* show an exaggerated homeostatic response reclaiming three times the amount of rest that was lost during the deprivation. In contrast, *per01*, *Clkjrk* and *tim01* flies recover 100% of lost rest during the first 12 hours of recovery while flies with an intact clock recover 40% of rest lost (figure 1). When the rest deprivation protocol was extended past 10 hours *cyc01* flies began to die suggesting that the increase in recovery sleep after shorter deprivations reflected an acceleration of the deleterious effects of waking rather than an impairment of the recovery process. To investigate the possibility that the deaths in *cyc01* flies was due to an increased sensitivity to stress rather than to sleep loss per se, we subjected all genotypes to various stresses including chronic heat, desiccation, starvation, and oxidative stress. Results indicated that *cyc01* flies were less responsive to these stressors than either Cs flies or the other clock mutants ( $p < .01$ ). These data indicate that the *cyc01* mutants are not merely hyper-responsive to stresses but to prolonged wakefulness. Results from QPCR indicated that the increase in homeostatic drive and the deaths following 12 hours of rest deprivation in *cyc01* flies might be associated with the decline in the expression of chaperone proteins. Therefore, we attempted to rescue *cyc01* flies by inducing these genes prior to rest deprivation. Pretreatment of *cyc01* flies with heat exposure reduced the mortality rate compared to unheated flies ( $p < .01$ ). If chaperone proteins are involved in mitigating against the deleterious effects of prolonged waking, heat exposure should also reduce homeostatic drive. Indeed, the homeostatic response of *cyc01* flies to rest deprivation was reduced in preheated flies ( $p < .01$ ).

**Figure 1**



**Table 1**

Mortality in clock mutants during 12 hrs of rest deprivation

Genotype	trials	n	% mortality	Range
<i>cyc</i> <sup>01</sup>	11	176	35 ± 6%	12%-60%
<i>Jrk</i>	7	119	0%	NA
<i>per</i> <sup>01</sup>	6	96	0%	NA
<i>tim</i> <sup>01</sup>	5	80	0%	NA
Cs	20	540	0%	NA

**Conclusions:** The lethality in *cyc01* flies potentially extends the vital importance of sleep beyond the rat and may

be the first step in identifying the molecules that constitute the sleep homeostat.

#### References:

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Research supported by The Neurosciences Research Corporation

### 139.I

#### EFFECT OF SLEEP LOSS ON C-REACTIVE PROTEIN, AN INFLAMMATORY MARKER OF CARDIOVASCULAR RISK

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(1) Tufts University Medical School, Boston, MA. Department of Cardiology, Lahey Clinic Medical Center, Burlington, MA., (2) Harvard Medical School and Brigham and Women's Hospital, Boston, MA, (3) Harvard Medical School and Children's Hospital, Boston, MA, (4) University of Pennsylvania School of Medicine, Philadelphia, PA., (5) Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA

**Introduction:** High sensitivity C-reactive protein (HSCR) concentrations are predictive of future cardiovascular morbidity. In epidemiologic studies sleep complaints have also been found to be associated with increased cardiovascular morbidity. This study was undertaken to examine the effect of acute and chronic sleep restriction on concentrations of HSCR in healthy human subjects.

**Methods:** In experiment 1, 10 healthy adult subjects stayed awake for 88 continuous hours. Samples for HSCR were taken every 90 minutes for 5 consecutive days encompassing the vigil. In experiment 2, 10 subjects were randomly assigned to either 8.2 hours (control) or 4.2 hours (partial sleep deprivation) of nighttime sleep for 10 consecutive days. Hourly samples for HSCR were taken during a baseline night and the 10th day of the study protocol.

**Results:** HSCR concentrations increased during both total (Figure 1) and partial (Figure 2) sleep deprivation conditions, but remained stable in the control condition. The increases in HSCR concentrations crossed boundaries of quintiles associated with increasing risk of cardiovascular events in population based studies.

Figure 1

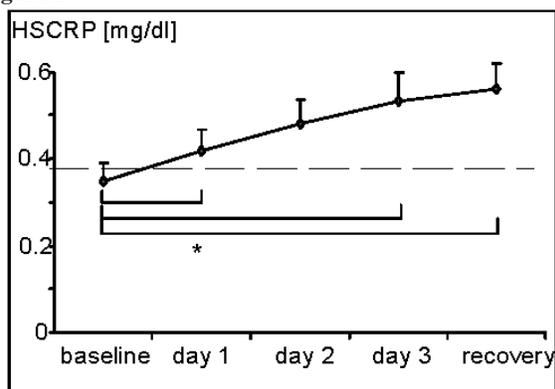
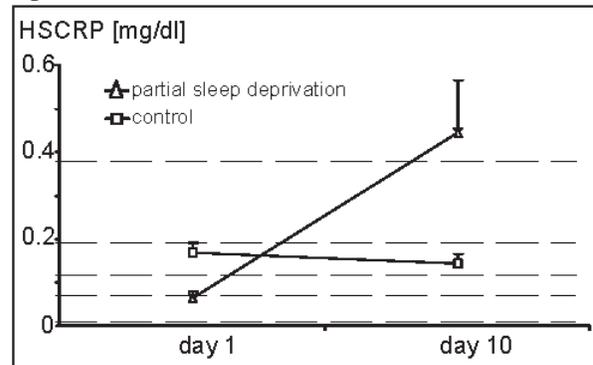


Figure 2



**Conclusions:** Both acute and chronic sleep loss led to increased CRP, a stable marker of inflammation that has been shown to be predictive of cardiovascular morbidity. We propose that sleep loss may be one of the ways that inflammatory processes are activated and contribute to the association of sleep complaints and cardiovascular morbidity observed in epidemiological surveys.

Research supported by NIMH MA60641

### 140.P

#### SLEEP IN TYPE II DIABETES: A SURVEY STUDY

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(1) The University of Chicago, Chicago, IL,

**Introduction:** Recent investigations have identified impairments in metabolism as one of the consequences of sleep loss, suggesting that decrements in sleep duration and/or quality may increase the severity of metabolic disorders, particularly diabetes. This study tests the hypothesis that there is a relationship between glycemic control in Type II diabetics and sleep duration and quality.

**Methods:** The subjects are adult male (n=69) and female (n=151) patients with Type II diabetes treated at the University of Chicago. These subjects are not recently diagnosed and had blood tests within 90 days of the interview. The survey includes questions about history and management of diabetes, height, weight, and the Pittsburgh Sleep Quality Index (PSQI). Glycohemoglobin (GHb) or hemoglobin A1c (HbA1c) data are obtained from the patients' medical records. Both measures reflect glycemic control over the past three months. HbA1c values less than 6.0% are considered to be in the normal range. There is a standardized formula of conversion where  $HbA1c = 0.72 * GHb + 1.35$ . The results from the GHb test were converted to HbA1c.

**Results:** The mean ( $\pm$ SD) age is 57.4 ( $\pm$ 12.9) years, mean BMI is 35.6 ( $\pm$ 9.9) kg/m<sup>2</sup>, and mean HbA1c is 8.2 ( $\pm$ 2.1) %. The mean amount of self-reported sleep is 6.10 ( $\pm$ 1.66) hours on the weekdays. On weekdays, sleep duration is significantly lower than the national average of 7.0 hours reported in the NSF 2001 sleep poll ( $p < 0.001$ ). The mean difference between preferred and actual weekday sleep is 1.83 ( $\pm$  2.01) hours, which is an indication of perceived sleep debt. The mean PSQI score is 8.6 ( $\pm$ 4.6) and 71% of these patients have a score

greater than 5, which is clinically diagnostic for poor sleep. There is a significant positive association between HbA1c and PSQI ( $r=0.201$ ,  $p=0.003$ ) (Figure 1), and between HbA1c and perceived sleep debt ( $r=0.202$ ,  $p=0.003$ ). Thus, there is an association between worse sleep and perceived sleep debt with poorer glycemic control. There is a trend towards a negative association between HbA1c and amount of weekday sleep ( $r=-0.131$ ,  $p=0.053$ ). Thus, less reported sleep is also associated with worse glycemic control. Because of the association of pain with diabetes, those who respond that their sleep is disrupted by pain ( $n=47$ ) more than twice a week are factored out in a separate analysis. In this subgroup ( $n=172$ ), the association between HbA1c and PSQI remains significant ( $r=0.163$ ,  $p=0.034$ ) (Figure 2), as does the relationship between HbA1c and perceived sleep debt ( $r=0.220$ ,  $p=0.004$ ). There is still a trend relating HbA1c to weekday sleep duration ( $r=-0.141$ ,  $p=0.065$ ). In this group, 67% of these patients have PSQI scores greater than 5, and the mean weekday sleep duration is 6.35 ( $\pm 1.61$ ) hours, which is also significantly lower than the 7.0 hour national average ( $p<0.001$ ).

Figure 1

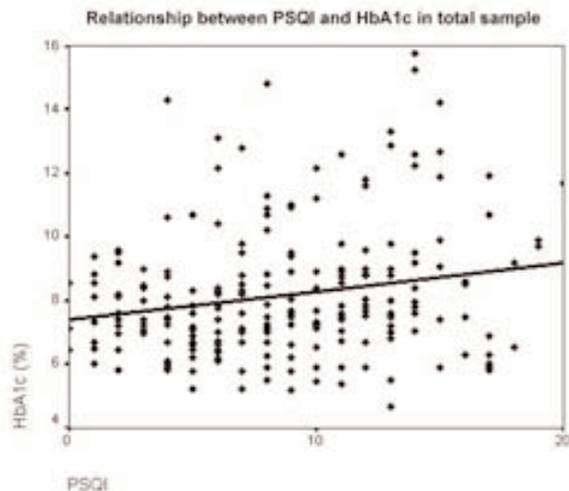
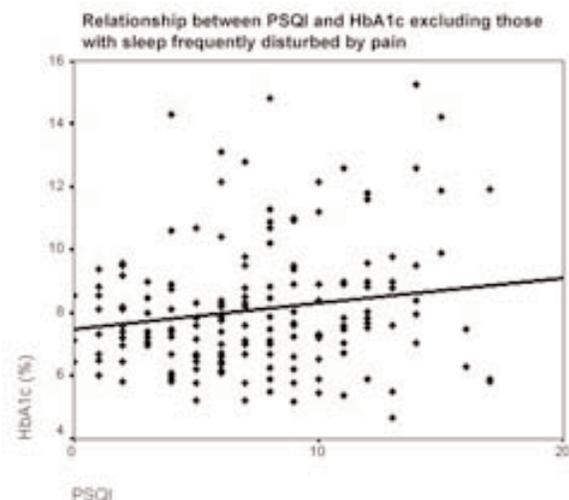


Figure 2



**Conclusions:** In this study, a high proportion of Type II diabetics are found to have disturbed and reduced sleep relative to the general population. The data support an association between glycemic control and sleep quality and quantity. These findings suggest that sleep hygiene should be a part of diabetes management.

**Research supported by the Research Network on Socio-economic Status and Health of the MacArthur Foundation.**

### 141.I

#### HUMAN HOST RESPONSE DURING CHRONIC PARTIAL SLEEP DEPRIVATION

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**Introduction:** Adequate sleep is commonly thought to be important for host protection and recovery from infection. The purpose of our study is to determine the host response to lipopolysaccharide (LPS), commonly referred to as endotoxin, during ongoing chronic sleep restriction. We expect that chronic partial sleep deprivation moderates the early immune response to an experimental bacterial component challenge.

**Methods:** Healthy screened volunteers, housed in a temperature controlled clinical research facility, were randomized to either 4 or 8 hours of sleep per night for 10 days. On day 11, participants were further randomized to received endotoxin (2ng/kg E. coli) or placebo in a double-blinded design. Temperature was measured via a rectal probe and serum levels of human growth hormone (hGH), cortisol, and LPS-binding protein (LPS-BP) were measured in blood samples drawn at frequent intervals via an indwelling forearm catheter. Frequent sampling continued for >11 hrs following injection of endotoxin or placebo at 2300h. The following preliminary data are from the initial 8 participants of the larger study. While this is a double blind study, based on temperature results, we can infer that 3 of these subjects received endotoxin.

**Results:** Temperature peaks at approximately 0300, 4 hours post endotoxin injection in both the 4-hour and 8-hour subjects. Although the temperature increases in both groups, it appears to be attenuated in the 4-hour sleep condition. The circadian nadir of cortisol (between 2200-2300h in these subjects) is similar among all subjects prior to injection. Cortisol begins to rise 1 hour post endotoxin injection and peaks at the same time as temperature (about 0300). After the peak of the evoked response (0700/8hrs post injection), the normal circadian rise in cortisol secretion is observed in both the placebo as well as the 8-hr/endotoxin group. However, cortisol secretion is attenuated in the 4hr/endotoxin group. hGH peaks after sleep onset in unchallenged subjects. However, in participants receiving endotoxin, the surge in hGH begins earlier and the amplitudes are higher. Furthermore, after endotoxin injection, hGH secretion follows a bimodal distribution not seen with placebo. The evoked response to endotoxin has both immediate and delayed features. Whereas temperature and cortisol peak simultaneously, LPS binding protein levels only began to rise at about 0400 (5 hour post injection). Levels remain ele-

vated long after the most acute phase of the response has subsided.

Figure 1

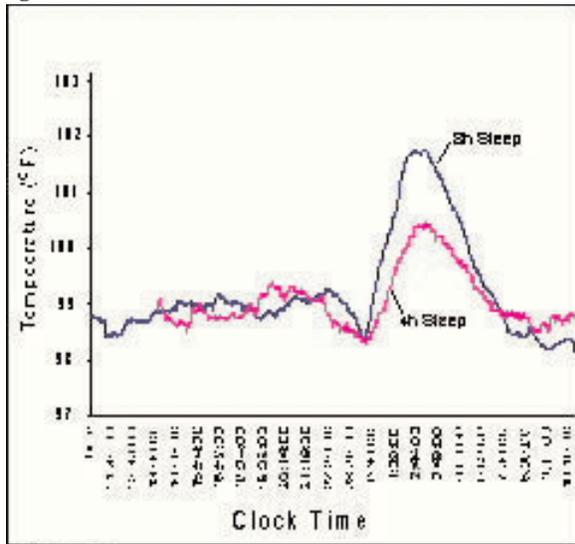
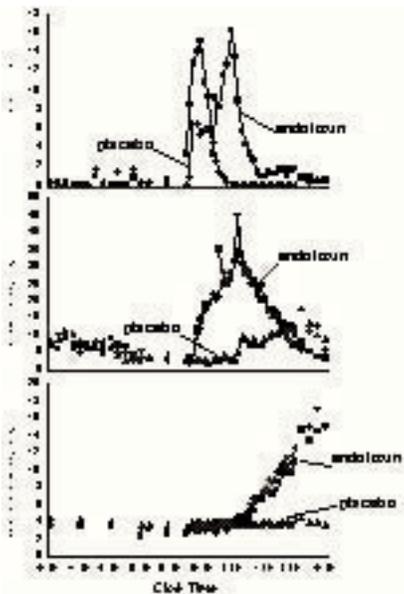


Figure 2



**Conclusions:** These initial data suggest differences in the temperature response curves associated with endotoxin challenge during chronic sleep restriction. These data suggest attenuation in the febrile host response to endotoxin challenge with chronic partial sleep deprivation.

Research supported by NIMH MA60641

## 142.I

### A PROSPECTIVE STUDY OF SLEEP DURATION AND CORONARY HEART DISEASE IN WOMEN

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**Introduction:** Chronic sleep deprivation is common in today's society with 31% of Americans reporting less than 6 hours of sleep per night.<sup>(1)</sup> Recent human studies have shown that short-term sleep deprivation in normal subjects results in adverse physiologic effects such as decreased glucose tolerance and increased sympathetic nervous system activity. This suggests that long-term sleep deprivation may have adverse health consequences. The purpose of this study was to investigate whether decreased sleep duration (from self-reports) is associated with an increased risk of coronary events.

**Methods:** We studied a cohort of 71,617 U.S. female health professionals (aged 45 to 65 years old) without reported cardiovascular disease at baseline and who were enrolled in the Nurses' Health Study. Subjects were mailed a questionnaire in 1986 that asked about average *Total hours of actual sleep in a 24-hour period*. Subjects were then followed until 1996 for the occurrence of coronary heart disease (CHD) events.

**Results:** A total of 934 coronary events were documented (271 fatal, 663 nonfatal) during ten years of follow up. Both decreased and increased self-reported sleep durations (compared to the reference value of 8 hours per night) were significantly associated with an increased age-adjusted relative risk of CHD (see Table below). After adjusting for a number of potential confounders; the relative risks decreased but were still significantly elevated in both short (< 5 hrs/night) and long ( $\geq 9$  hrs/night) sleepers.

Table 1

Odds Ratios and 95% Confidence Intervals

	Hours ≤ 5	Of 6	Sleep 7	Per 8 <sub>±</sub>	Day 9+
Total CHD*					
Age-adjusted Relative Risk	<u>1.82</u> (1.34- 2.41)	<u>1.30</u> (1.08- 1.57)	1.06 (0.89- 1.26)	1	<u>1.57</u> (1.18- 2.11)
Multivariate model without diabetes or hypertension**	<u>1.45</u> (1.1- 1.92)	1.18 (0.98- 1.42)	1.09 (0.91- 1.30)	1	<u>1.38</u> (1.03- 1.86)
Multivariate model including diabetes and hypertension**	<u>1.39</u> (1.05- 1.84)	1.18 (0.98- 1.43)	1.10 (0.92- 1.31)	1	<u>1.37</u> (1.02- 1.85)

Significant results (p < 0.05) are underlined

\* Includes both nonfatal myocardial infarctions and fatal coronary heart disease events

\*\* Adjusted for: shiftworking, hypercholesterolemia, body mass index, smoking, snoring, exercise, alcohol, depression, aspirin use, postmenopausal hormone use, and family history of myocardial infarction

⊥

**Conclusions:** Our results indicate that both short and long self-reported sleep duration are independently associated with a modestly increased risk of coronary events in women.

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### 143.I

#### SLEEP DURATION PREDICTS MORTALITY: THE FRAMINGHAM STUDY

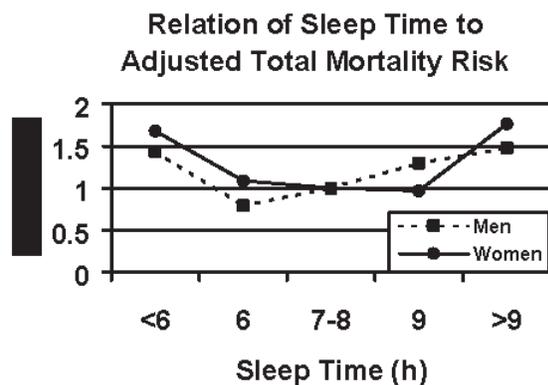
Gottlieb DJ,<sup>1,3</sup> Schulman DA,<sup>1,3</sup> Nam BH,<sup>1</sup> D'Agostino RA,<sup>2</sup> Kannel WA<sup>2,3</sup>

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- (3) The NHLBI's Framingham Heart Study,

**Introduction:** Previous reports have suggested that both unusually long and unusually short sleep times are associated with increased mortality. We have further evaluated the association of sleep time and mortality in the Framingham Heart Study Original Cohort.

**Methods:** Subjects are 2009 men and 2532 women completing a physical activity questionnaire at the Framingham Heart Study Cycle 4 Exam (1954-56). The relation of self-reported usual sleep duration to mortality over 14 years of follow-up was assessed using sex-specific Cox regression analysis, using a sleep time of 7-8 hours as the referent group, and adjusting for age, BMI, total cholesterol, systolic blood pressure, and smoking status.

Figure 1



**Results:** An increase in total mortality was seen in both men and women who reported sleeping <6 h per day or >9 h per day. After adjustment for all covariates, the risk ratio (RR) for all-cause mortality in subjects sleeping <6 h per day was 1.4 in men and 1.7 in women; the RR for all-cause mortality in

those sleeping >9 h per day was 1.5 in men and 1.8 in women. When only cardiovascular mortality was considered, the increased mortality risk was observed primarily in those reporting sleep times >9 h. In contrast, excess non-cardiovascular mortality was more strongly associated with sleep times of <6 h. Similar results were obtained excluding subjects with known cardiovascular disease at the Cycle 4 Exam.

**Conclusions:** We conclude that sleep times of <6 h or >9 h are associated with increased mortality. The mechanism underlying the association of sleep time and mortality is unknown. Long sleep times may be a marker of diseases such as obstructive sleep apnea that are thought to cause cardiovascular disease. A short sleep period, reflecting either insomnia or voluntary sleep time restriction, is reported to impair immune function and increase sympathetic nervous system activity. These effects might lead to increases in malignant, infectious, or cardiovascular mortality. As approximately 15% of the US adult population reports sleeping for <6 h per night, a causal association of short sleep time with mortality would be of great public health importance.

Research supported by NIH/NHLBI Contract No. N01-HC-38038

### 144.I

#### SLEEP DEPRIVATION REDUCES PROLIFERATION OF NEW CELLS IN THE RAT HIPPOCAMPUS.

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**Introduction:** A growing body of evidence indicates that new neurons are produced throughout adulthood (neurogenesis) in several regions of the brain including cortex, olfactory bulb and hippocampus. Adult neurogenesis has been shown in several species including rodents, primates and humans. Both positive regulators (exposure to estrogens, living in a complex environment, hippocampus dependent learning and use of antidepressants) and negative regulators (aging, exposure to glucocorticoids, and stressful experience) influence neurogenesis (1). The deleterious effects of sleep deprivation (SD) have been recognized for some time. Short periods of SD can result in cognitive deficits in humans whereas in rats prolonged SD causes a characteristic syndrome (weight loss and increased energy expenditure). Some investigators have proposed that the neural activity associated with prolonged waking may damage brain cells and eventually lead to cell death (2). We hypothesized that SD may act as a negative regulator of neurogenesis.

**Methods:** Male rats (300 g) were implanted for chronic EEG and EMG recording. After one week of recovery from surgery rats were acclimated to SD apparatus, placing them inside a chamber positioned over a treadmill. During SD, the treadmill moved for 3 sec every 15 sec (3 sec on, 12 sec off), at a speed of 10 cm/sec. One day before SD began, rats were injected (150 mg/kg i.p.) twice with the thymidine analog bromodeoxyuridine (BrdU) which is incorporated into the DNA of cells in S-phase of the cell cycle. After 72 h of SD, animals

were deeply anesthetized and perfused transcardially, brains removed and processed for BrdU immunostaining. Every sixth section (40  $\mu$ m) throughout the hippocampus was processed for BrdU (this ensures that the same neuron will not be counted in two sections). The number of BrdU-positive cells in each rat was counted in the dentate gyrus from the hippocampus in three different sections per rat which were matched with corresponding sections in control group (n=3 rats per group).

**Results:** During 72 h of sleep deprivation the percentage of waking was 96.172%. Sleep deprived rats exhibited fewer BrdU stained cells compared with cage control (78.7 + 16.17 SD vs 119.55 + 19.23 control \* p < 0.05 T-test for independent groups).

**Conclusions:** These results support the hypothesis that SD is a negative regulator of cell proliferation in the rat hippocampus.

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## 145.I

### REM SLEEP-DEPRIVED KITTENS HAVE INCREASED EEG DELTA ACTIVITY AND REDUCED LEVELS OF TYROSINE HYDROXYLASE (TH) IMMUNOREACTIVITY IN LOCUS CERULEUS (LC)

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**Introduction:** Recent studies in kittens during a critical period of brain development (1) have found that combining two weeks of monocular deprivation with REM sleep deprivation (RD), coincident with the second week, leads to increased plasticity in geniculocortical relay cells (2). Mechanisms of this heightened plasticity are not yet understood. However, LC neurons, which are silent during REMS and are the primary source of cortical norepinephrine (NE), play an important role in developmental brain plasticity. We investigated whether TH-immunoreactivity (-ir) in LC is affected by one week of REMS-deprivation during the second week of a two-week period of monocular deprivation.

**Methods:** On postnatal day (PN) 34 or 35, kittens (n=6) were implanted with standard sleep-recording electrodes for electrocorticograms (ECoG) and electromyograms (EMG). After recovery, animals (PN40-PN49) were REMS-deprived by a computerized system that shook the cages at REMS entries. Control kittens received the same number and intensity of perturbations as the matched RD-animals but only in the last five minutes of each half-hour and only in Wake. Fast Fourier

Transforms were performed on 30-uncontaminated, 4-sec samples of SW sleep from each animal, taken throughout the 7-day experiment. Kittens were perfused with 4% paraformaldehyde. Brains were sectioned at 60-microns and reacted immunohistochemically for TH. Neuronal population, density, and volume of LC in the REMS-deprived- and control kittens were estimated using stereological counting methods.

**Results:** Repeated measures ANOVA indicated that REMS and WAKE proportions were different between the two groups. However, SWS quantity was not affected (REMS, F = 604.8, p<0.0001; SWS, F = 0.2, NS; WAKE, F = 8.4, p<0.0001). SWS delta activity during the experiment was increased in the control animals relative to the RD group (F = 18.03, p<0.0001). Neuronal population, density, and volume values in the control group were significantly larger than in the RD group (p<0.05). Average cell size of the control brains was significantly larger than in the RD group (Mann-Whitney, U = 0.000, p = 0.05).

**Conclusions:** Larger TH-ir values in control animals could have arisen because of increased expression of TH-ir in LC or from overall reduction in RD animals. Data from two untreated, normal kittens suggest the possibility of both increased (in controls) and decreased (in RD-animals) expression of TH-ir. TH up-regulation has been reported in LC in post-mortem brains from patients with major depression (MD) (3), in stressed animals, and in animal models of MD, such as chronic mild stress. Other studies have shown that REMS-deprivation has ameliorative effects on MD patients. In addition, it is known that antidepressants, which also suppress REMS, down-regulate TH expression in LC cells of MD animal models. Reductions in TH expression in RD animals may reflect the extended periods of LC activity caused by RD, itself. Accordingly, additional waking LC activity may be utilizing the sufficient, available TH to supply ongoing NE expression in visual cortex. Increases in NE availability could account for the increases that we have previously observed in geniculocortical cell plasticity in monocularly deprived- and RD kittens (2).

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**Oral Presentation  
Medical Disorders:  
Impact on Sleep Quality**

**146.P****POLYSOMNOGRAPHIC CHANGES INDUCED BY AN EXPERIMENTAL PAINFUL HYPERTONIC SALINE INFUSION**

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**Introduction:** Sleep of chronic musculoskeletal pain patients is reported to be of poor quality. The specific influences of pain on sleep are unclear. However, we previously reported the effect of thermal pain on sleep across sleep stages; nevertheless, the influence of deep tissue pain is unknown. Classically, sensory/noxious influences are thought to be attenuated or abolished during REM sleep (1). But recent animal experiments question this thinking in showing that relevant sensory stimuli applied during REM sleep can induce a rise in sensory neuron activity (2). To better understand this complex relationship, we analyzed electrophysiological changes induced by an experimental infusion of hypertonic-noxious saline (Hyper; 5%) in comparison to random administration of isotonic-control saline (Ctrl; 0.9%) in the right or left deltoid muscle (vol.=0.3ml at 45ml/h) of asymptomatic subjects.

**Methods:** Nine healthy young subjects (mean age=23.9 yr) without histories of pain, sleep, anxiety or mood problems were included. Repeated experimental noxious and control infusions were done while awake and during sleep stages 2, 3+4 and REM. Polysomnographic recordings of EEG, EMG and EKG were used to score sleep perturbations such as arousals, awakenings, sleep stage shifts and behavioral-motor nocifensive reactions (3). To further characterize EEG changes, we proceeded to spectral analysis of the C3A2 derivation.

**Results:** Awake, subjects reported, on a 100 mm visual scale, low to moderate pain intensity with hypertonic-noxious infusion (mean Hyper=27.1 mm vs. Ctrl=2.3 mm;  $p<0.002$ ). During sleep, there were similar levels of response in stages 2 and REM but much less response in stages 3+4 ( $p<0.05$ ). However, hypertonic saline induced more arousals ( $p<0.05$ ) in stages 3+4 (26.7% vs.0%), stage 2 (60.7% vs. 27.8%) and REM (64.6% vs.12.5%) in comparison to control infusions. We observed behavioral-motor responses in 34% of hypertonic-noxious pain infusions in comparison to 11 % of isotonic-control infusions. Using spectral analysis, we found more alpha+beta EEG power (fast activity) of REM sleep only this for hypertonic-noxious stimulations ( $p<0.05$ ).

**Conclusions:** Noxious muscle stimulation disrupted REM as frequently as stage 2. Similarly to recent animal data, this study suggests that the influences of pain on REM sleep should not be overlooked.

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**147.P****THE EFFECTS OF COOL DIALYSATE ON BODY TEMPERATURE AND SLEEP IN PATIENTS ON CHRONIC HEMODIALYSIS**

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**Introduction:** The body temperature (BT) increase that often accompanies hemodialysis (HD) may be related to a cytokine mediated pyrogenic reaction, an increase in metabolic rate from fluid removal, or direct heat transfer from the warm dialysate bath (typically 37 degrees C) to the patient (1). This heat load may impair hemodynamic stability and enhance the hypotension that frequently complicates treatment. In many subjects, the use of cool dialysate (35 degrees C) stabilizes blood pressure, possibly due to a reduction in heat-induced vasodilatation (2). Our previous work indicates that HD associated increases in BT may also have iatrogenic effects on the sleep/wake cycle (3). Therefore, we studied the effects of cool versus warm dialysate on BT rhythms and daytime and nocturnal sleep.

**Methods:** Five HD patients participated in this three phase, double blind, randomized study conducted in the General Clinical Research Center. During phase I, an acclimatization period (18 to 20 hours), subjects were admitted at 6 PM the night before HD, received treatment the next morning (dialysate temperature 37 degrees; set via a calibrated, internal machine control), and were then discharged. Nocturnal and daytime sleep were continuously recorded using the Oxford ambulatory polysomnographic system (MR 95, standard montage). Axillary BT was recorded every minute using a MINI-LOGGER 2000 (Mini-Mitter). During each of the next two phases, subjects were admitted at 6:00 PM and discharged 42 hours later, a period that included one HD on the morning following admission. Sleep and BT were monitored as described above. All subjects received HD in two conditions, warm dialysate HD (37 degrees C) and cool dialysate HD (35 degrees C) - in random order during the two study phases. BT data from 6 AM the morning before HD until 6AM the following day were selected for this preliminary analysis. These data were normalized (converted to z-scores) for each subject, averaged for the group in each condition, and then graphed. Sleep scoring was performed using conventional criteria (from lights on the day of HD until lights on the following morning). Descriptive statistics were used to compare data from the two conditions.

Figure 1

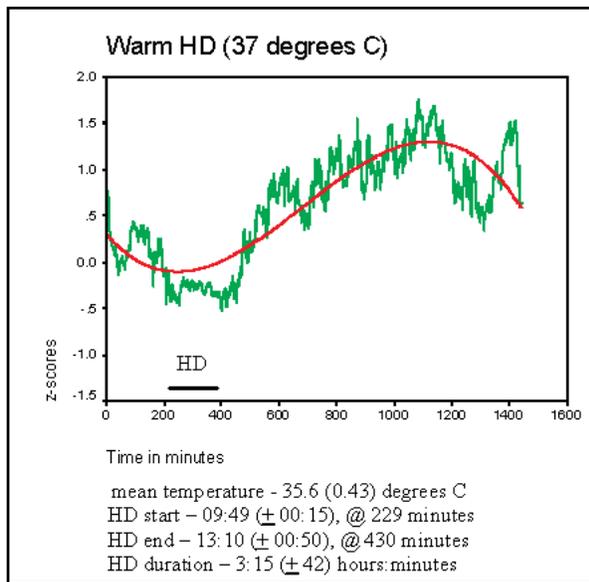
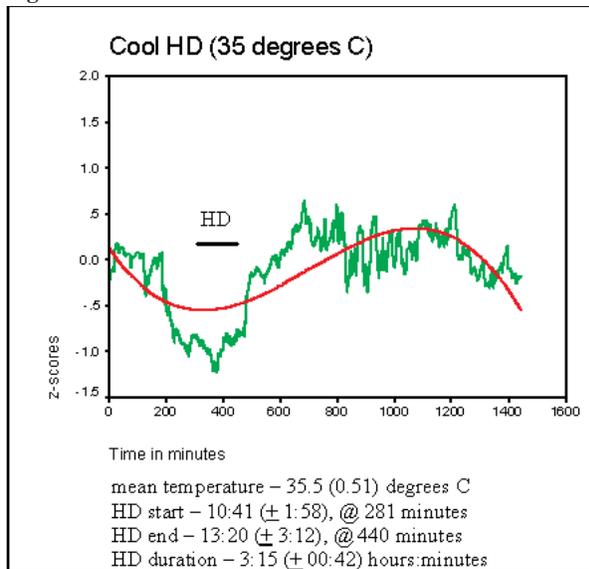


Figure 2



**Results:** The axillary BT data (raw data and the calculated cubic curve) for the 24-hour period in the two conditions are presented in Figures 1 and 2. In both conditions, an intradialytic drop in BT was followed by a temperature increase. However, in the warm condition, this increase continued and peaked at midnight (1085 minutes into study period), then trended downward. In the cool condition, the temperature increase was less and BT peaked at approximately 5:30 PM (685 minutes into study period), then trended downward. In the cool condition, total daytime sleep (lights on until lights off) decreased slightly from 64.4 ( $\pm$  54.6) minutes in the warm condition to 50.8 ( $\pm$  90.3) minutes. However, the mean nocturnal total sleep time increased markedly to 392.0 ( $\pm$  70.9) minutes with a sleep efficiency of 69.4% ( $\pm$  14.6) in comparison to the warm condition,

294.10 ( $\pm$  120.1) minutes and 59.4% ( $\pm$  31.8), respectively.

**Conclusions:** These results suggest that dialysate temperature affects BT rhythms and that the use of cool dialysate results in a more normal temperature pattern. These effects may be associated with decreased daytime sleep and improved nocturnal sleep quantity and quality.

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**148.P**

**SLEEP DISRUPTION AND RECOVERY FROM CABG SURGERY**

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**Introduction:** The purposes of this study were to describe changes in sleep during coronary artery bypass graft (CABG) surgery and to explore the relationship between sleep parameters and recovery from CABG surgery. Most patients who experience CABG surgery report at least short-term sleep disturbances following the procedure. These disruptions in sleep may have a profound effect on patients in addition to the serious nature of their illness and need to recover from major surgery (1).

**Methods:** Twenty-five elective CABG patients completed questionnaires related to their sleep patterns and cognitions about sleep 1-3 days pre-operatively and 6 weeks post-operatively. The subjects were predominantly Caucasian men from the midwestern USA. Mean age was 64.5 years (SD=10.1, range =47-82 yrs.). Median length of stay in intensive care was 18 hours (range=7-93 hrs.). Median time on the ventilator was 6 hours (range=2-47 hrs.). Median hospital stay was 6 days (range=4-24 days). The predominant secondary diagnosis was hypertension, with atrial fibrillation, angina, COPD, documented tobacco use, and diabetes, respectively, in descending order. Five sleep parameters were self-reported, see Table 1. Health status was measured by the SF36. Standard scoring rules were used to create transformed factor scores for subjective health status. The Wilcoxon signed-ranks test was used for analyses whenever assumptions for the paired-t test were not met.

**Results:** Table 1 shows descriptive and inferential results for self-reported sleep parameters before and after surgery. Sleep latency (SL) and waking duration after sleep onset (WASO) significantly increased after surgery. Bedtimes and sleep amount did not change, but awaking times were extended by

approximately 40 minutes. Pre-operatively, later bedtimes were correlated with later times of awaking ( $r=.42, p<.05$ ) and less sleep ( $r=-.41, p<.05$ ). WASO was also negatively correlated to sleep amount ( $r=-.43, p<.05$ ). The pattern was different post-operatively: Although sleep amount was still negatively correlated with WASO ( $r=-.54, p<.01$ ), it also was negatively correlated with SL ( $r=-.45, p<.05$ ) and positively correlated with time of morning awakening ( $r=.63, p<.001$ ), with SL correlated to WASO ( $r=.57, p<.01$ ). Overall, SF36 factor scores were below US population averages for all factors both before and after surgery, see Table 2. When pre- and post-operative SF36 scores were compared, only the Bodily Pain scores were significantly different. Patients reported less pain at 6-weeks post-operatively ( $t(24) = 2.07, p<.05$ ). The only sleep parameter correlated with pain scores was pre-operative WASO ( $r=.59, p<.01$ ).

**Table 1**

Mean and Standard Deviation for Sleep Parameters Before and Six Weeks After CABG Surgery

Sleep Characteristic	Pre-operatively		Post-operatively		Z
	M	(SD)	M	(SD)	
Bedtime	10:54 pm	(64 min.)	10:54 pm	(83 min)	0.15
Awaking time	06:47 am	(68 min.)	07:25 am	(83 min)	2.54*
Sleep amount	6.71 hrs.	(80 min.)	6.68 hrs.	(110 min)	0.24
Sleep latency	23 min.	(23 min.)	37 min.	(49 min.)	2.59**
Waking duration	18 min.	(24 min.)	45 min.	(51 min.)	2.73**

\* two-tailed  $p < .05$   
 \*\* two-tailed  $p < .01$

**Table 2**

SF36 Scores for Patients Pre-operatively and Post-operatively Compared to US Average Scores

	GH	PF	RP	BP	VT	SF	RE	MH
Pre-Op:	66.44	51.40	36.00	68.12	50.80	70.50	57.33	70.40
Post-Op	67.82	55.00	23.00	59.92	53.00	73.00	66.67	74.24
US Ave:	70.10	82.97	77.93	70.23	57.00	83.56	83.10	75.22

GH=General Health; PF=Physical Functioning; RP=Role Participation; BP=Bodily Pain; VT=Vitality; SF=Social Functioning; RE=Role Functioning-Emotional; MH=Mental Health

**Conclusions:** On average this sample of elective CABG patients had typical sleep parameters for their age group prior to surgery, but much poorer sleep six-weeks post-operatively. During recovery both sleep initiation and sleep maintenance became more difficult and sleep efficiency decreased as subjects time in bed increased by extending the sleep period later into the morning. Subjects' subjective health status at 6 weeks into recovery had not improved significantly from pre-surgery levels except for a decrease in pain. Although pain accounted for 35% of the variance in WASO before surgery, the increases in WASO after surgery appear due to other factors, unidentified at this time.

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Research supported by the Center for Health Research, Wayne State University

**149.P**

**SLEEP DISTURBANCES IN PATIENTS SCHEDULED FOR CARDIOVASCULAR SURGERY**

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**Introduction:** The purpose of the current report is to describe sleep disturbances in patients scheduled for cardiovascular (CV) surgery. The association between CV disease and sleep related breathing disorders (SRBD) is well established, although is poorly understood. Sleep deprivation has multiple effects in healthy volunteers, but unknown consequences in sick individuals.

**Methods:** Competent adults scheduled for cardiovascular surgery were asked to participate. A full polysomnogram (PSG) with an ambulatory unit was performed the night before surgery (included 4 EEG, 2 EOG, submentalis and leg EMG, 2 EKG, oxymetry, airflow and 2 respiratory effort channels) in the patient hospital room. After surgery, in recovery room, a limited continuous PSG (4 EEG, 2 EOG, submentalis EMG, oxymetry and 2 EKG channels) was done until hospital discharge or the patient elected to no longer participate in the study. Studies were interrupted during times of physical activity.

**Results:** A total of 8 patients (2 women) 39 to 85 years old (mean 64), were recruited between 2/01 and 7/01 for cardiovascular procedures. (Table 1) The night before surgery showed decreased sleep efficiency: mean 36.6% (11 to 58% range). Sleep architecture was disrupted with a mean of 47.6% of the time spent in stage 1 sleep and only 10.6% in REM sleep. SRBD (AHI>5) was present in 5 (62.5%) of the patients with a mean minimal oxygen saturation of 85% (68 to 89%). Cheyne-Stokes breathing occurred in 2 patients. (Table 2) After surgery half of the patients had continuous recording for 58 to 81 hrs (mean 67 hours), with an average of 9.2 hrs of total sleep during that period (approximately 9 hours during 3 days), and only 13.6 minutes of REM sleep.

**Table 1**

	Age (y/o)	Sex	Procedure
1	85	m	Left popliteal aneurysmectomy plus left RSVG fem-pop bypass
2	75	f	Bilateral aortorenal thromboendarterectomy
3	81	m	R common femoral to proximal peroneal reverse saphenous vein bypass
4	71	m	MVR; CABG x 1; ASD repair-PFO closure
5	44	f	Ao-bifem bypass
6	58	m	popliteal to popliteal bypass
7	60	m	CABG x 4 with LIMA
8	39	m	Ao-bifem bypass

Table 2

	Rec. time min.	Wake min.	Sleep min.	SE %	S1 %	S2 %	SWS %	REM %	RDI	Min Sats	Cheyne Stokes
1	912	643	177	19	74	24	1	1	74	89	x
2	372	155	217	58	79	0	0	0		85	
3	663	329	320	48	37	31	16	15	13	89	
4	750	629	84	11	27	45	10	17	14	68	
5	543	487	56	10	42	34	23	0		91	
6	600	264	330	55	27	52	3	17	3	86	
7	576	282	284	49	32	32	13	22	5	89	
8	387	218	168	43	22	63	1	13	70	83	x

**Conclusions:** Patients scheduled for cardiovascular procedures are sleep deprived the night before surgery. The little sleep obtained was very disrupted. There is a very high incidence of previously undiagnosed SRBD as a comorbid condition, which may be explained in part by the commonality of risk factors with CV disease. After surgery, severe sleep disruption and deprivation continues to be present as noted by Aurell et al. more than 15 years ago in spite of multiple advances in patient care (1). Further studies are needed to evaluate the impact of alterations of the sleep/wake cycle or sleep disorders on outcomes after CV surgery.

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Research supported by Grant from Cardiovascular Center, (CVC Mckay grant), University of Michigan.

**Oral Presentation  
Physiologic Studies in Parasomnias**

**150.M**

**A CONTROLLED CHALLENGE FOR EXPERIMENTALLY-INDUCED SLEEP BRUXISM (SB) IN RELATION TO AROUSAL.**

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**Introduction:** SB is an abnormal involuntary rhythmic masticatory muscle activity (RMMA) during sleep. It was recently confirmed that SB is a transient motor activation secondary to sleep arousal (AR: including microarousal and awakening) [1,2]. Accordingly, we challenged these findings using experimental AR in SB patients and normal subjects to investigate the link between arousal mechanisms and RMMA.

**Methods:** 7 SB patients (5M;2F, 21-27 y) and 8 normal subjects (4M;4F, 21-26 y) were matched for age and gender. The diagnosis of SB was made according to validated laboratory criteria [3]. No subject had any sleep or medical disorder. Two types of stimulus (1 sec duration) were used to induce AR. The first was a combination of vibrotactile and auditory stimulation (VT+AD) produced by an AC motor in contact with the arm of the subject. The second one was an auditory stimulus (AD) produced by an AC motor attached to the bed. Vibratory and auditory signals were of low (30Hz and  $\pm 0.7G$  / 39dB), medium (70Hz and  $\pm 3.1G$  / 42dB) and high intensity (115Hz and  $\pm 12.8G$  / 45dB). Stimuli were applied in random order during REM sleep and during sleep stages 2 and 3+4 after 30 sec of EEG and EMG stability. Post-stimulus ARs were visually identified using EEG criteria. The change in masseter EMG tone was calculated, using EMG spectral analysis, before and after stimulation (2 sec duration). Trials with body movements and oromotor activity occurring after stimulation were excluded from spectral analysis. SB episodes were scored with polygraphic and audio-video records. Repeated measure ANOVA and Mann-Whitney test were used appropriately.

**Results:** Regardless of sleep stage and stimulus type, the probability of the occurrence of AR increased significantly as stimulus intensity increased (ANOVA,  $p < 0.001$ ). The overall probability of experimentally-induced AR was similar in the two groups. During stimulus-induced AR, tonic masseter EMG activity significantly increased from the pre-stimulus level ( $p < 0.001$ ) without any difference between groups. Interestingly, RMMA episodes were observed following experimentally-induced AR in all 7 SB subjects, this occurred on  $11.1\% \pm 2.0$  (mean  $\pm$  SEM in a group) of trials. In normals, only one subject showed RMMA on  $1.5\% \pm 1.5$  of trials (Mann-Whitney test,  $p < 0.001$ ).

**Conclusions:** These results suggest that SB patients exhibit normal arousal thresholds and tonic masseter EMG levels during sleep. However, the higher incidence of experimental RMMA episodes in patients may indicate that SB motor activation [1,3] is associated with higher trigeminal motor excitability in relation to a previously reported, central oscillatory arousal process [2].

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Research supported by FRSQ, CIHR and J.A.-DeSève Foundation.

## 151.M

**EVIDENCE OF HYPOCRETIN IMMUNOREACTIVITY AND FUNCTION IN THE URINARY BLADDER: IMPLICATIONS FOR NOCTURIA AND ENURESIS**Morgan KA,<sup>1</sup> Shiromani PJ,<sup>1</sup> Greco MA,<sup>1</sup> Thatte H,<sup>1</sup> Yalla SV,<sup>1</sup> Sullivan MP<sup>1</sup>

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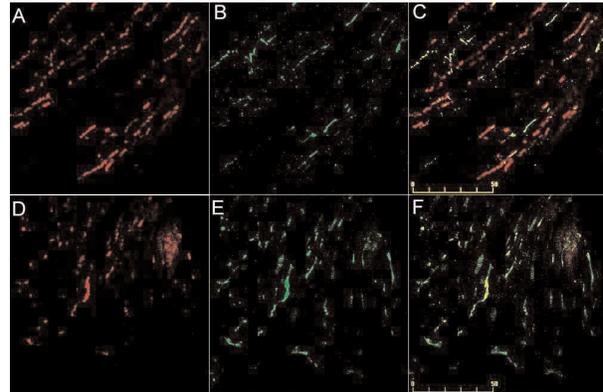
**Introduction:** Obstructive sleep apnea (OSA) is often associated with nocturia and nocturnal enuresis and treatment of sleep apnea results in resolution of enuresis (Kramer et al., 1998); however, the mechanisms responsible for these symptoms are unknown. One possibility is that peptides increased as a result of the frequent arousal associated with OSA could increase bladder activity. One such peptide that is associated with wakefulness is hypocretin. Hypocretin-containing neurons project throughout the central nervous system, especially innervating neuronal populations implicated in wakefulness. Increased hypocretin function leads to wakefulness. The frequent arousals associated with sleep apnea could alter the hypocretin system, although increased CSF levels of hypocretin have not been found in patients with OSA. Nevertheless, as recent data suggest, hypocretin pools may exist outside the CNS. For instance, a hypocretin system has been demonstrated within the digestive system: prepro-hypocretin and hypocretin receptor-1 mRNA are present in the myenteric plexus of rat small bowel and exogenous hypocretin 1 stimulates colonic motility (Kirchgessner et al., 1999). This finding has important physiologic implications for the urinary bladder since many neurotransmitters and peptides initially described in the brain and enteric nervous system have subsequently been identified in the lower urinary tract. Moreover, the overlapping innervation pathways of visceral organs support the activity of common neurotransmitters/peptides in the regulation of organ function. These factors prompted the investigation of hypocretin in the urinary bladder.

**Methods:** The presence of a hypocretin system in the rat bladder was determined by RT/PCR and visualized by ethidium bromide staining of PCR products generated from total RNA. To determine the distribution of hypocretin and its receptor and to assess their co-localization with parasympathetic and sympathetic neurotransmitters, immunofluorescence imaging was used. Studies were then performed on isolated whole bladders to measure spontaneous contractions before and after the addition of increasing concentrations of hypocretin.

**Results:** We detected hypocretin receptor-1 mRNA expression in the base and body of the bladder, as well as hypocretin receptor-1 immunoreactive fibers distributed throughout the bladder. Hypocretin receptor-1 immunoreactivity co-localized with a pan-neuronal marker, but not with vesicular acetylcholine transporter (a marker protein for cholinergic processes, Figure 1A-C). Neuronal fibers immunoreactive for hypocretin receptor-1 completely colocalized with dopamine beta-hydroxylase, a label for noradrenergic neurons (Figure 1D-F). A similar distribution and colocalization pattern was detected for hypocretin-1. The addition of hypocretin-1 (0.03-1  $\mu$ M) to the isolated whole bladder preparation induced a statistically significant, dose-dependent increase in spontaneous bladder

contractions.

Figure 1



Hypocretin receptor-1 colocalizes with sympathetic (D-F) but not with parasympathetic fibers (A-C). Figures A and D identify hypocretin-1 immunoreactive fibers innervating the bladder. Figure B denotes vesicular acetylcholine transporter labeled fibers. Figure C identifies HCRTR1-ir does not colocalize with VAChT-ir. Figure E shows dopamine beta hydroxylase-ir, and figure F shows colocalization of HCRTR1-ir with DBH-ir.

**Conclusions:** The expression of hypocretin receptor-1 mRNA and the distribution of hypocretin and its receptor suggests that a hypocretin system is present in the rat bladder. Moreover, we provide the first evidence that hypocretin and its receptor are present within sympathetic neurons in the bladder. The dose-dependent increase in spontaneous bladder contractions induced by hypocretin suggests that the hypocretin system may play an important role in the neural modulation of bladder function. Thus, these findings offer the intriguing possibility that abnormalities in the hypocretin system induced by sleep disturbances associated with sleep apnea or aging may contribute to the symptoms of nocturia and nocturnal enuresis.

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**Research supported by the Veterans Administration Medical Center Medical Research Service.**

## 152.M

**SLEEP IN MICE LACKING THE HISTAMINE H3 RECEPTOR, A PUTATIVE GENETIC ANIMAL MODEL FOR REM SLEEP BEHAVIOR DISORDER**Dugovic C,<sup>1</sup> Koehl M,<sup>1</sup> Rontal AD,<sup>1</sup> Toyota H,<sup>1</sup> Lovenberg TW,<sup>2</sup> Turek FW<sup>2</sup>

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**Introduction:** The histamine H3 receptor regulates the release of histamine and other neurotransmitters and has been implicated in a wide number of brain functions. Our recent development of a transgenic line of mice devoid of these receptors

allowed us to further explore their physiological role. In view of the central role played by the histaminergic system in the regulation of sleep and wake states, our initial interest in the H3 receptor-deficient mice was to examine their sleep-wake patterns.

**Methods:** Male H3  $-/-$  (n=9) and wild-type littermates (H3  $+/+$ , n=10) C57Bl/6J mice (3 months of age) were chronically implanted with EEG and EMG electrodes for standard polygraphic sleep monitoring. Two weeks after surgery, the animals were habituated to the recording procedure for 4 days. Following this adaptation period, sleep was recorded in baseline conditions in a 12:12h light-dark cycle and after a 6-h sleep deprivation period performed by gentle handling during the first part of the light phase.

**Results:** Under baseline conditions, the circadian amplitude of REM sleep time was significantly attenuated in H3  $-/-$  mice (ANOVA,  $p=0.002$ ). In addition, H3  $-/-$  mice showed an increase in sleep fragmentation, as indicated by a 60% increase ( $p=0.003$ ) in the number of shifts between states during the dark phase. There were no significant differences between H3  $-/-$  and wild-type mice in the times spent in wake, NREM and REM sleep over the 24h light-dark cycle. The most salient observation in this study was that H3 receptor-deficient mice exhibited abnormal characteristics in their EMG activity during REM sleep, including excessive muscle twitches (4 times more twitches per min of REM sleep,  $p=0.001$ ) and abrupt periods of increased muscular tone. These patterns are reminiscent of REM sleep behavior disorder-like symptoms described in lesion animal models. After a 6h sleep deprivation, both genotypes showed a significant REM sleep rebound increase and H3  $-/-$  mice appeared to have even more frequent muscle twitches as compared to baseline conditions.

**Conclusions:** The present data confirm that H3 receptors are involved in the regulation of sleep-wake states. The discovery that mice lacking the H3 receptor exhibit episodes of REM sleep with excessive muscle twitching and short periods of elevation of muscle tone indicates that these mice may represent an exciting new genetic model for REM sleep behavior disorder in humans.

Research supported by NIH grants AG-18200 and HL-59598

### 153.M

#### ANALYSIS OF TONIC AND PHASIC MUSCLE ACTIVITY DURING REM SLEEP IN REM SLEEP BEHAVIOR DISORDER AND NARCOLEPSY

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**Introduction:** REM sleep behavior disorder (RBD) is characterized by complex behavior during REM sleep and was reported to also occur in patients with narcolepsy (1). However, muscle activity during REM sleep has not yet been analyzed systematically in patients with RBD or narcolepsy. We

aimed to quantify tonic and phasic muscle activity during REM sleep in patients with idiopathic RBD, narcolepsy and controls.

**Methods:** We analyzed the percentage of REM sleep, that was associated with tonic or phasic muscle activity in patients with idiopathic RBD, narcolepsy and controls. No patient with narcolepsy had a history of RBD. All patients and controls underwent at least two nights of polysomnography. An increase in chin or limb EMG amplitude of at least 50% compared to the immediately preceding atonic baseline was defined as increased muscle tone. Tonic muscle activity during REM sleep was scored for each 10-second epoch, in which tonic muscle activity lasted at least one second; to be scored as tonic muscle activity, each single muscle tone elevation had to last at least 0.5 seconds. Muscle tone increase of less than 0.5 seconds was scored as muscle twitch. Excessive twitching (phasic muscle activity) was scored for one 10-second epoch if the number of twitches during this epoch was at least 10.

**Results:** Patients with RBD (n=8, 69.2±7.6 years, 1 woman, 7 men) had significantly more tonic muscle activity than controls (n=9, 69.4±5.5 years, 3 women, 6 men): RBD: 54.1±31%, controls: 18.5±12.3%,  $p=0.015$ . However, phasic muscle activity was higher in controls than in RBD: RBD: 4.3±8.1%, controls: 20.2±23.6%,  $p=0.027$ . Although not statistically significant, there was a similar trend in patients with narcolepsy: tonic muscle activity in controls: 12.6±6.7%, in narcolepsy: 17.1±9.3%; phasic muscle activity in controls: 11.8±18.8%, in narcolepsy: 2.3±2.3%,  $p>0.190$ ), (controls: n=9, 53.2±16.2 years, 2 women, 7 men; narcolepsy: n=9, 53.2±15.8 years, 4 women 5 men). Tonic muscle activity was higher than phasic muscle activity during REM sleep in patients with RBD and narcolepsy ( $p<0.0001$ ). In controls, tonic and phasic muscle activity during REM sleep was equally distributed.

**Conclusions:** In RBD and narcolepsy, tonic muscle activity during REM sleep is increased at the expense of phasic muscle activity. Patients with RBD have more tonic but less phasic muscle activity during REM sleep than controls. The similar distribution of tonic and phasic muscle activity during REM sleep in patients with narcolepsy and RBD (increased tonic at the expense of phasic) suggests some pathophysiological relationship of these two syndromes. Analyses of muscle activity during REM sleep might be useful in diagnosing RBD, especially when complex motor behavior during REM sleep is absent in the night of diagnostic polysomnography. results are given as mean ± standard deviation

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**Oral Presentation**  
**Understanding and Treating**  
**Fatigue and Sleepiness**

**154.I**

**PSYCHOMOTOR PERFORMANCE IMPROVEMENTS WITH A SHORT WORKPLACE NAP ON THE NIGHT SHIFT: THE BENEFITS OF STAGE 1 SLEEP.**

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**Introduction:** It is widely accepted that a short period of sleep during a night shift is effective in maintaining or improving the alertness and performance of individuals. This view has been supported by a number of laboratory studies which have indicated the benefits of short naps [e.g. 1] although field studies examining this issue are rare [2]. Naps taken in the workplace may be short and fragmented due to the conditions they are taken under, therefore may contain a large proportion of S1 sleep. Such sleep has recently been suggested to have little recuperative value [3]. The present study sought to determine whether a short workplace nap during a scheduled break on the night shift led to improvements in the psychomotor performance of operational air traffic controllers (ATCs).

**Methods:** Twenty-eight ATCs (mean age = 35.5 years, 19 males and 9 females) were involved in the study on 4 night shifts, two starting at 2230 hours and two at 2330 hours. On one early, and one late starting night shift, ATCs were provided with a 40-minute nap opportunity during a scheduled break. On the remaining night shifts ATCs were required to remain awake. Polysomnographic data was collected during the nap opportunity and was viewed by two experienced sleep scorers. During each night shift ATCs completed 3 x 10-minute psychomotor vigilance tests (PVT); before beginning work, after the nap opportunity (or a similar time if no nap opportunity was provided), and at the end of the night shift. Mixed model analyses were used to investigate if the amount of sleep during the nap opportunity (all stages or minus S1) influenced a range of PVT outcome variables.

**Results:** ATCs had a mean of 17.7 minutes (SD = 12.2, Range 0 - 47, N = 54) total sleep during the nap opportunity. For those who slept, on average 5 minutes was S1 sleep (SD = 2.9, Range = 0.3 - 12.3, N = 49) and the remainder of time was spent predominantly in S2 sleep (mean = 12.8, SD = 8.5, Range = 0 - 30.5, N = 49). Participants experienced a mean of 2 awakenings (SD = 1.4, Range = 0 - 5.50, N = 49) and 5 ASDA arousals (SD = 2.8, Range = 0 - 12.5, N = 49) during the nap sleep. Results from the mixed models indicated that greater amounts of total sleep improved a number of PVT outcome variables (see Table 1) and when S1 sleep was subtracted from the amount of sleep obtained fewer significant findings were seen.

**Table 1**

*Results of Mixed Model ANCOVAs for the Effect of Nap Sleep (All Stages and Minus S1) on Psychomotor Performance.*

Dependent Variable*	All Sleep Stages	Minus S1 Sleep
Mean RT	$F_{(1,71.7)} = 6.26, p = .015$	
Fastest 10%	$F_{(1,71.7)} = 4.70, p = .033$	$F_{(1,72.3)} = 3.94, p = .050$
Slowest 10%	$F_{(1,88.4)} = 6.26, p = .009$	

\*All dependent variables were transformed using a reciprocal function

**Conclusions:** Despite the limited duration and the fragmented nature of the sleep, pre-planned naps in this operational setting produced significant improvements in psychomotor performance. The findings also indicate that S1 sleep contributed significantly to these performance changes.

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**155.I**

**DO NAPS DURING THE NIGHT SHIFT IMPROVE PERFORMANCE IN THE EMERGENCY DEPARTMENT?**

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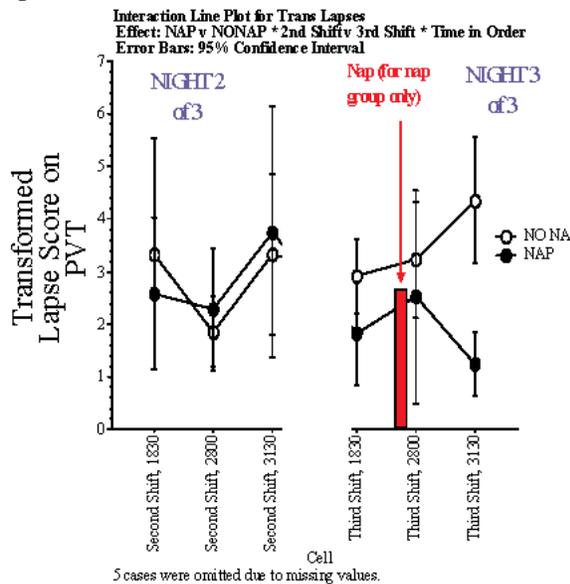
**Introduction:** Emergency medicine physicians and nurses are involved in rotating shift work to provide patient care 24 hours a day. This places them at risk for many problems associated with circadian disruption and sleep deprivation. It has been well documented that shift workers sleep less, perform less effectively on manual and cognitive tests, and make more mistakes during night shifts<sup>1,2</sup>. To investigate the effectiveness of a mid-shift nap intervention as a countermeasure to fatigue encountered by physicians and nurses during emergency department night shifts, we examined whether a 40-minute mid-shift nap affected performance and alertness<sup>3</sup>.

**Methods:** After IRB approval, 17 subjects have participated in

this study thus far. Each subject was studied during two consecutive 12-hour night shifts, a baseline shift and an intervention shift. For the intervention night, subjects were randomized into “nap” or “no nap” groups. Nap subjects took a 40-minute mid-shift nap (between 0300 and 0400). During the baseline and intervention shifts, subjects completed a battery of tests and surveys at three times each night (pre-shift: 1830-1930, mid-shift:0400-0500, and post-shift: 0800-0930), including Probe Recall Memory (PRM) test, CathSim intravenous insertion virtual reality simulation, Psychomotor Vigilance Task (PVT), Profile of Mood States questionnaire, and Stanford Sleepiness Scale. During the nap period, standard electroencephalograph data was recorded. Statistical analyses were conducted using repeated measures ANOVA for shift x nap effects.

**Results:** The nap subjects had reduced PVT mean slowest 10% Reciprocal Reaction Times ( $F_{s(1)S}=5.91, P<0.05$ ) and Transformed Lapses ( $F_{s(1)S}=7.21, p<0.05$ ) at the post-shift testing period as compared to no nap subjects. Preliminary indications suggest that the total time required to successfully perform a CathSim intravenous insertion was faster among the nap group. Mean pre-shift to post-shift insertion time improved by 2.2% among the nap subjects compared to an 18.2% increase in total time for the no nap subjects. A mean pre-shift to post-shift PRM score improvement of 23% was seen within the nap subjects as compared to a mean score decrease of 29% for the no nap subjects. For the 17 subjects so far, there were not statistically significant shift x nap effects for mood or subjective self-reported sleepiness.

Figure 1



**Conclusions:** Preliminary results suggest that taking a 40-minute mid-shift nap can significantly improved post-shift performance on at least certain manual and cognitive tests. Limitations to obtaining statistically significant data include the low number of subjects enrolled and this is currently being addressed.

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**Research supported by the Veterans Health Administration through the Patient Safety Center of Inquiry at VA Palo Alto Health Care System.**

**156.U**

**THE RECUPERATIVE VALUE OF BRIEF AND ULTRA-BRIEF AFTERNOON NAPS**

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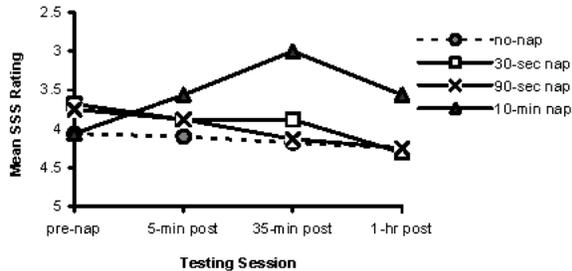
**Introduction:** It has recently been shown that brief naps may be at least as effective as longer naps in improving alertness and performance(1,2). These previous findings challenge the homeostatic Process S model of sleep, which predicts that longer naps will be more beneficial as they comprise a greater proportion of delta wave activity, and it is postulated here that nap benefits may result from sleep onset itself. In addition to this theoretical implication, the possible benefit of sleep onset may have important methodological implications for sleep research and diagnostic clinical practice, considering that the MSLT commonly utilises either a 1-epoch (ie, a 30-sec nap) or 3-epoch (ie, a 90-sec nap) sleep onset criterion.

**Methods:** Sixteen young adult healthy sleepers (M=22.50 yrs, SD=3.86) participated in a repeated measures experiment comprising four conditions: no-nap, ultra-brief naps of 30-secs and 90-secs and a brief 10-min nap. Naps were scheduled to terminate at approximately 15:00 hrs. On the evening preceding each laboratory session, participants limited their nocturnal sleep to between 24:00 and 05:00 hrs (M=4.70 hrs, SD=0.13). Subjective alertness (Stanford Sleepiness Scale), fatigue, vigour, symbol-digit substitution task (SDST) performance and letter cancellation task (LCT) performance were assessed pre-nap, 5 minutes post-nap and 35 minutes post-nap. Subjective alertness was additionally assessed one hour post-nap. Objective alertness (sleep latency) was assessed pre-nap and one hour post-nap.

**Results:** The no-nap, 30-sec and 90-sec naps, showing no significant differences for any of the dependent variables ( $p>.10$ ), were combined into one variable to reduce the number of subsequent analyses. Five minutes after napping, subjective alertness, fatigue, vigour, SDST and LCT performance showed trends of improvement associated with the 10-min nap, although interactions were not significant at  $p<.05$ . At 35 minutes post-nap, the 10-min nap evidenced significantly improved subjective alertness, fatigue and SDST performance,

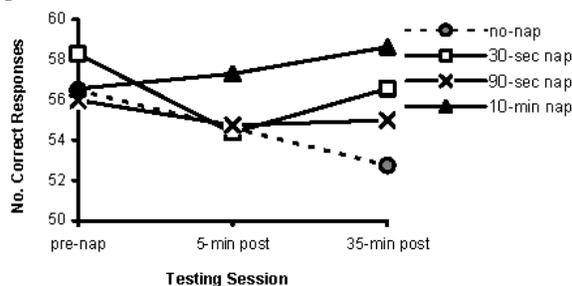
relative to the other conditions combined. Although vigour and LCT performance showed similar trends, interaction effects were not statistically significant. One hour after napping, the 10-min nap showed significantly improved subjective and objective alertness.

Figure 1



Change in subjective alertness produced by no-nap, the 30-sec nap and the 90-sec nap.

Figure 2



Change in SDST performance produced by no-nap, the 30-sec nap and the 90-sec nap.

**Conclusions:** On balance, the findings of the current investigation indicate that, following mild nocturnal sleep restriction, a 10-min afternoon nap reduced subjective fatigue and improved cognitive performance for at least 35-mins and improved alertness for at least one hour. In contrast, ultra-brief naps of 30 and 90-secs produced no measurable benefits within one hour of napping. These findings suggest that the beneficial effects of brief naps are not due to the onset of stage 1 sleep and further suggest that the MSLT, confined to no more than three epochs of sleep, does not alter subsequent alertness.

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**157.U**

**SLEEP DEBT, SLEEPINESS AND ACCIDENTS AMONG MALE PROFESSIONAL DRIVERS AND MALES IN THE GENERAL POPULATION**

Carter NE,<sup>1</sup> Ulfberg J,<sup>1</sup> Nyström B,<sup>1,2</sup> Edling C<sup>2</sup>

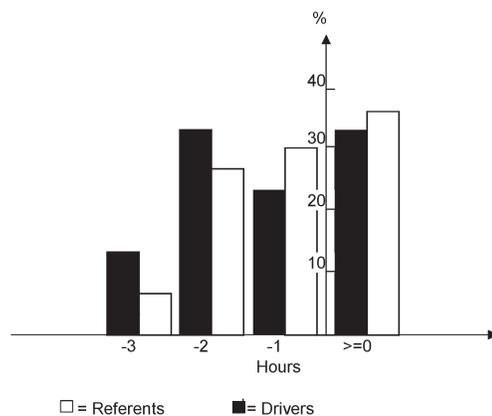
- (1) Department of Medical Sciences/Occupational and Environmental Medicine, University Hospital, Uppsala, Sweden,
- (2) Sleep Disorders Center, Avesta Hospital, Sweden.,

**Introduction:** Sleepiness and reduced vigilance are important risk factors for accident proneness at work (Åkerstedt, 1994). Sleepiness and sleep disturbances have been shown to increase the frequency of occupational accidents (Ulfberg et al., 2000, Lindberg et al., 2000). Driver alertness may have a great impact on safety and sleepiness and reduced vigilance are hypothesized to reduce the capability of a driver to comply with the traffic milieu. This study assessed the accident likelihood in different situations in daily life among male professional drivers and males in the general population according to sleep-disordered breathing and self-reported sleep debt.

**Methods:** Men from the general population and male professional truck and bus drivers were surveyed with regard to sleep habits and different types of accidents. A random sample of four thousand Swedish men in the general population of Dalarna County were mailed a questionnaire and served as referents. A total of 1389 male professional lorry and bus drivers from this county responded to the same questionnaire. One hundred sixty one of the drivers also underwent a sleep study in their homes.

Figure 1

Proportion of sleep debt among professional drivers (N=1389) and male referents (N= 1865) from the general population. Sleep debt in hours = reported hours of sleep -reported desired hours of sleep.



**Results:** The drivers reported more sleep debt than the referents,  $p < 0.001$  (Figure 1). The proportion of total accidents was higher among the commercial drivers as compared with the males in the population,  $p = 0.03$ . Reports on traffic accidents were the same in both groups, but the drivers reported more accidents at leisure compared with referents,  $p < 0.0001$ . Accidents of any kind, traffic accidents included, among those affected by both snoring and apneas, was not reported more in either of the groups. At the sleep study, 17% of those exam-

ined, received the diagnosis of obstructive sleep apnea syndrome. Accidents in traffic at leisure among the referents was increased in proportion to sleep debt,  $p < 0.001$ . Accidents at work among the referents increased in relation to proportion of sleep debt,  $p = 0.002$ . Accidents in traffic among the referents on the way to and from work increased in relation to proportion of sleep debt,  $p = 0.006$ .

**Conclusions:** Sleep debt was found to be common among commercial drivers. The results show that self-perceived sleep debt is directly related to accident likelihood for males in the general population and male professional drivers. However, our results did not corroborate earlier studies claiming that sleep-disordered breathing is a risk factor for involvement in both traffic and other kinds of accidents. These results stress the importance of informing about and complying with our biological need of sleep.

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**Research supported by a grant from the Swedish Council for Work Life Research.**

## 158.U

### APNEA AND SLEEP BEHAVIOR CO-DETERMINE SLEEPINESS AND ALERTNESS IN COMMERCIAL TRUCK DRIVERS

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**Introduction:** Obstructive sleep apnea (OSA) and habitual undersleeping may contribute to excessive sleepiness in commercial motor vehicle operators. As part of a recently completed population-based study investigating the prevalence and consequences of OSA in commercial drivers, we examined the relationships of apnea severity as determined by in-lab PSG and sleep duration at home (determined by wrist actigraphy) on sleep propensity assessed by the Multiple Sleep Latency Test (MSLT) [1] and on behavioral alertness assessed by the psychomotor vigilance test (PVT) [2].

**Methods:** A random sample of 4826 holders of commercial drivers licenses (CDL) residing in Philadelphia and the surrounding counties of Pennsylvania was obtained from the Pennsylvania Department of Motor Vehicles. The multivariable apnea prediction (MAP) questionnaire [3] was sent to each CDL holder in a 2-stage stratified sampling scheme designed to enrich the sample with regard to the number of subjects with OSA. Respondents (N=1391, 30.9%) and non-respondents had comparable age, gender and zip code distributions. The population was divided into higher (n=550) and

lower (n=841) risk strata. We over-sampled those at higher risk recruiting 247 higher risk and 158 lower risk drivers. Subjects wore actigraphs for 1 wk, and then underwent in-lab PSG, and daytime evaluations for the MSLT, PVT and other assessments. The apnea hypopnea index (apneas +  $\geq 3\%$  desat $\pm$ air-flow arousal/hr sleep) was categorized:  $\geq 30$ /hr (severe), 15- $< 30$  (moderate), 5- $< 15$  (mild), and  $< 5$  (none). Action-W software (Ambulatory Monitoring, Inc., 1996) was used to analyze the actigraphy data, but some subjects had so much movement the use of AMI's sleep estimation algorithm was not considered reliable. Therefore, the main period of relative inactivity at night as well as the cumulative duration of periods of inactivity during the night were determined as estimates of sleep duration. Multiple linear regression was used to assess the relationships of MSLT and PVT measures to OSA severity and sleep bout duration at home. Models also controlled for age, gender, BMI, health-related quality of life and examined the effects of snoring, smoking, and alcohol consumption.

**Results:** Statistically significant linear trends were found between increased sleep propensity (MSLT) and increased severity of OSA ( $p = 0.011$ ); and between MSLT and decreased sleep bout time at home ( $p = 0.003$ ). The estimated difference (SE) in mean MSLT between drivers with severe OSA relative to no OSA was -3.0 (1.2). The estimated difference (SE) in mean MSLT between drivers with  $< 6$  hr mean at-home sleep duration compared to  $> 8$  hr mean was -2.9 (1.0). Thus, the effect of these factors had almost identical contributions to increasing daytime sleep pressure. Similar results were observed for behavioral alertness as measured by PVT lapses. Linear trends were significant for OSA ( $p = 0.030$ ) and for at-home sleep bout duration ( $p = 0.0499$ ). The estimated difference (SE) in mean PVT lapses between drivers with severe OSA relative to no OSA was +2.3 (1.1). The estimated difference (SE) in mean PVT lapses between drivers with  $< 6$  hr mean at-home sleep duration compared to  $> 8$  hr was +1.5 (0.6).

**Conclusions:** Obstructive sleep apnea and reduced sleep time at home are simultaneously associated with increased objectively measured daytime sleepiness and decreased behavioral alertness. Interventions designed at reducing excessive daytime sleepiness in commercial drivers should include both sleep apnea and sleep duration components.

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**Research supported by FHWA contract DTFH61-93-C-00088 and NIH grants P50 HL-60287 and M01 RR-00040.**

## 159.U

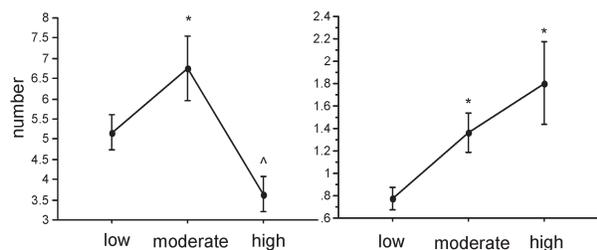
**ERROR-MAKING AND PERFORMANCE SELF-MONITORING OF FATIGUED LOCOMOTIVE ENGINEERS IN A RAIL SIMULATOR**Dorrain J,<sup>1</sup> Roach GD,<sup>1</sup> Fletcher A,<sup>1</sup> Dawson D<sup>1</sup>

(1) The Centre for Sleep Research, The University of South Australia,

**Introduction:** Investigations have identified fatigue as a contributing factor in numerous rail accidents. It has been proposed that an individual's safety-protecting response to increasing fatigue is cued by self-awareness of rising performance impairment. Thus, the aim of the current study was to investigate the effects of fatigue on safety-critical aspects of train driving behaviour, error-making in particular, and to test the ability to self-monitor driving performance.

**Methods:** Twenty male locomotive engineers completed experimental conditions; (i) low fatigue, conducted from 1000 to 1800h, after participants had a full night in bed; and (ii) high fatigue, conducted from 2300 to 0700h, after participants had worked 2-3 consecutive nightshifts. Each condition consisted of four 2-hour sessions that included a 10-minute vigilance task (PVT) and 100 minutes of driving in a rail simulator. Numerous indicators of driving performance were collected, including measures of brake and throttle error, fuel consumption, inter-train forces, trip time and rule violations. Before each driving session and vigilance task, participants rated their alertness, and predicted various aspects of their performance using 100mm Visual Analogue Scales. Participants' fatigue score was calculated for each 2-hr session using Dawson and Fletcher's (2001) fatigue model (1). For the purposes of analysis, performance scores for each session were treated as independent observations, and were assigned to three groups according to fatigue score: low, moderate and high. These levels were defined using previous laboratory validations of the model (2).

Figure 1



Heavy brake reductions (left) and extreme speed violations (right) at low, moderate and high levels of fatigue. \*indicates that scores are significantly different from those at a low fatigue level. ^indicates that scores are significantly different from those at a moderate fatigue level.

**Results:** ANOVA revealed significant ( $p < 0.05$ ) changes in the number of braking errors, extreme speed violations (greater than 25% above the speed limit) and penalty brake applications across fatigue level. The number of braking errors

increased from low to moderate fatigue levels and subsequently decreased from moderate to high levels. In contrast, the number of extreme speed violations and penalty brake applications progressively increased with increasing fatigue level (see Figure 1). While correlations between predicted and actual brake efficiency, fuel efficiency and rule violations were significant ( $p < 0.05$ ), correlations between predicted and actual throttle efficiency, trip time and inter-train forces were not significant.

**Conclusions:** Overall, the differential effect of fatigue on different types of errors and safety violations can be explained through the principle of cognitive disengagement. That is, between moderate and high levels of fatigue engineers became cognitively disengaged from the train such that their interaction with the simulator declined dramatically. In this way, errors or violations involving an action (braking errors) decreased, while those involving a failure to act (extreme speed violations, penalty brake applications) increased. In addition, while individual ability to appreciate fatigue-related performance changes was reasonable for certain aspects of rail operating, it was negligible for others.

**References:**

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**Research supported by The Australian Shift Work and Work Load Study**

## 160.U

**CHRONIC FATIGUE, AGE, SLEEP, ANXIETY, AND DEPRESSION: RELATIONSHIPS AND SHIFT-RELATED DIFFERENCES IN CRITICAL CARE NURSES**Ruggiero J<sup>1,2</sup>

(1) College of Staten Island, City University of New York, Staten Island, NY, (2) Rutgers, the State University of New Jersey, Newark, NJ,

**Introduction:** The study of health care provider fatigue is of crucial importance to the promotion of safe patient care environments (Institute of Medicine, 2000). The daily demands of critical care nursing, including psychosocial stressors, heavy patient workloads and noxious sensory stimuli in the ICU make the nurse particularly vulnerable to fatigue, and subsequently accidents and errors (Triolo, 1989). The purpose of this study was to explore the relationships and shift-related differences among chronic shiftworker fatigue, age, sleep quality, anxiety and depression in a representative sample of critical care nurses.

**Methods:** The random, nationwide sample included 142 female registered nurses who were full-time providers (8, 10, or 12 hour shifts) of direct patient care in critical care units (M age = 45 years; SD = 8.31). Of this sample, 67 nurses worked permanent day shifts without night rotation, and 75 worked permanent night shifts. Participants completed the Standard Shiftwork Index Chronic Fatigue Scale, the Beck Depression

Inventory- II, the Beck Anxiety Inventory, and the Pittsburgh Sleep Quality Index (PSQI) as indicators of chronic shift-worker fatigue, depression, anxiety, and global sleep quality. In addition, PSQI sleep efficiency, duration, and disturbance subscores were explored.

**Results:** Chronic fatigue was inversely related to age ( $r = -.21$ ;  $p < .01$ ), and positively related to poorer global sleep quality ( $r = .49$ ;  $p < .01$ ), lower sleep efficiency ( $r = .20$ ;  $p < .01$ ), more sleep disturbances ( $r = .47$ ;  $p < .01$ ), anxiety ( $r = .46$ ;  $p < .01$ ), and depression ( $r = .63$ ;  $p < .01$ ). Independent t-tests revealed that night nurses experienced significantly more depression ( $t = -2.60$ ;  $df = 140$ ;  $p < .01$ ), poorer sleep efficiency ( $t = -2.24$ ;  $df = 123$ ;  $p < .01$ ), shorter sleep duration ( $t = -1.94$ ;  $df = 140$ ;  $p < .05$ ), and worse sleep quality ( $t = -2.94$ ;  $df = 140$ ;  $p < .01$ ) than day nurses. Hierarchical multiple regression analysis revealed that among the variables of age, day or night shift, habitual sleep quality, depression, and anxiety, depression was the strongest predictor of chronic fatigue ( $\beta = .45$ ;  $t = 6.0$ ;  $p < .001$ ), followed by sleep quality ( $\beta = .24$ ;  $t = 3.11$ ;  $p < .001$ ).

**Conclusions:** Critical care nurses, occupational health providers and hospital administrators need to be aware of the fact that depression and poor sleep quality are more prevalent in night nurses than day nurses, and that they are predictors of chronic fatigue. More educational programs regarding sleep promotion, and counseling services should be made available to critical care nurses on all shifts. Decreased chronic fatigue is likely to result in improved health and safety for critical care nurses and improved patient care in acute care settings.

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- (1) Institute of Medicine. To err is human 2000. Washington, DC: National Academy Press.
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**Research supported by Sigma Theta Tau International Alpha Tau (Rutgers, the State University of NJ) and Mu Upsilon Chapters (The College of Staten Island, CUNY); Dean's Dissertation Fund and the Dorothy J. DeMaio Nursing Research Award (Rutgers University College of Nursing Alumni Association).**

## 161.L

### NIGHT TO NIGHT VARIABILITY IN ALPHA-EEG, CAP FREQUENCY AND SYMPTOMS IN PATIENTS WITH FIBROMYALGIA

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(1) Sleep Disorders Clinic of the Centre for Sleep & Chronobiology, Toronto, CANADA,

**Introduction:** Patients with fibromyalgia (FM) have been shown to have phasic (alpha-delta sleep) and tonic alpha-EEG, and increased rates of cyclic alternating pattern (CAP)<sup>1,2</sup>. There is no information on the variability of the sleep anomalies and symptoms in this population. The purpose of this study was to determine the night-to-night variability of sleep physiology and symptoms in a community-based sample of patients with FM.

**Methods:** 20 female subjects (mean age 42.3 yrs, s.d. = 11.6

yrs) diagnosed with FM were free of all medications for at least 2 weeks. Two sleep recordings (C3A2 & C4A1, OzA2 EEG, right & left oculogram, submental EMG, EOG, right and left anterior tibialis, respiratory effort, airflow and oximetry) were performed on all subjects. Night 2 was performed 2 to 63 days after Night 1. The sleep studies were staged according to standard criteria of Rechtschaffen and Kales, 1968. Two raters, previously shown to have high inter-rater reliability, scored alpha-EEG activity (7.5-11.5 Hz) according to sleep stage<sup>3</sup>. Alpha EEG sleep disorder was rated if alpha occupied 60% or more of NREM stages. CAP frequency of >10/hour of sleep were rated as significant.<sup>2</sup> Tonic alpha-EEG was defined as alpha-ratings which were unchanged across NREM stages 2, and SWS, whereas phasic alpha shows changes between stage 2 sleep and SWS. A paired t-test was used to compare difference between Night 1 & 2. Pearson Correlation Coefficients were used to determine the relationship between CAP and alpha-EEG, and between sleepiness & fatigue.

**Results:** No significant night to night differences were found in the following sleep measures: spontaneous arousals/hr, PLMS index, respiratory disturbance index, CAP frequency, tonic & phasic alpha-EEG sleep, total sleep time, Stage 1 latency, Stage 2 latency, REM latency, %Stages 1, 2 3 & 4, and sleep efficiency index. The only significant differences were found in wake after sleep onset (WASO – night 1=51.9 vs night 2=70.7 mins,  $p=0.024$ ) and %REM sleep (night 1=14.7 vs night 2=18.8,  $p=0.007$ ). No significant night-to-night differences were found in fatigue, sleepiness and pain before and after sleep. There was a positive correlation between i) alpha-EEG and the CAP frequency ( $r=0.42$ ,  $p=0.007$ ); and ii) changes in the fatigue and the sleepiness before & after sleep ( $r=0.6$ ,  $p<0.0001$ ).

**Conclusions:** In patients with fibromyalgia:1) Phasic & tonic alpha-EEG sleep and CAP frequency show no significant night-to- night variability;2) REM sleep increased on the 2nd night, and a reverse 1st night effect was noted with regard to WASO, which increased on the 2nd night. All other measures of sleep architecture showed no significant night-to-night variability;3) Patients with higher CAP frequencies show higher tonic & phasic alpha-EEG sleep;4) There is no night-to-night variability in symptoms, but there is an inter-relationship of fatigue and sleepiness.

#### References:

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**Research supported by Vela Pharmaceuticals**

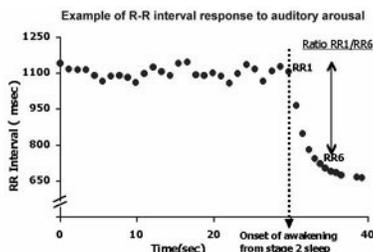
**Oral Presentation**  
**Circadian Rhythms:**  
**Processes and Mechanisms**

**162.E****CIRCADIAN RHYTHM IN CARDIAC REACTIVITY**Hilton MF,<sup>1</sup> Sugarbaker RJ,<sup>1</sup> Shiels SA,<sup>1</sup> Shea SA<sup>1</sup>

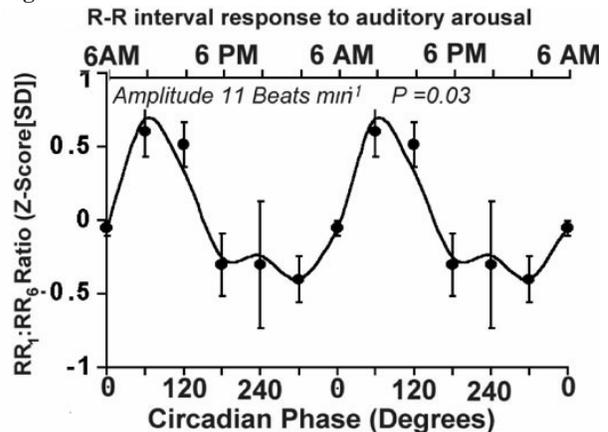
(1) Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, M,

**Introduction:** The window of 9 AM to 11 AM has been identified as a peak time for sudden cardiac death and myocardial infarction<sup>1</sup>. This may be related to underlying circadian rhythms in cardiac vulnerability. For instance the myocardial response to a physiological or environmental challenge may vary according to circadian phase. We tested this hypothesis by examining the heart rate response to auditory arousal from sleep as a function of circadian phase.

**Methods:** Five subjects (1F, 4M) participated in a 10-day protocol conducted in dim light (<8 lux) and temporal isolation. The subjects' sleep-wake cycles were desynchronized from the circadian clock by extending the day length to 28-hours (9.33-h scheduled sleep). Thus, sleep occurred 4-hours later on subsequent 24-hour days such that sleep spanned all circadian phases. An auditory stimulus was given to the subjects on three occasions during each scheduled sleep episode. The stimulus was evenly distributed across each sleep episode and spanned all circadian phases. Only arousals from stage 2 sleep were considered for analysis. Arousals reproducibly elicited monotonically decreasing R-R intervals for a period of 6 intervals (Figure 1). The cardiac response to arousal was evaluated in terms of the size of the R-R decrease from first cardiac cycle (RR1) to the 6th cardiac cycle (RR6) after arousal onset. To normalize for baseline R-R differences, the ratio of RR1 to RR6 was examined. Circadian phase was determined by core body temperature (CBT) measurements (where zero is the CBT nadir). Circadian phases of the R-R interval results were computed using cosinor analysis.

**Figure 1**

**Results:** Figure 2 illustrates that the R-R response to arousal from light sleep has a significant ( $P < 0.03$ ) circadian rhythm with the peak cardiac response at 80-circadian degrees (10:10 AM  $\pm$  33-min). The average instantaneous heart rate (HR) increase in response to arousal from sleep was  $33(\pm 3)$  beats per minute (bpm) at a circadian phase of 80 degrees. The HR increased by  $22(\pm 5)$  bpm at circadian phases between 180 and 300 (approximately 5 PM to 1 AM).

**Figure 2**

**Conclusions:** These data suggest a circadian window around 10 AM where the myocardium has a maximal response to an environmental stimulus. The timing of the maximal cardiac reactivity corresponds to the reported epidemiological peak phase for sudden cardiac death<sup>1</sup>. The decrease in R-R interval at an arousal is a result of an increase in the sympatho-vagal balance. Circadian studies have identified a minimum resting vagal tone at a similar phase that the maximal HR response is seen<sup>2</sup>. Thus, at 10 AM there is (1) minimal vagal tone, which is known to decrease cardiac electrical stability and (2) a greater propensity for an increase in sympatho-vagal balance which has been associated with plaque rupture and myocardial infarction.

**References:**

- (1) Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E, and the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. *N Eng J Med* 1985;313:1315-1322.
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Research supported by NIH HL64815

**163.E****AN ENDOGENOUS CIRCADIAN RHYTHM TO CARDIAC SYMPATHETIC TONE IN HUMANS**Shiels SA,<sup>1</sup> Hilton MF,<sup>1</sup> Weiner ME,<sup>1</sup> Shea SA<sup>1</sup>

(1) Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA,

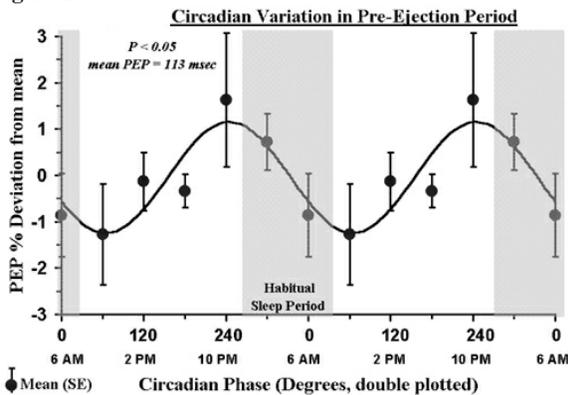
**Introduction:** Epidemiological studies show an increase in adverse cardiovascular events between 9 AM and 11 AM<sup>1</sup>, possibly related to an underlying circadian rhythm in autonomic cardiovascular control. Previous studies have shown a decrease in parasympathetic tone during the late morning attributed to influences from the endogenous circadian pacemaker<sup>2</sup>. However, a corresponding increase in sympathetic tone related to the circadian pacemaker has not been reported. Using cardiac isovolumetric contraction time (pre-ejection period) as a marker of sympathetic activity, we examined the

hypothesis that there is an endogenous circadian rhythm to cardiac sympathetic tone.

**Methods:** To examine circadian rhythms in the absence of environmental and behavioral variations, subjects underwent a dim light *constant routine* protocol (<8 lux). Six healthy subjects (5 male) remained semi-recumbent, relaxed and awake for 38-hours without knowledge of time. Data were collected at two-hour intervals under two conditions, each lasting 7 minutes: (1) *Normal Relaxed Breathing*; (2) *Controlled Breathing*, to control for respiratory influences on the cardiac autonomic nervous system (clamping the respiratory rate at 12 breaths/min and clamping end tidal PCO<sub>2</sub> at the subjects' basal level). Pre-ejection period (PEP) was estimated over each minute from beat-by-beat ensemble averages of thoracic impedance and EKG recordings. Circadian phase was calculated from core body temperature and all variables were aligned with the temperature nadir (assigned 0 degrees).

**Results:** There was a significant circadian rhythm in sympathetic activity as estimated from PEP during normal relaxed breathing (Figure 1). The minimum PEP (maximum sympathetic drive) occurred at 64 circadian degrees (approximately 11 AM). Individual subjects' circadian PEP amplitudes ranged from  $\pm 0.5$  to  $\pm 7.7$  msec (mean  $\pm 2.4$  msec). The circadian rhythm for PEP during controlled breathing approached statistical significance ( $P=0.07$ ), with a similar circadian phase, suggesting that variations in cardiac sympathetic drive occurred independent of respiratory influences. There was a significant circadian rhythm in heart rate, with a maximum at 176 circadian degrees (approximately 6:30 PM). The minimum PEP did not coincide with the maximum heart rate, suggesting that the circadian variation in PEP was not an artificial result of a circadian variation in heart rate.

Figure 1



**Conclusions:** These data, collected under constant behavioral and environmental conditions, demonstrate for the first time the existence of a significant circadian rhythm in sympathetic cardiac tone in healthy subjects, with the peak occurring at approximately 11 AM. In a compromised heart, an augmented sympathetic tone may be deleterious by increasing the likelihood of arrhythmia occurrence and the dislodgment of atherosclerotic plaques. We speculate that the circadian rhythm in sympathetic cardiac tone may contribute to the late morning peak in adverse cardiovascular events.

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- (1) Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E, and the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. *N Eng J Med* 1985;313:1315-1322.
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Research supported by NIH: HL62149, HL64815

#### 164.E

#### MORNING-EVENING DIFFERENCES IN RELATIVE REGIONAL GLUCOSE METABOLISM DURING WAKEFULNESS.

Buysse DJ,<sup>1</sup> Nofzinger EA,<sup>1</sup> Meltzer CM,<sup>1</sup> Wood A,<sup>1</sup> Ombao H,<sup>1</sup> Kupfer DJ<sup>1</sup>

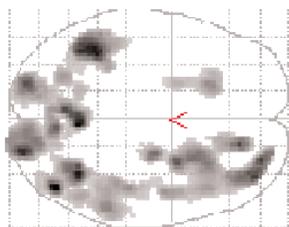
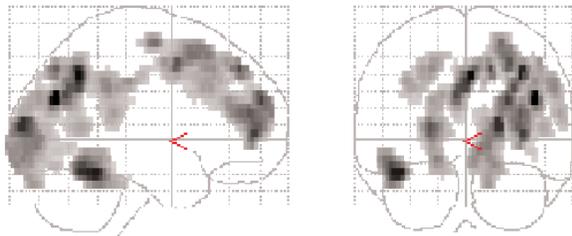
(1) University of Pittsburgh School of Medicine, Pittsburgh, PA, USA,

**Introduction:** Many aspects of wakefulness, including alertness, mood, and cognitive function, show circadian variation. Such variation may reflect increasing homeostatic sleep pressure or effects of the circadian pacemaker's alerting signal on cortical and subcortical structures. However, the functional neuroanatomic basis of circadian changes in waking function have not been examined. The aim of this exploratory analysis was to describe patterns of relative regional glucose metabolism during wakefulness in the morning and at night using 18F-FDG positron emission tomography (PET).

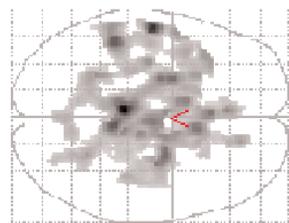
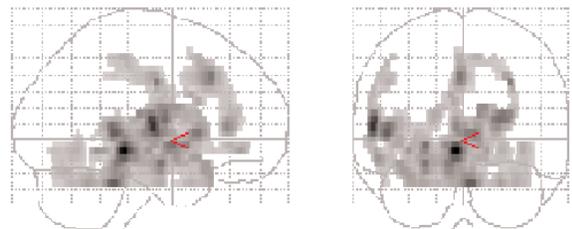
**Methods:** Subjects were 13 healthy young adults (10F, 3M, mean age 37.3 years) with no history of psychiatric, sleep, or medical disorders, and not taking any medications affecting sleep or wakefulness. A screening night of polysomnography, conducted to rule out sleep disorders was followed by a baseline night of polysomnography. The first PET scan was conducted during wakefulness 3-4 hours following sleep, and the second was conducted during wakefulness at subjects' usual bedtime. Each PET scan used 4-6 mCi of [18F]-2-fluoro-2-deoxy-D-glucose (18F-FDG) to measure regional brain metabolic rate. During the 20-minute uptake period, subjects remained seated with eyes closed and no specific mental task. Continuous EEG monitoring was performed to verify wakefulness. Subjects were then transported to the PET Center for imaging, using an HR+ ECAT scanner in 2-D mode. Six 5-minute emission frames beginning 60 minutes after injection were followed by a transmission scan. Each subject's PET scans were summed, co-registered to their high-resolution MRI scan, transformed into Talairach coordinates, and smoothed (10x10x10 mm). Analyses of relative regional cerebral glucose metabolism were performed with Statistical Parametric Mapping (SPM-99), using ANCOVA to correct for global differences. Contrasts involved regions with greater relative regional metabolism in a.m. compared to pre-sleep scans, as well as regions with greater relative regional metabolism in pre-sleep compared to a.m. scans. The threshold for identifying significant differences in SPM images was a corrected cluster-level p value of <0.05, with a height threshold of 0.05.

**Results:** Wakefulness comprised an average of 97.6% of the 20-minute uptake period in the a.m. scan, and 96.4% of the uptake period in the pre-sleep scan. Thus, regional metabolic differences cannot be explained by differences in sleep-wake state. Relative regional glucose metabolism was greater in the a.m. scan than the pre-sleep scan for broad regions of frontal, parietal, and temporal cortex (Figure 1). Greater relative regional glucose metabolism in pre-sleep compared to a.m. wakefulness was observed in midline structures including the upper pons and brainstem, thalamus, and anterior cingulate cortex (Figure 2).

**Figure 1**



**Figure 2**



**Conclusions:** These preliminary results suggest that patterns of relative regional glucose metabolism during wakefulness vary at different times of day. Most regions of cortex showed greater metabolic activity in the morning than at the usual bedtime. Conversely, the upper brainstem, thalamus, and anterior cingulate had greater relative metabolism in pre-sleep compared to morning wakefulness. The observed results may indi-

cate the effects of a circadian alerting signal, the cumulative effects of sustained wakefulness, or some combination of the two, on cerebral metabolic patterns.

**Research supported by MH 24652, MH 30915, RR 00056, AG 00972**

**165.E**  
**EFFECT OF WAVELENGTH ON PHASE ADVANCE OF THE MELATONIN RHYTHM**

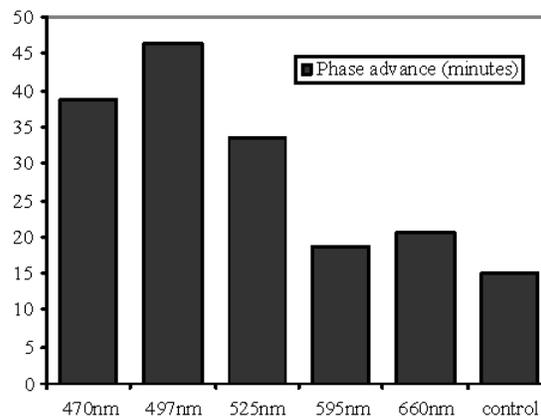
Wright HR,<sup>1</sup> Lack LC<sup>1</sup>

(1) Flinders University of South Australia,

**Introduction:** In an initial study we compared different wavelengths of light for melatonin suppression and phase delaying of salivary melatonin (1). When exposed to light from midnight to 02:00 h, light of shorter wavelengths showed the greatest melatonin suppression and were more effective in phase delaying the melatonin rhythm than light of longer wavelengths. More recently morning light exposure with red light has been shown to phase advance circadian rhythms (2). In the present study we compared the effectiveness of different wavelengths of light in phase advancing the salivary melatonin rhythm.

**Methods:** Fifty-four volunteers participated in the 3-day study and were randomly allocated to one of five wavelengths or the no light control condition (N=8). Light was administered via mono-chromatic light emitting diodes (LED) attached to spectacle frames, each LED positioned 12 mm from the cornea. The wavelengths had peaks at 470 nm (N=7), 497 nm (N=11), 525 nm (N=11), 595 nm (N=7) and 660 nm (N=10). All LEDs were equated for irradiance of 65 μwatts/cm<sup>2</sup>. Each experimental condition was conducted over three nights and two consecutive mornings with light administered on two mornings from 06:00 h to 08:00 h. Half-hourly saliva samples were collected on Night 1 from 19:00 h to 24:00 h and from 18:30 h until 23:30 h on Night 3. Dim light melatonin onset (DLMO) was calculated for Night 1 and Night 3 (pre and post light exposure). One-way ANOVA was performed on advance of DLMO on Night 2 compared to Night 1.

**Figure 1**



**Mean phase advance (minutes) for each condition**

**Results:** The ANOVA showed significant variation between wavelength conditions ( $F(5,48)=2.6, P<0.05$ ). Post Hoc analyses showed the shorter wavelength LEDs of 470nm and 497 nm produced greater phase advances than light of 595 nm, 660 nm and the no light control condition (Figure 1).

**Conclusions:** Light of shorter wavelengths of 470nm and 497nm showed significant salivary melatonin phase advances of 39 to 46 minutes. These results are consistent with the involvement of a scotopic mechanism in phase advancing the circadian rhythm.

**References:**

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### 166.E

#### EFFECT OF LIGHT WAVELENGTH ON SUPPRESSION AND PHASE DELAY OF THE MELATONIN RHYTHM

Wright HR,<sup>1</sup> Lack LC<sup>1</sup>

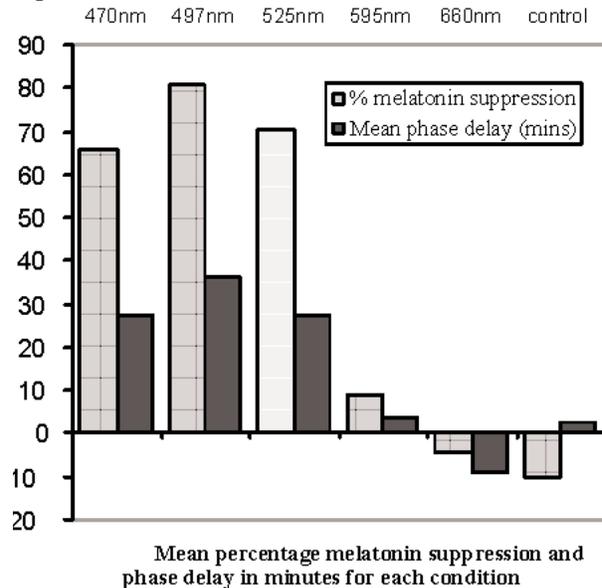
(1) Flinders University of South Australia,

**Introduction:** In an initial human study, Brainard et al. (1) found that melatonin suppression was greatest with light of a peak wavelength of 509 nm. More recently Brainard et al.(2) and Thapan et al. (3) have evidence showing 420-477 nm to be the most effective wavelength region for night time suppression of melatonin. We compared five different wavelengths of light both for melatonin suppression and phase shifting of nocturnal salivary melatonin rhythm.

**Methods:** Fifteen volunteers participated in all of the five wavelength conditions and a no light control condition. Light was administered via monochromatic light emitting diodes positioned 12 mm from the cornea, by attachment to spectacle frames. The wavelengths had peaks at 470 nm (blue), 497 nm (blue/green), 525 nm (green), 595 nm (amber) and 660 nm (red). All LEDs were equated for irradiance of 65 microwatts/cm<sup>2</sup>. Each experimental condition was conducted over two consecutive days with light administered on the first night only from midnight to 02:00 h. Half hourly saliva samples were collected from 19:00 h to 02:00 h on Night 1 and until 01:00 h on Night 2. Percent melatonin suppression and dim light melatonin onset (DLMO) were calculated. One-way ANOVAS were performed on the percentage melatonin suppression on Night 1 and on the delay of DLMO on Night 2 compared to Night 1.

**Results:** Percentage melatonin suppression on Night 1 was significantly greater with light of 470 nm, 497 nm and 525 nm than the control condition, and light of 595 nm and 660 nm wavelengths (Figure 1). Similarly the light of 470nm, 497 nm and 525 nm produced greater phase delays than that of the control condition and light of 595 nm and 660 nm wavelengths (Figure 1).

**Figure 1**



**Conclusions:** The shorter wavelengths of 470, 497 and 525 nm showed the greatest melatonin suppression between 65 to 81% and phase delay of dim light melatonin onset ranging from 27 to 36 minutes. The results were consistent with the involvement of a scotopic mechanism in the regulation of circadian phase.

**References:**

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- (3) Thapan K, Arendt J, Skene DJ. An action spectrum for melatonin suppression: Evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol* 2001; 535: 261-267.

### 167.E

#### LIGHT DURATION AND SLEEP/WAKE STATE INFLUENCE CIRCADIEN PHASE IN HUMANS

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(1) Department of Neurology, Northwestern University Medical School, (2) Faculte de Medecine, Universite Libre de Bruxelles, (3) Division of Pulmonary and Critical Care Medicine, Northwestern University Medical School,

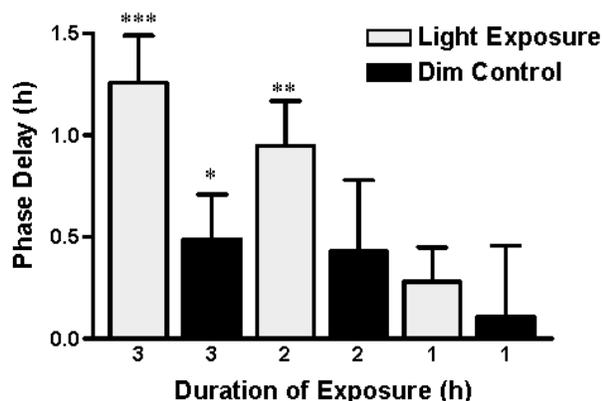
**Introduction:** It is well known that light is one of the most important entraining agents for the biological clock. Recent studies have shown that both the intensity and the timing of light are important determinants of the magnitude of phase shifts<sup>Begin superscript 1,2 End superscript</sup>. Little is known, however, about the response of the human biological clock to light

pulses of varying duration. Furthermore, it is unclear whether a single, short duration pulse of light is sufficient to shift circadian rhythms in humans maintained under a fixed sleep/wake cycle. In the present study, we assessed the effect of a single pulse of bright-intensity light or a control condition (lasting 1, 2, or 3 hours) on the circadian rhythmicity of serum melatonin and core body temperature.

**Methods:** Thirty-two healthy young subjects (10 male and 22 female,  $28.9 \pm 3.9$  years) were admitted for two stays in the Clinical Research Center at Northwestern Memorial Hospital, each lasting 4 nights/3 days. Subjects were maintained under a modified constant routine during waking hours (room light < 20 lux, semi-recumbent wakefulness in bed, snacks of 200-250 kcal every two hours) and slept for 8 hours in the dark at their usual bedtime on baseline and post-treatment nights. Core body temperature (CBT) was monitored continuously with a rectal thermometer. Following a habituation and baseline night, subjects were awoken and exposed to either bright-intensity light (3,000 lux) or a control condition (dim light < 20 lux) in a repeated measures design. The duration of the light pulse was 1, 2, or 3 hours, bordered by 15-30 minutes of intermediate illumination. The light pulse was centered at 3 hours before the baseline core body temperature nadir. Blood samples were collected at 20-30 minute intervals and analyzed using radioimmunoassay. Serum melatonin levels were converted to percent-of-maximum (average of the three greatest values) and fitted using a Lowess curve-fit procedure (Graphpad Prism software). Phase shifts in the melatonin rhythm were assessed as the difference in the baseline and post-treatment melatonin profiles at the midpoint (50%) of the rising and declining phases.

**Results:** Exposure to bright-intensity light (3,000 lux) in the middle of the night delayed the circadian melatonin rhythm ( $p < 0.001$ ) in a duration-dependent manner (figure 1), for 3h light pulse ( $p < 0.001$ , baseline vs. post-tx), 2h light pulse ( $p < 0.01$ , baseline vs. post-tx), and 1h light pulse. There was a tendency for subjects in the control condition to also exhibit small delays in melatonin rhythm ( $p = 0.063$ ) with an interaction between the magnitude of phase shifts and the treatment condition (light vs. control,  $p < 0.05$ ). Awakening for 4 hours in the middle of the night (control condition) also resulted in a delay in the circadian melatonin rhythm ( $p = 0.05$ , baseline vs. post-tx).

Figure 1



**Conclusions:** These results indicate that a single pulse of bright-intensity light lasting 2 to 3 hours is sufficient to delay the phase of circadian rhythms in humans. Furthermore, disruptions in sleep timing can also produce small delays in circadian rhythms. Taken together, these results indicate that the duration of light exposure, as well as alterations in sleep and wake times, can affect the timing of the circadian clock.

**References:**

- (1) Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. *Nature* 1996;379:540-42.
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Research supported by R01 HL67604-01, P01 AG11412, NCR-0048, K01 AG00810, R25 RR15404-01

**168.E**

**NEUROBEHAVIOURAL FUNCTIONING DURING CHRONIC SLEEP RESTRICTION AT AN ADVERSE CIRCADIAN PHASE**

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**Introduction:** Several studies have described detrimental effects on neurobehavioural functioning following sleep restriction (for review see 1). All but one previous study (2), however, have only examined the effects of 4 days or less of sleep restriction. Further, sleep was typically placed nocturnally (normal circadian phase). Many people (e.g., shiftworkers) commonly experience chronically reduced sleep (quality and quantity) due to sleeping during the day (adverse circadian time). The present study aimed to examine neurobehavioural effects of 3 doses of chronic (10d) sleep restriction (4h, 6h, 8h TIB) with sleep placed at an adverse circadian phase (i.e. diurnally).

**Methods:** Forty-four healthy subjects (29m; 15f; aged 21-44y) completed this 15-day (14-night) in-laboratory protocol. Following one night of baseline sleep (2330h-0730h) subjects remained awake for 28 hours, followed by an 8h diurnal sleep period (1130h-1930h). Subjects were randomly assigned to a diurnal sleep restriction condition (4h: 1530h-1930h; 6h: 1330h-1930h; 8h: 1130h-1930h) that was maintained for 10 consecutive days, followed by 2 recovery days with a 10h nocturnal sleep period (2330h-0930h). Subjects remained in the laboratory throughout the protocol, with light levels <50lx and ambient temperature at  $24^{\circ}\text{C} \pm 1^{\circ}\text{C}$ . Every 2 hours during wakefulness subjects completed a 35-min neurobehavioural assessment battery (NAB), containing both objective tests of neurobehavioural performance (e.g., psychomotor vigilance task [PVT]; digit symbol substitution task [DSST]) and subjective measures of sleepiness (e.g. Karolinska sleepiness scale [KSS]) and mood. Salivary melatonin and core body temperature were measured to assess changes in the circadian system. Polysomnographic recordings of sleep and wake periods were collected.

**Results:** Preliminary analyses suggested that PVT lapses (i.e. RTs >500ms) and fastest 10% of RTs demonstrated the greatest decrement across days of the protocol in the 4h condition ( $p < 0.001$ ), with levels of neurobehavioural decrement in the 6h and 8h conditions being comparable. The 8h condition demonstrated greater performance decrements relative to a previous study, where subjects were allowed a nocturnal 8h TIB for 14 days (2), underlining the importance of the timing of sleep for its restorative potential. Remarkably, there was little difference across the current conditions in subjective ratings of sleepiness, measured using the KSS.

**Conclusions:** These preliminary findings suggest that the ability of neurobehavioural functioning to adjust to a large shift of the circadian timing of sleep may be slower than previously hypothesised (i.e. one day for every hour shifted). In addition, it appears that self-assessments of sleepiness are poorly correlated with changes in neurobehavioural performance. This finding points to a deficiency in the ability to judge one's own performance deficits resulting from reduced sleep at an adverse circadian phase. Analysis of additional neurobehavioural and subjective variables and sleep-wake physiology, combined with statistical modeling of the changes across days will elucidate the full scope of effects due to chronic sleep restriction at a diurnal circadian phase.

**References:**

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- (2) Dinges DF, et al., Chronic sleep restriction: Neurobehavioral effects of 4hr, 6hr, and 8hr TIB. *Sleep* 1999, 22: S115-S116.

Research supported by NIH R01-NR04281, M01-RR00040 and NASA cooperative agreement NCC9-58 with the NSBRI.

### 169.E

#### MORNINGNESS/EVENINGNESS (M/E), PHASE ANGLE, SLEEP RESTRICTION, AND MSLT: A PILOT STUDY IN ADOLESCENTS

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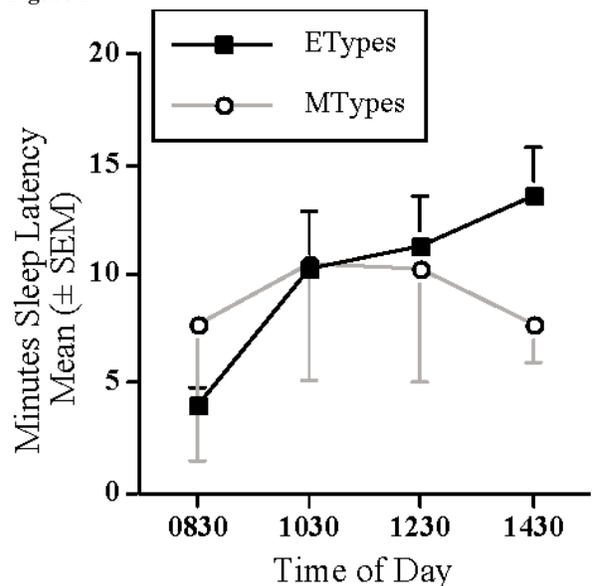
**Introduction:** As more is learned about how the timing of sleep and sleepiness are regulated by sleep-wake homeostatic and circadian timing mechanisms, models arise for predicting temporal effects of changes in sleep behavior. Extreme morning type (MType) and extreme evening type (EType) individuals appear to show differential alignment of entrained sleep-wake schedule to the circadian timing system (1): MTypes wake further from markers of the circadian night (e.g., phase of core body temperature minimum) and ETypes wake closer to such markers. We have shown that clock-dependent alerting is lowest near the end of the circadian night and rises across the day, and wake-dependent sleepiness is least in the morning after a night of sleep and increases across the waking day (2). These findings together allow us to predict the pattern of

sleepiness occurring after sleep restriction. Waking with a sleep deficit AND close to the minimum of clock-dependent alerting (ETypes) will predispose to morning impairment with greater alertness across the day in association with rising clock-dependent alerting. On the other hand, MTypes waking with the same sleep deficit but at a phase where the clock-dependent alerting signal is higher will experience less morning sleepiness than ETypes but greater sleepiness later in the day.

**Methods:** Participants were selected from a group of 87 healthy, normal-sleeping adolescents (screened to exclude extremes of M/E) in a larger study of sleep restriction if their M/E scores (3) exceeded the group average by at least one standard deviation. Those reaching criterion included 3 MType (2 girls) and 6 EType (2 girls) ages 9.3 to 12.5 years. Melatonin onset phase was determined at the end of one week on a self-selected school-night schedule. Participants later had one week of sleep restriction to 6.5 hours a night at home confirmed by actigraphy. Four SLTs were done at the end of the week: 0830, 1030, 1230, and 1430. Statistical comparisons are precluded by the small sample size.

**Results:** The average time between melatonin onset phase and usual wake-up on the self-selected schedule was  $661 \pm 37.8$  minutes in MTypes and  $613 \pm 38.4$  in ETypes. The figure illustrates MSLT patterns averaged for MTypes and ETypes.

**Figure 1**



**Conclusions:** We saw the predicted pattern of MSLT scores in this small group of moderate MType and EType adolescents: sleep-restricted ETypes showed rising scores across the day; scores for MTypes fell in the afternoon. Predicted group differences in phase angle were also apparent, greater for MTypes than ETypes. These data provide preliminary support for a model predicting sleepiness from behavior and circadian phase preference.

**References:**

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self-reported preference for morning or evening activity in young and older people. *J Investig Med* 1999;47:141-150.

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Research supported by NR04270 and MH01358

## 170.E

### EFFECT OF BODY TEMPERATURE MANIPULATION ON PULSE WAVE AMPLITUDE AND SLEEP ONSET LATENCY

Van Someren EJ,<sup>1</sup> Raymann R,<sup>1</sup> Drosopoulos S,<sup>1</sup> Collins S,<sup>1</sup> Vis R,<sup>1</sup> van Krevelen G,<sup>1</sup> Swaab D<sup>1</sup>

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**Introduction:** Thermoregulatory processes, with special emphasis on skin temperature, have been proposed to be involved in the circadian modulation of sleep onset propensity<sup>1</sup>. The increase in distal (hand and feet) skin temperature seen in the evening is a consequence of redistribution of the blood to the more distal, arteriovenous anastomose-rich parts of the body, in order to dissipate heat and thus lower core temperature. This distal vasodilation is associated with sleep onset latency<sup>2</sup>. We studied the relationship between finger pulse-wave amplitude (PWA) as measure of vasodilation and sleep onset latency (SOL) in conditions where core body temperature and skin temperature were independently manipulated experimentally.

**Methods:** 8 volunteers participated in 2 consecutive 22 hours experimental protocols. During daytime, core body temperature, proximal skin temperature and distal skin temperature were independently manipulated in slightly warm and cold directions in the comfortable and thermoneutral range, using a thermosuit, computer-controlled circulating thermostat baths and hot/cold food and beverages. Subjects stayed in bed under dim light conditions and a fixed body position schedule. Within each temperature manipulation condition (two days, circadian balanced 2x2x2 manipulations = 16 per subject), SOL was determined polysomnographically according to the MSLT protocol. Peripheral arterial tonus by means of volume plethysmography (PAT, Itamar Medical) was continuously monitored. PWA was calculated for every 30 second wake/sleep epoch, and averaged for every SOL determination over the interval from lights-out until falling asleep. After removal of artefactual epochs, SOL and PWA were standardized within subjects in order to allow for preliminary analyses.

**Results:** ANOVA revealed that SOL was shorter during the cold core conditions as compared to the warm core conditions ( $p < .03$ ). Opposite effects occurred with skin warming and cooling: SOL was shorter during the warm as compared to the cold conditions, nonsignificantly for distal skin manipulations, but significantly for proximal skin manipulations ( $p < .04$ ). PWA during the time from lights-out until sleep onset was significantly affected by proximal skin temperature

manipulations only, and higher in the warm condition ( $p < .003$ ). SOL was moderately negatively correlated to PWA ( $r = -.211$ ,  $p < .02$ ).

**Conclusions:** Although correlations have been reported before, the present study is the first to show that under balanced and controlled conditions - independently manipulating the temperatures of the core and proximal and distal skin - a slightly cooler core and/or warmer skin facilitate sleep onset. A warmer proximal skin also results in a higher mean PWA during the time from lights-out until sleep. It might be that the relative large surface of proximal skin temperature manipulation is more effective than the relative small surface distal skin manipulation in inducing a vasodilation in the distal parts as well, as measured with the PAT. So the warm proximal skin induced both increased PWA (and hence distal vasodilation) and decreased sleep onset latency. The significant negative correlation between PWA and SOL confirms the previously reported correlation between sleep onset and distal vasodilation. The data provide the first experimental evidence for the hypothesis that skin temperature feeds back on thermosensitive neurons in sleep-regulating brain areas<sup>1</sup>.

#### References:

(1) Van Someren et al (2000) *Chronobiol Int* 17:313-54; 2. Krauchi et al (2000) *Nature* 401:36-7

Research supported by Itamar Medical, Royal Auping, Braun, Cambridge Neurotechnology, Flaga, NIBR, NWO (projects SOW 014-90-001 and Vernieuwingsimpuls), RVVZ, Japan Foundation for Aging and Health.

### Oral Presentation Molecular and Cellular Aspects of Sleep and Sleep Deprivation

## 171.A

### GROWTH HORMONE-RELEASING HORMONE AND INTERLEUKIN-1BETA INCREASE CALCIUM LEVELS IN GABAergic NEURONS CULTURED FROM RAT FETAL HYPOTHALAMUS

Churchill L,<sup>1</sup> De A,<sup>1</sup> Taishi P,<sup>1</sup> Broom L,<sup>1</sup> Obal Jr. O,<sup>1</sup> Simasko S,<sup>2</sup> Krueger JM<sup>1</sup>

(1) Washington State University, (2) University of Szeged, Szeged, Hungary,

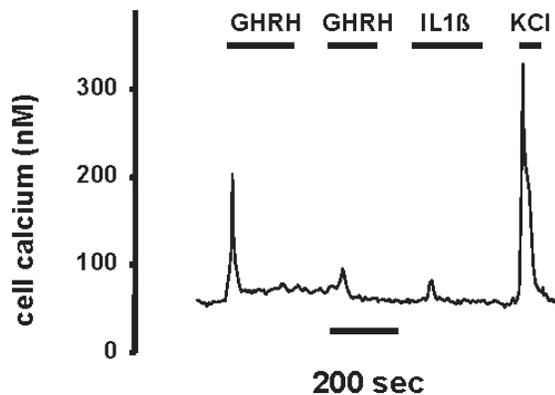
**Introduction:** There is substantial evidence implicating the brain cytokine network and growth hormone releasing hormone (GHRH) in non-rapid eye movement sleep (NREMS) regulation. The medial preoptic area near the anterior hypothalamus contains GHRH receptors and microinjection of GHRH into this region increases NREMS (Zwang et al., 1999). Lesions of this region produce insomnia in humans and rats and microinjection of a GABAergic agonist into the posterior hypothalamus of rats with anterior hypothalamic lesions recovers sleep (Sallanon et al., 1989), suggesting that GABAergic neurons in the anterior hypothalamus/medial preoptic area are involved in sleep regulation. Since both GHRH and IL1beta increase cytosolic calcium levels in fetal hypothalamic cultures (De et al., Sleep, this volume), we hypothesized that some of these neurons might be GABAergic. There-

fore after measuring their cytosolic calcium response with optical imaging, we stained for glutamate decarboxylase (GAD) immunoreactivity, a marker for GABAergic neurons, and relocated these individual neurons. We found that most of the cells responsive to IL1beta and/or GHRH colocalize with GAD immunoreactivity.

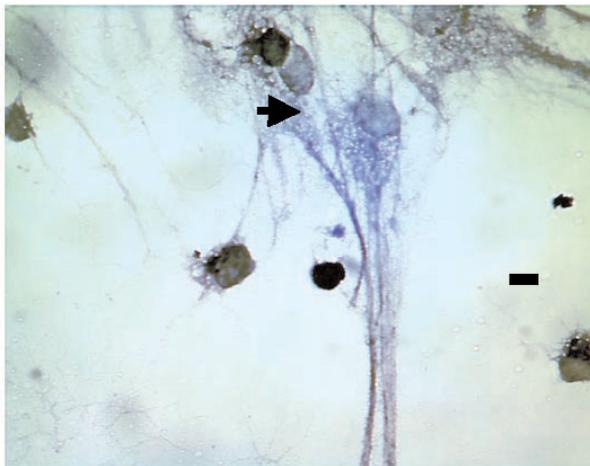
**Methods:** N/A

**Results:** Increases in calcium levels are evident with single cell imaging of individual cells cultured from fetal hypothalamus when perfused with either GHRH (100 nM) or IL1beta (20 ng/ml) (Fig. 1). A significant increase in the calcium response to both GHRH and IL1beta are evident in this cell. The response to KCl also demonstrates that this cell is a neuron. Localization of this neuron after performing glutamate decarboxylase (GAD) immunoreactivity demonstrates that this neuron contains GAD, as evident by the darkly stained cell with extending fibers near the arrow (Fig. 2). We have observed GAD immunoreactivity in 42 out of 45 (93%) GHRH responsive neurons, 10 out of 14 (71%) IL1beta responsive neurons and 3 out of 3 (100%) neurons that response to both GHRH and IL1beta.

**Figure 1**



**Figure 2**



**Conclusions:** These data indicate that many GHRH- or IL1beta-responsive neurons in cultures of fetal hypothalamus are GABAergic.

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- (2) Zhang J, Obal F, Jr, Zheng T, Fang J, Taishi P, Krueger JM: Intrapreoptic microinjection of GHRH or its antagonist alters sleep in rats. *J Neurosci* 19:2187-2194, 1999.

**Research supported by NIH, NS25378 and NS 27250.**

#### 172.A

#### INTRACELLULAR EFFECTS OF ADENOSINE IN CHOLINERGIC NEURONS: A COMPARATIVE STUDY OF BASAL FOREBRAIN AND LATERODORSAL TEGMENTAL NUCLEUS

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**Introduction:** There is now considerable evidence that adenosine, acting in the basal forebrain (BF), is a homeostatic sleep factor regulating the increased propensity to sleep following increased duration of wakefulness. In vivo microdialysis studies provide evidence for long term increase in extracellular adenosine in cholinergic zone of BF but not in mesopontine cholinergic nuclei (1, 2). Adenosine's immediate effects on post-synaptic membrane ionic mechanisms are similar for cholinergic or noncholinergic neurons of mesopontine laterodorsal tegmental nucleus (LDT) and BF. Adenosine as well as A1 agonists cause hyperpolarization by activation of inwardly rectifying potassium current, and /or blockage of I<sub>h</sub> currents (3) in these areas. In order to understand the functional significance of sleep deprivation-induced selective increase of extracellular adenosine in BF we compared long-term intracellular effects by examining the intracellular signal transduction pathway in response to adenosine in both regions. First we investigated whether or not adenosine was capable of inducing an increase in cytosolic calcium, further determining the source of the this increase and the involvement of the IP<sub>3</sub> receptor and/or ryanodine receptor of endoplasmic reticulum, and the adenosine receptor type(s) mediating these effects. Furthermore, we investigated if sleep deprivation induced nuclear translocation of NF- $\kappa$ B occurs in the cholinergic neurons of both regions.

**Methods:** Male Long Evans rats (350-300 g) were used. Acute Brain Slices (200:μ thick) from anesthetized animals were collected from BF and LDT in carboxygenated ACSF. For calcium assays three slices/ animal were hemisected and loaded with calcium orange dye (10:μM, final concentration). A BioRad MRC 1024ES Multiphoton Imaging system was used for quantitative fluorescence imaging of samples in epifluorescence mode. Labeled neurons in the brain sections were identified by XYZ scanning generally at depths of 30-170 μm. Images were reconstructed and processed using the BioRad LaserSharp and Metamorph (Universal Imaging, West Chester, PA) software. In another experiment the animals were sleep deprived for 3 hours by gentle handling from 7AM to 10 AM and perfused with formalin transcardially and the brains

collected. Undisturbed sleeping controls killed at the same circadian time served as controls. Immunofluorescence labeling of 40 $\mu$  coronal sections was done using specific ChAT goat antibody (AB 144) and NF- $\kappa$ B rabbit antibody (SC109). FITC conjugated anti-goat and Cy5 anti-rabbit secondary antibodies were used for detecting ChAT and NF- $\kappa$ B respectively. Samples were imaged using multiphoton microscopy.

**Results:** Treatment of slices with adenosine resulted in increased intracellular calcium in both basal forebrain and LDT cholinergic neurons. The increase in intracellular calcium was independent of the calcium in external medium suggesting the source of calcium being intracellular in both the regions. The basal level of fluorescence (untreated resting cell) was equal in BF and LDT neurons. However, basal forebrain showed a pronounced increase (600% increase,  $p < 0.001$ ,  $t$  test), whereas LDT neurons showed a 200% increase ( $p < 0.01$ ) when compared to respective untreated controls. Moreover, The effect of adenosine was predominantly mediated via A1 adenosine receptor in BF. Preliminary observations show that the effect in LDT is mediated via A3 adenosine receptor. Furthermore, sleep deprivation induced nuclear translocation of NF- $\kappa$ B was detected in basal forebrain but not in LDT cholinergic neurons.

**Conclusions:** Our preliminary results indicate that adenosine elicits differential effects on cytoplasmic calcium increase from IP3 regulated intracellular stores in BF and LDT cholinergic neurons. The nuclear translocation of NF- $\kappa$ B observed in BF neurons may be due to the distinctive role played by the A1 receptor mediated signal transduction pathway leading to high levels of intracellular calcium. Together, these results suggest that a selective functional response to adenosine in BF cholinergic neurons by sleep-deprivation induced adenosine may play a role in long term effects of sleep deprivation.

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## 173.A

### NUCLEAR TRANSLOCATION OF TRANSCRIPTION FACTOR NF- $\kappa$ B IS CHOLINERGIC NEURON- AND SITE-SPECIFIC: A SLEEP DEPRIVATION AND MICROINJECTION STUDY

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**Introduction:** Several lines of study implicate the role of adenosinergic system in the basal forebrain (BF) in sleep induction and maintenance. Adenosine in general is an inhibitory neuromodulator, acting mainly on the A1 receptors, either by hyperpolarizing the postsynaptic membrane/blocking Ih or by blocking the release of excitatory neuromodulators from the presynaptic terminals. Microdialysis studies done in our lab have shown that levels of extracellular adenosine is high during wakefulness than in slow wave sleep and rapid eye movement sleep in the BF and sleep deprivation induces monotonic increase in extracellular adenosine with each hour of sleep deprivation (1). We have also shown that either 3 h sleep deprivation or *in vitro* adenosine treatment of BF slices resulted in increased DNA binding activity of the transcription factor NF- $\kappa$ B, mediated via the adenosine A1 receptors (2). However it was not clear whether (a) the adenosine-mediated nuclear translocation of NF- $\kappa$ B is specific to A1 receptors, (b) occurred in cholinergic and /or other neuronal types and (c) is specific to BF. The following experiments were carried out to answer these points.

**Methods:** Twenty seven Long Evans male rats (250-350 g) maintained at constant temperature (23  $\pm$  1 $^{\circ}$ C) and 12:12 LD cycle (light-on period from 0700 h to 1900 h) with *ad libitum* food and water were used in this study. *Experiment 1:* Six rats were sleep deprived for 3 h (0700 h to 1000 h) by gentle handling. Undisturbed sleeping animals (n=6) sacrificed at 1000 h served as controls. *Experiment 2:* Under anesthesia, 4 animals were fixed on to the stereotaxic instruments and 0.5  $\mu$ l of 25 nM adenosine (n=2) or 0.5  $\mu$ l of ACSF (n=2) as control were microinjected into basal forebrain at co-ordinates (AP -0.30, ML -2.2, DV -8.0). *Experiment 3:* Similarly, 0.5  $\mu$ l of 100nM, A1 receptor agonist, CHA (n=5) or 0.5  $\mu$ l of 10 nM, A3 receptor agonist, AB-MECA (n=4) or 0.5  $\mu$ l of ACSF (n=2) were microinjected into BF. A2a receptor agonist microinjections were not attempted based on our previous results showing absence of A2a receptor ligand binding in this area of the BF (3). Immediately after sleep deprivation and one hour after microinjection, the rats were perfused and brains collected. 40  $\mu$ m thick sections of BF were triple labeled using antibodies against A1 receptors, NF- $\kappa$ B and ChAT. The immunofluorescence stainings were imaged using multi-photon microscope.

**Results:** Sleep deprivation for 3 h induced nuclear translocation of NF- $\kappa$ B in BF. All neurons that had nuclear translocation of NF- $\kappa$ B were ChAT +ve and were immunopositive for adenosine A1 receptor antibody. Nuclear translocation of NF- $\kappa$ B did not occur in ACSF injected control animals. Moreover, nuclear translocation of NF- $\kappa$ B occurred in ChAT +ve neurons in the ipsilateral side of adenosine injected rats without any effect on the side contralateral to the injection.

tion. Similarly, nuclear translocation of NF $\kappa$ B occurred only in ChAT +ve neurons in the CHA-injected side, without any effect on the contralateral side. Microinjection of AB-MECA did not induce any nuclear translocation of NF $\kappa$ B.

**Conclusions:** Together, our results show that adenosine mediates nuclear translocation of NF $\kappa$ B by acting on the A1 receptor and occurs only in cholinergic neurons of BF. It is possible that the transcription factor NF $\kappa$ B may promote transcription of proteins important in the long-term effects of sleep deprivation.

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## 174.A

### HEAT SHOCK PROTEIN EXPRESSION IN SLEEP DEPRIVATION AND RECOVERY SLEEP: A QUANTITATIVE IMMUNOHISTOCHEMICAL STUDY

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**Introduction:** Recovery sleep (RS) following sleep deprivation (SD) is characterized by increased slow-wave sleep amount and EEG slow wave amplitude. These changes in sleep architecture are thought to reflect the expression of a restorative or homeostatic process that is presumed to have a molecular and cellular basis. Using cDNA arrays, previous studies in our laboratory have identified genes that are upregulated in SD and RS relative to circadian time-matched controls (1). Three heat shock proteins (HSPs), HSP27, endoplasmic reticulum-related protein (ERp) 72, and glucose-regulated protein (GRp) 78, were among the genes found to be elevated in the mouse cerebral cortex during SD. Quantitative real-time PCR analysis of five HSPs was performed in seven brain regions and ERp72, GRp78, and GRp94 were found to be elevated in cortex during both SD and RS (1). In the present study, we have used immunohistochemistry to investigate whether protein expression of these three HSPs is elevated in the cortex during SD and RS.

**Methods:** Male C57BL/6 mice were sampled in four experimental conditions (n=4 per group): 1) SD: 6 h SD initiated at lights on (Zeitgeber time 0 (ZT)) followed by decapitation at

ZT6; 2) C6: controls that had undisturbed sleep and were sacrificed by decapitation at ZT6; 3) RS: 6 h SD initiated at ZT0 followed by 4 hr recovery from ZT6-ZT10 and then decapitation at ZT10; 4) C10: controls that had undisturbed sleep and were decapitated at ZT10. SD was performed by disturbing the cage bedding around the mouse and stroking the vibrissae using an artist's brush. The mice were perfused with paraformaldehyde, brains were equilibrated in sucrose, and 30  $\mu$ m sections were cut. Standard immunohistochemistry procedures were performed using rabbit-anti-ERp72, GRp78 or GRp94 as a primary antisera (1:5000; Stressgen, Victoria BC) and 0.05% 3,3' diaminobenzidine (DAB) as the chromogen. Counts of ERp72-, GRp78-, and GRp94-immunoreactive (ir) neurons in two cortical regions, the dorsal cingulate cortex and a region of lateral cortex dorsal to the rhinal sulcus, were made on photomicrographs by an observer blind to the experimental condition.

**Results:** In the dorsal cortex, ERp72-, GRp78-, and GRp94-ir cells were increased in SD (33-45% increase, p= .008, .002, and .007, respectively), but no significant increase was seen in RS for any of the three HSPs. In contrast, ERp72-, GRp78-, and GRp94-ir cells were significantly increased in both SD (21-66%; p=.004, .001, .02) and RS (31-39%; p=.04, .05, and .001) in the lateral cortex.

**Conclusions:** Our results demonstrate that ERp72, GRp78, and GRp94 are induced in both dorsal and lateral cortical neurons during SD and induced in lateral, but not dorsal, cortex in RS. Since HSPs are induced in response to cellular trauma and to increased protein demands, HSP expression during SD may relate to cellular stress whereas HSP expression in RS may relate to the restorative function of sleep.

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## 175.A

### SLEEP-WAKING DISCHARGE PATTERNS OF MEDIAN PREOPTIC NUCLEUS NEURONS IN RATS

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**Introduction:** Recently, a large population of cells exhibiting sleep-related c-fos protein immunoreactivity has been found within the rat median preoptic nucleus (MnPN)(Gong et al., 2000). To further elucidate the role of MnPN neurons in the regulation of sleep-waking cycle, we examined the dynamics of extracellularly recorded MnPN neuronal activity during wakefulness (W), slow-wave sleep (SWS), and paradoxical sleep (PS) in the chronic rat preparations.

**Methods:** Experiments were conducted on 5 unrestrained unanaesthetized rats, which were surgically prepared for chronic recordings of MnPN neuronal activity using the

microwire technique and polygraphic monitoring of EEG and EMG to detect behavioral states. Recorded cells were classified into groups based on firing rate pattern in W, SWS, and PS using cluster analysis. An one-way repeated measures ANOVA followed by the Turkey HSD post-hoc test was used to examine the inter-stage differences in the mean firing rates for statistical significance.

**Results:** The mean firing rate of 89 MnPN units was at its minimum during W and gradually increased in parallel with transition to SWS ( $p < 0.001$ ) and then to PS ( $p < 0.01$ ). However, neurons showed functional heterogeneity in terms of sleep-waking discharge pattern and, following cluster analysis, were subdivided into 3 groups: 1) state-indifferent neurons ( $n=10$ ); 2) W/PS-related units ( $n=11$ ) showing insignificant differences in the level of firing during W/PS with decreased activity during SWS; 3) sleep-related cells ( $n=68$ ) exhibiting higher level of functional activity during sleep in comparison with W. Neurons belonging to the third group were subdivided into three populations: 1) SWS-related neurons ( $n=9$ ) firing at the highest rates during SWS; 2) PS-related cells ( $n=7$ ) showing selective activation in PS; 3) SWS/PS-related neurons ( $n=52$ ) exhibiting a 55% increase of discharge rates in SWS and further elevation of firing ( $n=32$ ) or insignificant changes ( $n=20$ ) during PS as compared to SWS. The latter population included a subset of units which gradually decreased firing rates on transition from one successive SWS episode to another as well as within each SWS episode. Most of recorded cells showed a tonic pattern of activity during all the stages of sleep-waking cycle. However, PS-related cells switched to burst firing mode with the appearance of theta-activity in the EEG.

**Conclusions:** These data show a high concentration of sleep-active cells within MnPN confirming the finding of sleep-related c-fos expression in this nucleus (Gong et al, 2000). The largest and the most interesting population of cells are SWS/PS-related neurons similar to those previously found in the VLPO of cats (Suntsova, Burikov, 1995) and rats (Szymusiak et al., 1998). We hypothesize that they act as the elements of "anti-waking" system participating in the mechanisms of sleep onset and maintenance by inducing progressive waking network inactivation via inhibitory actions on multiple arousal systems. Some MnPN cells show changes in activity coinciding with a dynamics of process S that reflects the homeostatic regulation of sleep (Borbely, 1982). Such neurons could play an important role in the mechanisms which determine the duration and depth of SWS episodes.

## 176.A

### ACTIVITY OF VENTRAL PERIAQUEDUCTAL GRAY NEURONS DURING WARMING OF THE PREOPTIC/ANTERIOR HYPOTHALAMIC AREA

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**Introduction:** The ventral periaqueductal gray (VPAG) has extensive reciprocal connections with preoptic/anterior hypothalamic (POA) and basal forebrain regions involved in sleep-

wake control. The VPAG has been implicated in several physiological and behavioral functions, including respiration<sup>1</sup>, blood pressure and heart rate<sup>2</sup>. The onset of sleep is accompanied by changes in these variables. POA and VPAG interactions could contribute to state-dependent modulation of cardio-respiratory control. The POA is also a critical thermosensing and thermointegrating region<sup>2</sup>. We hypothesize that warm-sensitive, sleep-active neurons in the POA<sup>3</sup> modulate the activity of VPAG neurons. To test this hypothesis, we examined the responses of VPAG neurons to local POA warming.

**Methods:** Sprague-Dawley rats (300-450g) were anesthetized with a ketamine-zylazine mixture and surgically implanted with instrumentation to permit monitoring of the EEG and the electromyogram (EMG). In addition, multi-wire electrodes were directed at the VPAG cell columns. Unit recording electrodes consisted of ten, 25 stainless steel wires attached to a microdrive that could be advanced in small increments. A stainless steel, water-perfused thermode was placed in the POA. A microthermocouple was implanted within 1 mm of the tip of the thermode to measure T<sub>poa</sub>. The thermode and VPAG microwire bundle were placed on the same side of the brain. Leads from EEG, EMG and microwire electrodes were soldered to a small electrical connector, which was encased in dental acrylic and anchored to the skull. Electrophysiological recording began 10 days after surgery. Baseline neuronal activity was recorded during both waking and slow wave sleep (SWS). T<sub>poa</sub> was increased 1-1.5 C by perfusing warm water through the thermode. The EEG, EMG, and unit activity were continually recorded during POA warming. Firing rates were determined before and after POA warming during both waking and SWS.

**Results:** Each recorded VPAG cell was characterized by its spontaneous sleep-waking discharge profile, and its response to POA warming. State-related (wake-active or sleep-active) neurons were operationally defined as those demonstrating a minimum change in firing rate of 25% during SWS vs. wakefulness. Warming-responsive neurons were defined as those demonstrating a minimum change in firing rate of 10%/°C during POA warming as compared to the pre-warming rate during the same sleep-wake state. Of 79 recorded VPAG neurons, 54 (68%) were wake-active, 15 (19%) were sleep-active and 10 (13%) were state-independent. During waking, 51% of wake-active and 36% of the sleep-active VPAG neurons exhibited decreases in firing rate in response to POA warming; 10% of the wake-active and 36.4% of the sleep-active VPAG neurons exhibited increases in firing rate in response to POA warming. The remaining 38.5% of wake-active and 27.3% sleep-active VPAG neurons were unresponsive to POA warming. During SWS, 33.3% of the wake-active and 53.8% of the sleep-active VPAG neurons exhibited decreases in firing rate in response to POA warming; 35.4% of the wake-active and 30.8% of the sleep-active VPAG neurons exhibited increases in firing rate in response to POA warming. The remaining 31.2% wake-active and 15.4% sleep-active VPAG neurons were unresponsive to POA warming.

**Conclusions:** These preliminary results suggest a significant subpopulation of VPAG neurons are wake-active and exhibit suppression of spontaneous discharge in response to POA warming during both wakefulness and SWS. It is well-documented that POA thermosensitive neurons play a key role in

the modulation of sleep-wake state<sup>3</sup>. These findings support the hypothesis that modulation of VPAG neuronal activity by POA warm-sensitive, sleep-active neurons contributes to state-dependent cardio-respiratory function.

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### 177.H

#### AGE-RELATED CHANGES IN ACTIVITY OF ENZYMES OF ADENOSINE METABOLISM IN SLEEP REGULATORY REGIONS

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**Introduction:** Altered sleep patterns are among the most pronounced behavioral changes that occur with advancing age. The central neuro-modulatory action of adenosine and its role in homeostatic regulation of sleep and wakefulness has been studied extensively but limited information exists on how age affects different components of the adenosinergic system. It has been demonstrated that with age, the activity of 5'-nucleotidase is augmented in most regions of the rat brain. This suggests that changes in the activity of enzymes affecting adenosine levels might play a role in changes in sleep with age. To address this hypothesis, we evaluated how age impacts the activity of adenosine metabolic enzymes i.e., adenosine deaminase (ADA), adenosine kinase (AK), and cytosolic- and ecto-5'-nucleotidase (5'-N) in brain regions relevant to sleep regulation.

**Methods:** Experiments were performed on male Fischer 344 rats aged 2, 12 and 24 months (n=7-10 in each age group). Samples of brain containing the vertical and horizontal limbs of the diagonal band, ventrolateral preoptic area, tuberomammillary nucleus, dorsal raphe, locus coeruleus, and the cerebral cortex were obtained by micro-punch. Enzymatic assays were performed with established techniques [1-3]. Protein concentration was estimated by the BCA method using BSA as a standard. Differences in enzymatic activities were examined by a mixed model ANOVA.

**Results:** For ADA there was a significant main effect for brain region, indicating overall differences in ADA activity among regions averaged over three age groups (F[6,23]=31.33;

p=0.0001); there was no significant effect of age (F[2,23]=0.23; p=0.793). Adenosine kinase demonstrated significant regional differences (F[4,21]=15.16; p=0.0001), a significant main effect for age (F[2,21]=3.68; p=0.043), as well as an interaction between age and region (F[8,21]=3.27; p=0.014). The overall differences in AK activity with age ranged from 54% to 58% between 2 and 24 months. Distribution of cytosolic-5'-N was significantly different among brain regions (F[6,19]=20.24; p=0.0001) and between age groups (F[1,19]=10.70; p=0.004). There was a significant main effect for the brain region, age group, as well as the interaction between age group and region in the activity of ecto-5'-nucleotidase (F[1,19]=61.62; p=0.0001; F[6,19]=5.515; p=0.003; F[6,19]=5.43; p=0.002, respectively). The changes in the activity of both cytosolic and ecto-5'-nucleotidase with age were large, ranging from 25% to 103% in different brain regions for cytosolic-5'-nucleotidase and 48% to 138% for ecto-5'-nucleotidase.

**Conclusions:** (1) ADA activity in the brain is not affected by age; (2) the activity of AK is only slightly affected by aging; (3) 5'-nucleotidase activity increases significantly (both cytosolic and ecto) with age in all brain regions including the key sleep regulatory areas. These increases in 5'-nucleotidase activity will likely lead to increases in the adenosine level in sleep regulatory regions with age.

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### 178.H

#### CHANGES IN ADENOSINE LEVELS IN AGED RATS: A POSSIBLE MECHANISM FOR THE DECLINE IN SLEEP DRIVE WITH AGING.

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**Introduction:** There are significant changes in sleep with age (for review see 3). Those changes include fragmentation of sleep, increased wake time as well as decrease in REM sleep. Moreover, old rats have less sleep rebound in response to 12h-prolonged wakefulness (W) (3) indicating a reduction in sleep drive with age. This decline cannot be attributed to loss of neurons implicated in sleep since the numbers of neurons in the ventral lateral preoptic area, a region implicated in generating sleep, is similar between young (3.5 mos) and old (21.5 mos) rats (3). Nevertheless, at the molecular level there is a decline because in response to 12h-prolonged W old rats have less transcriptional activation of immediate-early genes, such as c-Fos, and less DNA binding activity (3). One possibility for the

reduced sleep drive with age is that sleep-wake active neurons may be stimulated less as a result of a decline in endogenous sleep factors. Adenosine (AD) is one such sleep factor that increases after prolonged W (2). Here, we hypothesize that AD levels are lower in old compared to young rats in prolonged W and this could contribute to the reduction in sleep drive in old rats.

**Methods:** Animals and surgery. 21 month old male F344 rats (n=4) were implanted with sleep recording electrodes and a guide cannulae (IC guide. BAS) placed stereotaxically into the magnocellular area of the basal forebrain (A= -3.5; L= 2.0; H= 8.5). The rats were then placed in a cage with unrestricted mobility and housed at constant temperature (21 ±1°C) and under controlled light-dark cycle (lights on: 07:00 to 19:00h). Microdialysis sampling procedure. The microdialysis probe (BAS 1mm of length) was inserted 24h before the sampling and AD levels were found to equilibrate 7h after probe insertion (flow rate= 0.25 µl/min). The following day at 07:00h and for the ensuing 2h, samples were collected during 20 min. Then animals were kept awake for 6h (09:00-15:00h) by lightly tapping the cage or introducing novel items. Thereafter, rats were allowed to sleep. Microdialysates samples (5 µl) were collected during baseline, 6h prolonged waking and during the 3h sleep rebound period. Adenosine analysis. Samples were analyzed using a high-performance liquid chromatograph. A microbore column (BAS) attached to the injector (CC-5e) and to the detector (UV-116A, BAS) achieved separation. Chromatographic data were compared to known standards (Chromatograph Report software. BAS).

**Results:** Preliminary results indicate a consistent low level of AD during the baseline conditions (Mean ± SEM pg= 87.11 ± 44.0). AD levels increased during prolonged W reaching the highest value at the end of the 6h of W (318.58 ± 89.8). Finally, during the ensuing sleep period, levels decreased significantly (108.13 ± 3.0) [One-way ANOVA with Bonferroni/Dunn as a post hoc test, p<0.05].

**Conclusions:** It has been shown that AD increases after prolonged W and decreases with sleep (2). However, this result was described in young animals. Here, we show that AD in aged animals also increase with prolonged W. Now, we can proceed to determinate whether there are differences in AD levels between young and old animals.

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## 179.A

### SLEEP DEPRIVATION IMPAIRS LONG TERM POTENTIATION IN RAT HIPPOCAMPAL SLICES

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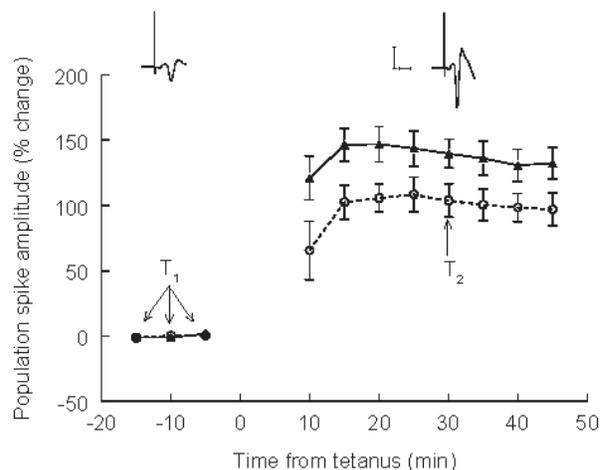
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**Introduction:** Homeostatic models of sleep propose that sleep serves a recuperative function for the brain. If, as some have hypothesized, sleep specifically provides recovery for plastic brain processes, sleep deprivation should impair plasticity. To determine whether sleep deprivation reduces neural plasticity, we compared long term potentiation (LTP) in hippocampal slices from control rats and rats deprived of sleep for 12 h.

**Methods:** Five rats that had adapted to a 12:12 LD cycle were deprived of sleep via forced locomotion for the 12 h light period. Rats were removed from the deprivation device at the end of the light period and decapitated. Five control rats were also decapitated at the end of a 12 h light period. After decapitation, the hippocampi were isolated and sectioned. CA1 population spike amplitude was measured in response to stimulation of Schaffer collaterals. After obtaining a stable baseline response, LTP was induced by giving a tetanizing stimulus. Post tetanic population spike amplitude was expressed as a percent of the mean pretetanus response. Mean LTP for each rat was determined by averaging the percent increase across 3 slices. In 3 sleep deprived rats and 3 control rats, corticosterone levels were measured in serum obtained at the time of decapitation.

**Results:** Long term potentiation of population spike amplitude was significantly (p<0.05) reduced in sleep deprived rats (Fig 1). Thirty minutes after tetanus, population spike amplitude increased 104 ± 13 % in sleep deprived rats, and 140 ± 11 % in control rats. Corticosterone levels in sleep deprived rats (37.5 ± 1.2 mg/dL) significantly (p<0.05) exceeded those in control rats (19.1 ± 4.9 mg/dL).

**Figure 1**—Potentiation of population spike amplitude (% change from pretetanus mean) was reduced in sleep deprived (○) vs. control (▲) animals. Insets at top show typical pretetanus (T<sub>1</sub>) and 30 min post tetanus (T<sub>2</sub>) spikes. Inset calibration bars are 1 mV and 1 msec.



**Conclusions:** Sleep deprivation has previously been shown to impair anatomical plasticity during development (1). Here we present evidence that sleep deprivation can impair functional plasticity in adult rats. This effect is consistent with the hypothesis that sleep provides homeostatic recuperation for cellular processes underlying neural plasticity. However, confounding factors must be ruled out. Chief among these is stress as shown by the elevated blood corticosterone levels. If future experiments establish that plasticity is reduced by sleep loss, rather than by nonspecific deprivation effects such as stress or locomotion, LTP provides a well established model to investigate the cellular processes of plasticity restored by sleep.

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**Oral Presentation**  
**Sleep Apnea: Physiology and Pathophysiology**

**180.J**

**RESPIRATORY LOOP GAIN (USING PROPORTIONAL ASSIST VENTILATION) IN HEALTHY YOUNG MALES AND FEMALES**

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**Introduction:** We hypothesize that gender differences in respiratory control could partly explain the higher prevalence of sleep apnea in males. Therefore, we measured respiratory loop gain (LG) using a proportional assist ventilator (PAV) in a group of healthy young males and females (Younes et. al., 2001). Loop gain is an engineering term used to describe the degree of inherent instability in a system governed by feedback control. Mathematically, it is defined as the ratio of a corrective action (e.g., hyperpnea) to a disturbance (e.g., hypopnea or apnea). If the corrective action is greater in magnitude than the disturbance ( $LG > 1$ ), then the system is said to be unstable and will develop sustained fluctuations (e.g., in ventilation or blood gases) when disturbed. Thus, individuals with a respiratory loop gain close to one are more likely to develop respiratory cycling.

**Methods:** We measured loop gain during sleep in 7 young males and females. Three females were studied during the follicular phase only, while 1 was studied during both the follicular and luteal phases. Each individual was allowed to fall asleep while connected to PAV. Respiratory elastance and resistance were then measured and entered into the PAV. Percentage assist was then incrementally increased until periodic breathing or "runaway" occurred. At each assist level, the tidal volume amplification factor ( $VTAF = \text{assisted tidal volume} / \text{unassisted tidal volume}$ ) was measured. At the point of periodic breathing, LG is the reciprocal of VTAF.

**Results:** Only 1 of 7 subjects (female) developed periodic

breathing on PAV (Table 1). The average VTAF was  $2.21 + 0.93$  in men and  $1.95 + 1.82$  in follicular phase females. Loop gain was not substantially different when measured in the luteal phase in subject 4.

**Table 1**

Subjects n = 7	Max VTAF	PB on PAV	Loop Gain
<b>Males</b>			
1	2.61	No	< .38
2	1.68	No	< .60
3	2.35	No	< .42
<b>Females (follicular)</b>			
1	1.73	No	< .58
2	1.70	No	< .59
3	1.28	Yes	= .78
4	3.10	No	< .32
<b>Females (luteal)</b>			
4	2.10	No	< .48

**Conclusions:** Young, healthy males and females are relatively resistant to periodic breathing. We were unable to demonstrate a significant gender difference in loop gain mainly because of an inability to amplify loop gain enough to induce periodic breathing without first inducing "runaway". Nonetheless, loop gain does not appear to be markedly different between the sexes in this small study. More subjects are needed to reach firm conclusions.

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**181.J**

**THE INFLUENCE OF CHANGING LUNG VOLUME ON GENIOGLOSSUS MUSCLE ACTIVATION AND PHARYNGEAL MECHANICS DURING NREM SLEEP.**

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**Introduction:** Substantial work has been done to identify the critical mechanisms controlling pharyngeal patency and the changes that occur in these variables during sleep in normal individuals and those with obstructive sleep apnea (OSA). Certainly sleep induced decrements in pharyngeal neuromuscular activity, and load compensation contribute to increased upper airway collapsibility in patients with obstructive sleep apnea (OSA). Previous studies have suggested that sleep induced changes in lung volume could influence upper airway patency and collapsibility. However, the independent influ-

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ence of lung volume on genioglossus (GGEMG) muscle activation/responsiveness and upper airway collapsibility (CLPS)/pharyngeal mechanics has not been well characterized.

**Methods:** We studied 5 normal subjects during stable NREM sleep (mean age 30.8 BMI: 23.8 kg/m<sup>2</sup> End superscript 2) in an iron lung ventilator adapted with a variable positive/negative pressure attachment for manipulations of extrathoracic pressure (Plung) [cm H<sub>2</sub>O End superscript 0]. We measured tonic (GGEMG t) and peak phasic (GGEMG p) genioglossus muscle activation (bipolar intramuscular electrodes), choanal/epiglottic pressure (Millar catheters), change in end-expiratory lung volume (ΔEELV) [chest/abdominal magnetometers] and pharyngeal collapsibility (CLPS) using brief negative pressure pulses under the following conditions: 1) Baseline, 2) Increased EELV +1 Liter and 3) Decreased EELV -0.5 Liter. An additional 4 subjects were studied only during baseline and increased EELV conditions.

**Results:** Table 1 below shows the group mean data for all subjects across the three conditions. \*p<0.05. \*\*\*p=0.08 compared to baseline. \*\*p<0.05 compared with +1 Liter

**Table 1**

	GGEMG t	GGEMG p	Rph	CLPS	Plung
-0.5 Liter	3.06 ± 1.0	11.40 ± 1.3**	3.16 ± 0.30	5.76 ± .72**	12.4 ± .9
Baseline	4.88 ± 1.5	7.27 ± 1.96	5.70 ± 1.9	4.19 ± .92	0
+1 Liter	3.10 ± .98	4.87 ± 1.48 ⊥	3.62 ± 1.1	2.99 ± 1.1*	-13.8 ± .9

**Conclusions:** Increasing lung volume led to decreases in both upper airway collapsibility and pharyngeal dilator muscle activation while decreasing lung volume increased muscle activation and collapsibility. These results suggest that lung volume has an independent influence on pharyngeal patency during NREM sleep in normal individuals. The muscles respond to the change in airway mechanics, but not sufficiently to preserve collapsibility. We speculate that during NREM sleep decrements in functional residual capacity contribute to upper airway collapse and that these changes may be more pronounced in patients with obstructive sleep apnea.

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**182.J**

**EFFECTS OF OBESITY ON UPPER AIRWAY COLLAPSIBILITY IN NORMAL SUBJECTS**

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**Introduction:** Previous studies<sup>1</sup> have demonstrated that obesity is a strong risk factor for obstructive sleep apnea (OSA). Increasing obesity in OSA patients is associated with increased upper airway collapsibility as determined by the critical closing pressure (Pcrit). However, the effect of obesity on the mechanical and neural determinants of Pcrit has not

been previously characterized in either OSA patients or normal subjects. We hypothesized that differences in the mechanical and neural determinants of Pcrit exist between obese and non-obese subjects without OSA.

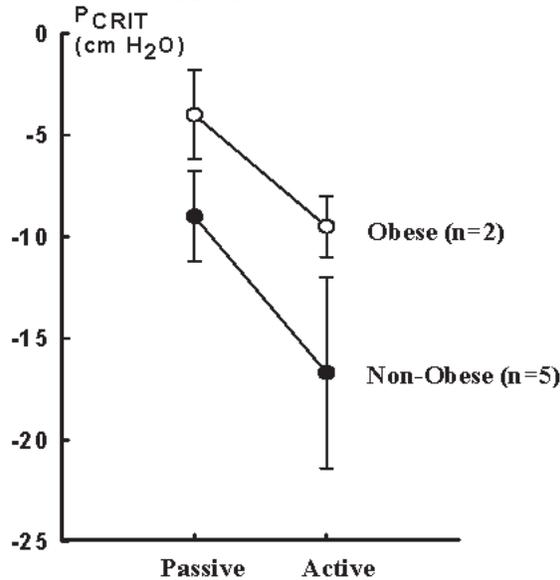
**Methods:** By manipulating nasal pressure (P<sub>sNS</sub>), we can distinguish between mechanical (passive) and neural (active) properties of the upper airway<sup>2,3</sup>. Pcrit was determined under two distinct conditions. First (passive state), subjects were maintained at an elevated P<sub>sNS</sub> (holding pressure) that eliminated inspiratory flow limitation. During periods of stable NREM sleep, P<sub>sNS</sub> was abruptly reduced for five breaths before it was returned to the holding pressure. P<sub>sNS</sub> was repeatedly lowered to different levels until airflow ceased. Second (active state), P<sub>sNS</sub> was reduced by 2-3 cm H<sub>2</sub>O after every 10-minute period of stable NREM sleep, until recurrent apneas occurred. The relationship between inspiratory flow and P<sub>sNS</sub> was then examined using least squares linear regression for each condition. Pcrit is determined by the P<sub>sNS</sub> at which inspiratory airflow ceases. Seven normal subjects without OSA were identified and stratified by body-mass index (BMI) into an obese (BMI ≥ 30 kg/m<sup>2</sup>) and non-obese (BMI < 30 kg/m<sup>2</sup>) group. Each subject had an overnight polysomnography study to determine the presence or absence of OSA. After completing full night polysomnography, subjects returned for two successive nights in the laboratory to determine their active and passive Pcrit.

**Table 1**

Char acteristics	Subject Baseline Characteristics	
	BMI <30 (n=5)	BMI ≥ 30 (n=2)
<b>Anthropometrics</b>		
Gender, (# males)	3	1
Age (years)	25.4 (2.4)	40.5 (7.8)
BMI (kg/m <sup>2</sup> )	26.5 (2.4)	37.7 (2.3)
<b>Polysomnographic</b>		
TST (minutes)	406.9 (48.0)	390.8 (25.8)
Sleep Efficiency (%)	89.4 (4.1)	94.9 (5.4)
<b>NREM</b>		
AHI (#/hr)	2.7 (0.8)	6.6 (1.3)
Avg. Baseline SaO <sub>2</sub> (%)	96.8 (0.9)	98.1 (0.7)
Avg. Low SaO <sub>2</sub> (%)	94.1 (2.1)	96.1 (1.4)
% Obstructive	96 (6.7)	97.5 (3.5)

**Results:** The characteristics (mean ± SD) of the obese (n=2) and non-obese groups (n=5) are shown in table 1. In the obese group, the mean Pcrit during the active and passive states (see figure) were -9.5 cm H<sub>2</sub>O (SE: 1.5) and -4.0cm H<sub>2</sub>O (SE: 2.2), respectively. In contrast, the mean Pcrit in the non-obese group during the active and passive states (see figure) were -16.7 cm H<sub>2</sub>O (4.7) and -9.0 cm H<sub>2</sub>O (SE: 2.2), respectively.

Figure 1  
**P<sub>CRIT</sub> in Obese vs. Non-Obese Individuals**  
**Passive vs. Active**



**Conclusions:** In the absence of OSA, obese subjects have increased upper airway collapsibility under active and passive conditions compared to non-obese subjects. The similar increase in both the active and passive Pcrit between obese and non-obese subjects suggests that obesity may impose a mechanical load on the upper airway that can lead to an increase in upper airway collapsibility.

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**183.J**

**NEURAL RESPONSES DURING A VALSALVA MANEUVER IN OBSTRUCTIVE SLEEP APNEA (OSA) PATIENTS REVEALED BY FUNCTIONAL MAGNETIC RESONANCE IMAGING.**

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**Introduction:** Obstructive sleep apnea patients exhibit atonia of the upper airway musculature in the presence of continued

diaphragmatic efforts during sleep. The loss of tone leads to cessation of airflow and transient rises in arterial pressure, combined with heart rate changes (1). The specificity of the deficit in respiratory muscle control suggests failure of discrete brain areas controlling breathing or in specific neural areas controlling blood pressure interactions with somatic tone. The latter responses include triggering of atonia by transient blood pressure elevation and loss of tone to hypotension, both reflexive actions normally required for homeostasis. We used functional magnetic resonance imaging (fMRI) to visualize brain areas recruited to a respiratory challenge that elicits pronounced cardiovascular sequences, the Valsalva maneuver. The maneuver, extreme expiratory resistance, activates discrete regions in multiple brain sites, as indicated by fMRI studies (2), and elicits aberrant autonomic responses in OSA patients (3).

**Methods:** We examined neural signal changes in 10 male, age-matched pairs of OSA and control subjects. A series of 20 image slices (25 repetitions, Echo Planar technique) was collected during 1 min baseline and 1.5 min challenge period in a GE 1.5T Signa scanner. Three Valsalva maneuvers were performed, each taking place over 18 secs (3 scan series), and each followed by a recovery period of 18 secs. Continuous ECG, end-tidal CO<sub>2</sub>, O<sub>2</sub> saturation, respiratory rate and expiratory force were also recorded. Valsalva Ratios (minimum R-R interval/maximum R-R interval) were also calculated. Image sets were motion corrected, intensity normalized and Gaussian smoothed, and baseline and challenge scans were compared using SPM99 and Medx imaging software packages. Voxels were significantly correlated to expiratory force ( $p < 0.001$ ), color-coded for percent change in signal intensity and overlaid onto a set of T1 anatomical images.

**Results:** Obstructive sleep apnea patients showed significantly decreased heart rate responses compared to the controls, during each Valsalva maneuver, as indicated by significantly decreased Valsalva Ratios (VR) in the OSA patients (OSA: VR=1.6±0.1; controls: VR=2.1±0.2; t-test,  $p < 0.01$ ). In addition, OSA subjects exhibited fewer regions of significantly correlated increases in signal than controls. Both control and OSA subjects showed significantly correlated increased signals in multiple areas, including the lentiform nucleus, insular cortex and prefrontal cortex. However, signal changes were remarkably reduced in the dorsal pons, fastigial nucleus of the cerebellum, amygdala and the hippocampus of OSA cases over controls; these areas were previously implicated in mediating the neural responses to blood pressure challenges

**Conclusions:** We conclude that brain areas normally controlling responses to challenges with a significant blood pressure component are deficient in OSA patients, and that those deficiencies are manifested even in the waking state.

**References:**

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184.J

AUDITORY AND RESPIRATORY EVOKED POTENTIALS DURING NON-REM SLEEP IN APNEICS AND CONTROLS

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**Introduction:** Inspiratory occlusion stimuli elicit K-complexes and produce a non-REM sleep evoked potential similar to auditory tones in young healthy subjects (1). Mild OSAS patients have a reduced amplitude N550 and a reduced ability to produce K-complexes in response to inspiratory occlusions presented during non-REM sleep (2). These data were interpreted as indicating a specific dampening of the processing of respiratory somatosensory information in the OSAS patients. Alternatively they may reflect an overall dampening of sensory processing, secondary to sleep fragmentation . The present study compared responses to respiratory and auditory stimuli in OSAS patients and controls to address this question.

**Methods:** Ten patients with mild to moderate OSAS (mean RDI 21 ± 11) were compared to ten controls (mean RDI = 1.7 ± 0.5). Silent, mid-inspiratory occlusions lasting 400 ms in duration and 50 ms 80dB auditory tones were presented during periods of stable stage 2 NREM sleep. EEG was recorded from 28 scalp sites referenced to linked ears. EOG, EMG, and mask pressure signals were also recorded. Data within modalities were compared between groups using independent samples t-tests.

Table 1

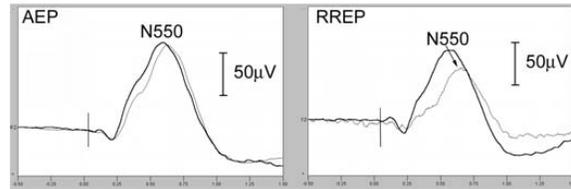
	OSAS	Control	t value
AEP KC%	49±22%	46±16%	-0.34 ns
RREP KC%	25±14%	43±9%	3.07 p<.01
AEP N550 Amp.	-93±42µV	-109±34µV	-0.86 ns
RREP N550 Amp.	-75±29µV	-106± 37µV	-1.99 p<0.5
AEP N550 Lat.	568±53 ms	600±61ms	1.19 ns
RREP N550 Lat.	682±59 ms	624±56ms	2.16 p<.05

Mean (SD) data for KC%, N550 amplitude and N550 latency for OSAS patients and control subjects. Data are presented separately for auditory and respiratory (inspiratory occlusion stimuli).

**Results:** The two groups did not differ significantly in KC%, N550 amplitude or N550 latency produced by auditory stimuli . However, OSAS patients produced significantly fewer KCs, had a smaller N550 amplitude and a longer N550 latency in

response to respiratory stimuli.

Figure 1



AEP and RREP for KC responses. The thicker lines represent data from control subjects and the thinner lines, data from OSAS patients. Data are presented at Fz, and the point of stimulus onset is indicated by the vertical line. Data are plotted with negative values up the Y-axis.

**Conclusions:** The RREP results confirm the findings of Gora et al (2) in that the production of K-complexes to inspiratory occlusions was reduced relative to controls, as was the amplitude of the N550 component in the K-complex average. The absence of these patient-control differences in response to auditory stimuli, indicate that the alteration of sensory processing seen during sleep in OSAS patients is specific to the respiratory modality, rather than reflecting an overall change in arousal modulation.

References:

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185.J

ELECTRICAL CO-ACTIVATION OF TONGUE PROTRUSORS AND RETRACTORS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA.

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**Introduction:** Pharyngeal wall stability, including the effect of tongue muscle contraction on pharyngeal collapsibility, can be characterized by the pressure at which collapse occurs, the Pcrit. Functional electrical stimulation (FES) of striated muscles provides a useful and important tool to assess their mechanical effect and has been largely employed for the study of pharyngeal mechanics (1). FES-induced contraction of dilator muscle has been shown to reduce pharyngeal collapsibility in animals, but how dilator muscles' contraction modulates upper airway flow dynamics and collapsibility in human remains to be evaluated.

**Methods:** Recent studies in rats have shown that co-activation of the tongue protrusor and retractor muscles improve pharyngeal patency and stability (2). The present study was undertaken to assess the effect of tongue muscle activation on pha-

ryngeal flow dynamics in OSA patients during sleep. For this purpose we measured airflow at multiple levels of nasal pressure (Pn), before and during FES-induced tongue muscle contraction. FES was applied to 6 patients with moderate to severe OSA during sleep, using an intra-oral, sublingual surface electrode. The electrode was divided into an anterior segment (A-FES), used to stimulate the genioglossus, the main tongue protruder (TP), and a lateral-posterior segment (L-FES), that activated the tongue retractors (3). A-FES, L-FES and A&L-FES were applied for single breaths over a range of Pn, to evaluate the effects of muscle contraction on Pcrit, upstream resistance (Rus) and peak inspiratory flow (Vmax).

**Results:** A-FES produced only small and variable changes. L-FES induced visible tongue retraction in all patients, reduced airflow at all Pn levels, increased Pcrit from 2.0±0.8 to 3.0±0.8 cmH2O and Rus from 16.1±2.1 to 26.1±2.1 cmH2O/l/s and reduced Vmax from 432±47 to 253±42 ml/s (mean ± SE, P<0.05). However, co-activation of TR with TP by combined A&L-FES improved pharyngeal stability, shifting the pressure-flow relationships toward lower pressures and lowering Pcrit from 2.5±0.6 to 0.1±1.1 cmH2O (P<0.05). The pressure at which flow limitation was first observed decreased from 8.8±2.0 to 7.0±1.6 cmH2O. Rus was unchanged (13.4±2.6 and 13.5±2.4 cmH2O/l/s) and Vmax increased insignificantly (from 468±53 to 502±50 ml/s).

**Conclusions:** We conclude that although unopposed TR contraction obstructs the pharynx, co-activation of TR with TP improves pharyngeal stability. Apparently, contraction of the anterior portion of the genioglossus may not affect pharyngeal compliance, but opposes TR sufficiently to prevent tongue retraction. The decrease in Pcrit without significant changes in Rus and Vmax suggests that A&L FES mainly stiffened the tongue. The magnitude of improvement in Pcrit was rather modest, suggesting that other muscles need to be co-activated in order to achieve normal levels of pharyngeal stability.

**References:**

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**186.J**

**VOLUMETRIC MRI TO PHENOTYPE THE UPPER AIRWAY - A FAMILIAL STUDY**

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**Introduction:** Upper airway soft tissues are known to be

enlarged in patients with sleep-disordered breathing. We believe that these differences result from genetic, heritable traits. We studied probands (apneics), siblings of probands, controls, and siblings of controls. Apneics (RDI > 15) were matched with controls (RDI < 5) by residence, gender, age and race. We hypothesized that volume of the upper airway soft-tissue structures would be the largest in probands, intermediate in proband siblings, and smallest in controls and their siblings. We studied 146 subjects: 43 probands (Pro) (age:47.0±9.4, BMI:36.3±7.9, RDI: 45.1±30.2), 43 siblings (P-Sib) (age:47.0±10.2, BMI:30.2±5.6, RDI:14.2±19.3), 30 controls (Con) (age:42.3±11.1, BMI:26.2±5.2, RDI:2.3±2.0), and 30 control siblings (C-Sib) (age:40.1±13.5, BMI:25.4±4.7, RDI:3.7±5.0).

**Methods:** Awake axial T-1 images were obtained using a 1.5 Tesla magnetic resonance scanner. The volume of the mandible, lateral parapharyngeal fat pads, lateral pharyngeal walls, soft palate, tongue, and airway were objectively quantified using Volumetric Image Display Analysis (VIDA). The minimum areas of the airway, separated into retropalatal (RP) and retroglossal (RG) regions were also determined using VIDA. VIDA has been previously described and validated (1,2).

**Table 1**

Soft Tissue and Bony Mean Volumes (mm <sup>3</sup> ) ± SD				
	Mean	S.D	Mean	S.D.
	Total Lat. Wall		Tongue	
Pro	14454.0 <sup>2</sup>	4839.6	85843.5 <sup>1,2</sup>	16580.0
P-Sib	13925.5 <sup>†</sup>	4565.2	77664.4 <sup>†‡</sup>	15543.4
Control	10362.2 <sup>2†</sup>	3116.4	61736.0 <sup>2†‡</sup>	11305.1
C-Sib	10404.7	3536.7	65853.2	12462.9
	Soft Palate		Fat Pad	
Pro	5354.1 <sup>2</sup>	2909.8	7355.1 <sup>2</sup>	3519.7
P-Sib	4573.1 <sup>†</sup>	1839.9	6736.1 <sup>†</sup>	2945.3
Control	3303.6 <sup>2†</sup>	1408.9	5361.0 <sup>2†</sup>	2037.6
C-Sib	3429.4	1333.3	5269.3	2482.6
	Total Soft Tissue		Mandible	
Pro	113006.8 <sup>1,2†</sup>	21889.3	43592.0	7287.5
P-Sib	102899.1 <sup>†‡</sup>	20908.3	41862.1	3510.8
Control	80762.7 <sup>2†‡</sup>	14517.3	41567.5	7300.2
C-Sib	84956.7	15015.1	43908.7	8390.3

**Results:** The volume of the parapharyngeal fat pads, lateral pharyngeal walls, tongue, soft palate, and total soft tissue were larger in apneics than all other groups (Table 1). There were significant differences between the volume of these structures in the apneics and the controls. The volume of the upper airway soft tissue structures in proband-siblings was intermediate between apneics and controls. There were no significant differences in the volume of the upper airway structures between controls and controls siblings. When controlling for age, gender, and BMI, the volume of the total soft tissues remained significantly larger in apneics compared to controls. Upper airway volume in the RP region was similar between groups (Table 2). However, the minimum airway area was significantly smaller in the apneics in the RP region. The mini-

imum airway area in siblings of apneics was intermediate in size between apneics and controls. When controlling for age, gender, and BMI, the minimum airway area remained significantly smaller in apneics compared to controls.

Table 2

Airway Volume and Area Means ± SD				
	Mean	S.D.	Mean	S.D.
	RP Airway Vol. (mm <sup>3</sup> )		RG Airway Vol. (mm <sup>3</sup> )	
Pro	3019.5 <sup>2*</sup>	1591.8	6524.5 <sup>1,2</sup>	3560.0
P-Sib	2981.6	1759.8	4375.3 <sup>1,†</sup>	2456.9
Control	3192.4 <sup>2*</sup>	1711.1	4554.8 <sup>2,†</sup>	2749.4
C-Sib	2980.3	1541.3	5471.9	3455.7
	RP Minimum Area (mm <sup>2</sup> )		RG Minimum Area (mm <sup>2</sup> )	
Pro	26.4 <sup>2*</sup>	17.0	111.7 <sup>2</sup>	77.0
P-Sib	32.4 <sup>†</sup>	21.9	82.6	51.3
Control	54.5 <sup>2*,†,‡</sup>	38.9	76.5 <sup>2</sup>	42.7
C-Sib	50.3	29.0	93.3	54.7

<sup>1</sup> indicates a p value of <.05 between proband and proband-sibling

<sup>2</sup> indicates a p value of <.05 between proband and control

\* indicates a p value of <.05 between proband and control, accounting for age, sex, and BMI

<sup>†</sup> indicates a p value of <.05 between proband-sibling and control

<sup>‡</sup> indicates a p value of <.05 between proband-sibling and control, accounting for age, sex and BMI

**Conclusions:** We were able to phenotype the upper airway with volumetric MRI. Our data demonstrate that the volume of the upper airway soft tissue structures (parapharyngeal fat pads, lateral pharyngeal walls, tongue, soft palate, and total soft tissue) are significantly greater in apneics than controls. These differences remained significant for the total soft tissue volume after controlling for age, gender and BMI. The volume of the upper airway soft tissue structures in siblings of probands was intermediate in size between apneics and controls. There were no significant differences in the size of the upper airway structures in controls and control siblings. Similar data were demonstrated for minimum airway area in the retropalatal region. Such data suggests that there is a genetic basis to the size of upper airway structures.

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Research supported by NIH Grants HL-57843, HL-60287

**187.J**

**FAMILIAL STUDY OF DIFFERENCES IN SYMPTOMS WITH SLEEP DISORDERED BREATHING**

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**Introduction:** A number of studies have examined differences in symptoms associated with sleep apnea exhibited by patients with sleep disordered breathing compared to those exhibited by controls. However, few studies have evaluated familial differences in these symptoms; therefore, we studied such differences in probands (apneics), proband siblings, controls and control siblings. We hypothesized that symptoms associated with sleep apnea, a disorder thought to have a genetic basis, would be most severe in the probands, intermediate in the proband siblings and least severe in the controls and controls siblings (equal between these groups).

**Methods:** Using questionnaires completed by participants of a genetic sleep apnea study, we studied symptoms associated with sleep apnea in 154 individuals (51 probands {47.43 ± 9.46 years; RDI: 45.10 ± 30.2}, 39 siblings of probands {46 ± 9.66 years; RDI: 14.2 ± 19.3}, 29 controls {38.59±10.15 years; RDI: 2.3 ± 2.0} and 35 siblings of controls {37.52 ±11.97 years; RDI: 3.7± 5.0}). By comparing the self-reported data of these questionnaires, we examined differences between these groups that might suggest family aggregation of symptoms associated with sleep apnea. The questionnaires were a compilation of demographic information (age, gender, race, and BMI) and several questionnaires: the Pittsburgh Sleep Quality Index, the SF-36 Health Survey, the Functional Outcomes of Sleep questionnaire, the Epworth Sleepiness Scale (ESS), and the MAP Sleep Symptom-Frequency questionnaire (MAP) which accounts for the symptoms apnea, snoring, snorting, and daytime sleepiness. As a whole, the questionnaires provide significant data about patients' quality of sleep, day-to-day functioning and overall physical and mental well-being.

Table 1

Mean Responses to Questionnaires ± SD				
	Mean	S.D.	Mean	S.D.
	PSQI - Global		FOSQ - Global	
Pro	7.27 <sup>*</sup>	4.25	16.09 <sup>*</sup>	3.19
P-Sib	6.10	3.46	17.48 <sup>†</sup>	3.35
Control	5.03 <sup>*</sup>	3.66	18.24 <sup>†</sup>	2.34
C-Sib	5.89	4.16	18.51	1.81
	Epworth Sleepiness		SF-36 RP	
Pro	11.87 <sup>*</sup>	5.59	52.94 <sup>*</sup>	42.91
P-Sib	9.31 <sup>†</sup>	5.43	83.33 <sup>†</sup>	28.87
Control	7.16 <sup>†</sup>	4.72	81.32 <sup>†</sup>	33.38
C-Sib	7.28	3.42	76.43	37.84
	SF-36 VT		SF-36 GH	
Pro	44.39 <sup>*</sup>	23.51	58.50 <sup>*</sup>	25.22
P-Sib	61.07 <sup>†</sup>	21.18	72.01 <sup>†</sup>	21.04
Control	60.18 <sup>†</sup>	23.31	72.04 <sup>†</sup>	22.70
C-Sib	57.29	24.74	73.17	21.04

Results: See Tables 1 and 2.

Table 2

Mean Responses to Questionnaires $\pm$ SD (mm <sup>3</sup> )				
	Mean	S.D.	Mean	S.D.
	MAP I1		MAP I3	
Pro	2.53*	1.26	1.40*	0.97
P-Sib	1.40 <sup>†</sup>	1.17	0.78 <sup>†</sup>	0.86
Control	0.59**†	1.04	0.56**†	0.71
C-Sib	0.57	1.02	0.55	0.68

\* indicates a p value of  $<0.05$  between proband and control

<sup>†</sup> indicates a p value of  $<0.05$  between proband and proband-sibling

**Conclusions:** In concordance with our hypothesis, the data reveal the most severe symptoms associated with sleep apnea were consistently reported by probands. Overall, the most significant disparity in the questionnaire results was between probands and controls. The symptoms reported by proband siblings varied in severity demonstrating that group's intermediate symptoms associated with sleep apnea. Specifically, they scored similarly to controls and control siblings on the SF-36 Health Survey regarding their physical role (RP), general health perceptions (GH) and vitality (VT) while they demonstrated severe symptoms of apnea, snoring and snorting on the MAP I1 and daytime sleepiness on the MAP I3. Controls and control siblings were similar in their scoring for most components of the questionnaires and demonstrated the least severe symptoms associated with sleep apnea. These data suggest that symptoms associated with sleep apnea may have a genetic basis.

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## 188.J

### INFLUENCE OF HLA TYPING ON SLEEP-ONSET REM PERIODS IN OBSTRUCTIVE SLEEP APNEA

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**Introduction:** Up to 25 percent of obstructive sleep apnea (OSA) patients demonstrate sleep-onset REM periods (SOREMPs) on polysomnography (PSG) or multiple sleep latency tests, without clinical evidence of narcolepsy. In some cases, SOREMPs remained despite continuous positive airway pressure (CPAP) therapy (1), suggesting genetic influences and the possibility of coexisting narcolepsy. In this study, we investigated the relationship of HLA serotypes to SOREMPs and other features of OSA.

**Methods:** Over eight years, 205 patients were found with SOREMPs, from a pool of patients with a confirmed diagnosis of OSA (apnea-hypopnea index (AHI)  $> 10$ ) and no history of cataplexy or other symptoms of narcolepsy. Patients underwent a PSG, MSLT on the following day; and HLA typing. HLA typing was available for 109 patients with SOREMPs; 96 patients with SOREMPs did not have HLA

typing for various technical reasons. The only factor determining inclusion in the analysis group was having typing performed; no other factors influenced selection. Comparisons of HLA positive (DR2, DQ6, DQ1) and negative groups were done with t-test, Mann-Whitney test, and Pearson correlation coefficient.

**Results:** 57.8% of patients were HLA positive, 42.2% were negative. This confirms previous data showing higher DR2/DQ1 HLA prevalence in these patients relative to the general population (25 to 40% depending on race). It is also consistent with data showing shorter REM latency in DR-positive non-narcoleptic individuals vs. DR-negative (2). HLA positive and negative subgroups did not differ in BMI ( $35.9 \pm 6.8$  vs.  $36.3 \pm 7.7$ ), AHI ( $48.0 \pm 31.6$  vs.  $45.0 \pm 31.1$ ), mean sleep latency (on MSLT,  $6.5 \pm 3.9$  vs.  $6.1 \pm 4.3$  minutes) or number of SOREMPs ( $1.8 \pm 1.2$  vs.  $1.7 \pm 0.9$ ). HLA-positive patients were older ( $51.7 \pm 13.7$  vs.  $46.6 \pm 14.4$ ;  $p = 0.06$ ). Since, in previous studies, MSLT latency differed significantly between OSA patients with and without SOREMPs (3), the correlation between number of SOREMPs and MSLT latency was investigated. Number of SOREMPs and mean sleep latency were correlated for the HLA-positive subgroup (Pearson coefficient  $r = -0.28$ ,  $p = 0.025$ ; Spearman coefficient  $r = 0.23$ ,  $p = 0.074$ ), but not correlated for the HLA-negative subgroup (Pearson coefficient  $r = -0.157$ ,  $p = 0.30$ ). Thus, sleepiness (shorter sleep latency) made SOREMPs more likely only when narcolepsy-associated HLA serotypes were present.

**Conclusions:** HLA phenotypes DR2(15) and DQ1(6) have a complex relationship to REM sleep physiology. Their higher incidence in OSA patients with SOREMPs and their association with shorter REM latency in normals supports this relationship. These serotypes may influence both sleepiness and propensity for SOREMPs, leading to an association between the two variables, whereas SOREMPs in patients lacking narcolepsy-associated HLA serotypes are likely governed by other factors, such as sleep deprivation. Molecular genetic subtyping and investigation of hypocretin/orexin status would be of interest in this population.

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**Oral Presentation**  
**Experimental Alteration of Sleep**

**189.U****A TWO-HOUR AUDITORY STIMULUS MODIFIES SUBSEQUENT SLEEP**Goel N<sup>1</sup>

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**Introduction:** Humans and other animals show changes in sleep as a result of exposure to environmental stimuli presented either while awake or asleep (1). A number of nonphotic stimuli, including social cues, stress and exercise can modify subsequent sleep quality when presented prior to sleep (1). By contrast, auditory stimuli's effects on sleep have only been assessed when stimulus presentation occurs during sleep itself (2). This study investigated the effects of a nonphotic auditory stimulus presented for two hours prior to bedtime on subsequent polysomnographic sleep.

**Methods:** Subjects were 13 research volunteers, 7 women and 6 men, ages 18 to 65 (mean age  $\pm$  SD, 43.1  $\pm$  19.4 y), in good general physical and psychological health, without sleep disturbance. Current use of central nervous system medications or extreme morningness/eveningness were exclusionary. Subjects maintained sleep logs for one week prior to study entry. During the first baseline night in the laboratory, subjects were screened for sleep pathology including the occurrence of apneas, oxygen desaturation and periodic leg movements. Subjects completed two four-day, four-night sleep laboratory sessions consisting of one baseline night, two stimulus/control nights, and one post-stimulus/post-control night. Sleep was polysomnographically recorded on all nights. Subjects remained in constant dim light (<20 lux) conditions, and received either a two-hour auditory stimulus (presented at 60 decibels) or a control stimulus from 0100 h-0300 h on Night 2 and Night 3. Subjects remained awake during presentation; compliance was monitored by infrared cameras and polysomnography. Subjects participated in both sessions, with presentation order counterbalanced. Sleep records were scored in 30-second epochs using Rechtschaffen and Kales' standard scoring criteria by trained scorers blind to the experimental conditions. Paired  $t$ -tests examined differences in polysomnographic sleep measures between each corresponding night in the control and stimulus conditions. Data are presented as mean  $\pm$  SEM and  $p < .05$  was considered significant.

**Results:** The auditory stimulus significantly decreased wake after sleep onset (WASO; 33.2  $\pm$  14.4 vs. 70.6  $\pm$  21.8;  $t(12) = 3.56$ ,  $p < .004$ ), increased the duration of slow wave sleep (SWS; 25.1  $\pm$  8.1 vs. 15.3  $\pm$  5.9;  $t(12) = 2.23$ ,  $p < .05$ ) and increased sleep efficiency (89.7%  $\pm$  3.5% vs. 81.7%  $\pm$  4.6%;  $t(12) = 3.23$ ,  $p < .007$ ) compared to the control stimulus on Night 2. Such differences did not reach significance for Night 3. By contrast, polysomnographic sleep measures did not differ significantly between the stimulus and control conditions for Night 1 (baseline) or Night 4 (post-stimulus/post-control).

**Conclusions:** Late night presentation of an auditory stimulus

promotes sleep by increasing the duration of SWS, increasing sleep efficiency, and decreasing WASO compared with a control stimulus. These findings contrast the sleep-disrupting, REM-altering effects produced when auditory stimuli are presented during sleep (2). However, the results are similar to other studies which have presented nonphotic stimuli prior to sleep and thus may suggest a common mechanism for altering nighttime sleep.

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**190.U****THE SOPORIFIC EFFECT OF MONOTONOUS STIMULATION AS A FUNCTION OF PERCEPTUAL SET AND DEMAND FOR SLEEP**Nau SD,<sup>1</sup> Borkovec TD,<sup>1</sup> Lichstein KL<sup>2</sup>

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**Introduction:** The tendency for monotonous stimulation (MS) to facilitate sleep onset is widely accepted. Most theoretical interpretations conceptualize the soporific effect as a direct stimulus-provoked phenomenon, assigning a passive role to the organism. Alternatively, Oswald (1961) hypothesized the likely presence of important active behavior. The usual MS procedure is the application of repetitive simple stimuli (tones or light flashes) to a reclining subject in a darkened room. Oswald asserted that the MS setting provokes a tendency to concentrate on the repetitive stimuli which is important for the capacity to promote sleep. The current exploratory research examined the effects upon sleep development during MS of attention-focusing instructions. A risk with attempts to manipulate attention-set is the possibility of setting up a persistent wake-promoting task orientation. The risk may be decreased if MS subjects are given explicit permission to become drowsy and fall asleep, but that could also expose sleep as the experimental objective. To test the limits of making the sleep promotion objective explicit, experimental instructions giving permission to sleep during MS (i.e., low demand for sleep) were contrasted with instructions that identified sleep induction as the experimental goal (high demand for sleep). The study was a 2 x 2 factorial design with "attend closely" (A) and "ignore" (I) attention sets crossed with low (LD) and high demand (HD). There was also a no stimulation control group (NS). Attending to the stimuli was viewed as a positive factor. High demand was seen as a potentially arousing, negative influence.

**Methods:** The subjects were 44 "good" sleepers (20 females, 24 males), who reported an average nocturnal sleep latency of 10 minutes or less. Eight subjects are not included in the results due to excessive 60 c/sec. noise in the recordings. The experimental stimuli were 30 minutes of 1000 c/sec. tones, 4 seconds in duration, on a variable interval schedule with an

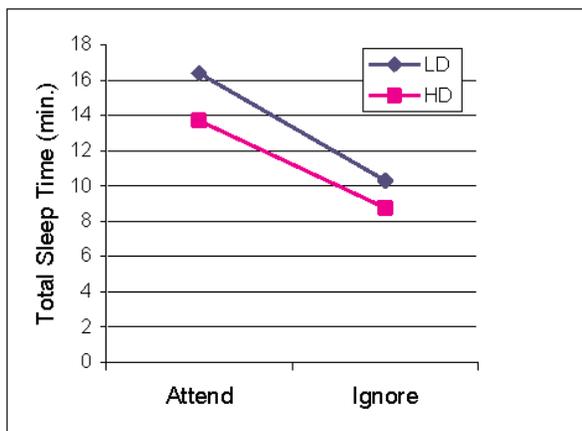
average inter-stimulus interval of 10 seconds. Stimulus intensity was approximately 65 dB. Testing sessions were daytime rest periods.

**Results:** Two-way ANOVAs (attention-set x demand) were performed on sleep latency and total sleep time. There were no significant main effects or interactions. The key group contrast was between the MS condition containing both positive factors (the A + LD group) and the NS control condition. Comparison of the latency data for these two groups indicated the A + LD subjects fell asleep significantly faster than NS,  $t(15) = 1.91$ ,  $p < .05$  and there was more sleep during A + LD than NS,  $t(15) = 1.76$ ,  $p < .05$ .

**Table 1**

Group	Latency		Total Sleep	
	M	SD	M	SD
A + LD	17.56	8.08	16.39	8.45
A + HD	19.14	9.83	13.69	9.83
I + LD	21.50	9.33	10.30	8.05
I + HD	25.30	7.12	8.75	9.70
NS	25.37	6.94	8.56	7.68

**Figure 1**



**Conclusions:** This study suggests that an “attend” perceptual set enhances the ability of MS to promote sleep. The “ignore” conditions showed less sleep than with “attend” instructions. When coupled with high demand for sleep, the ignore attention-set produced results like the worst group, the NS control condition. The data also suggested high demand for sleep is a negative factor, but the influence of demand for sleep appeared small (with this good sleeper sample).

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**191.U**

**THE EFFECT OF ACUTE STRESS ON REM SLEEP: MODULATION BY STRESS REACTIVITY AND SEEKING SOCIAL SUPPORT**

Germain A,<sup>1</sup> Hall M,<sup>1</sup> Buysse DJ<sup>1</sup>

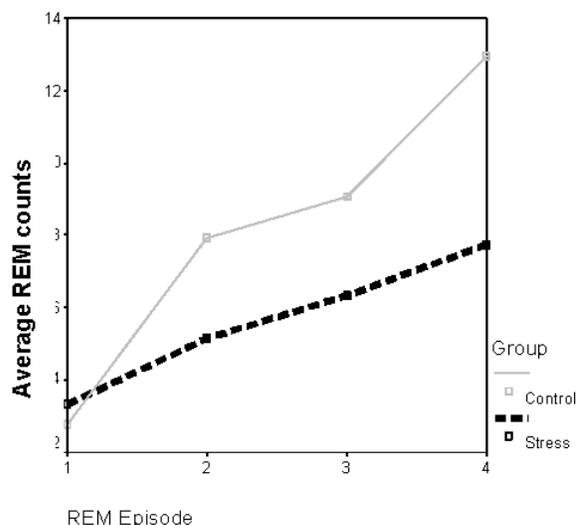
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**Introduction:** Only a few studies have investigated the impact of acute laboratory stressors on REM sleep in healthy individuals (e.g., 1-2), and none have explored possible modulating factors. The goal of this study was to investigate the impact of an acute laboratory stressor on REM sleep in healthy subjects, and to determine possible modulating factors.

**Methods:** Sixty-three subjects (32 men, 31 women, Mean age = 19.6 + 1.8) slept in the laboratory for one night, and were randomly assigned to one of two stress conditions: Subjects in the Stress condition (N = 32) were notified they would have to give a speech in the morning and that the topic would be divulged immediately preceding the speech. Subjects in the Control condition (N = 31) were told that they would have to read a magazine and that no questions would be asked on the content. All completed a visual analog stress scale (VASS), and the Ways of Coping Checklist (WCCL). Reactivity to stress was computed as VASS score immediately after task notification – VASS score at baseline. ANCOVAs with repeated measures (4 REM periods) were used to assess group differences in REM sleep. Baseline stress levels were used as a covariate. REM variables were REM latency, REM duration, %REM, eye movement density, and automated average REM counts (RC; Automated REM counts / REM duration in minutes). Predictors of REM sleep alterations were evaluated using hierarchical regressions.

**Figure 1**

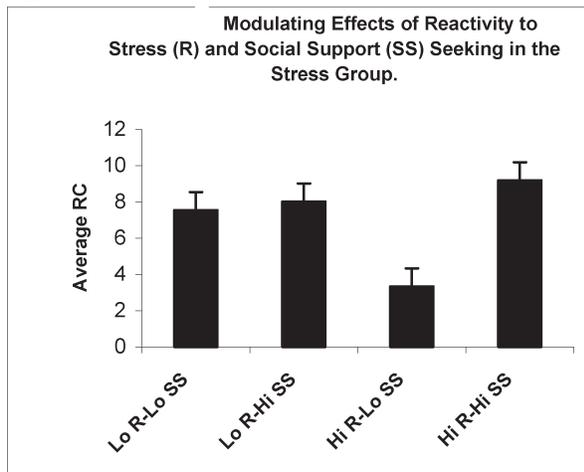
**RC progression across REM episodes in the Stress and Control groups.**



**Results:** Analyses revealed a significant Group X REM Period interaction for RC (F 3, 114 = 7.29, p = 0.05). RC showed

a larger increase across successive REM periods in the Control group whereas RC profiles were blunted in the Stress group (Figure1). Post-hoc comparisons revealed significant group differences in the fourth REM period ( $F_{1, 40} = 8.65, p = 0.005$ ). Reactivity to the stressor ( $\text{Beta} = 0.42, p = 0.007$ ) and Seeking Social Support ( $\text{Beta} = 0.30, p = 0.02$ ) significantly modulated RCA in the fourth REM period. As shown in Figure 2, RC values for the fourth REM period were lowest in the Stress group subjects with high Stress Reactivity and low Social Support Seeking. Conversely, greater Social Support Seeking buffered the effects of high reactivity in the Stress group subjects.

Figure 2



**Conclusions:** An acute laboratory stressor blunted the automated REM count average throughout the night. During the final REM episode, this difference was mediated by reactivity to stress, indicating that higher reactivity to stress was associated with lower RC. Results are consistent with recent findings demonstrating that acute stress is associated with attenuated level of parasympathetic activity during REM sleep (Hall et al 2001, submitted manuscript). Seeking social support as a way of coping with stress buffered the effect of reactivity to stress on RC4, suggesting that waking coping styles moderate the effects of stress on sleep.

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**192.C**

**PHARMACOLOGICAL SUPPRESSION OF REM SLEEP DOES NOT SUPPRESS DREAM RECALL IN HEALTHY SUBJECTS**

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**Introduction:** Although various forms of mentation are reported by subjects awakened during non REM sleep, the question whether dreaming is experienced exclusively during REM sleep is controversial (1). One way to answer this question is to determine if the pharmacological suppression of REM sleep suppress dream recall.

**Methods:** After an adaptation night, 14 healthy men, aged 19-26 years, received either oral clomipramine (50 mg, n=12; 75 mg, n=2) or placebo at 9 PM on two non-consecutive nights in a double blind, randomized, crossed order. Using a video-polysomnography, they were awakened every 60 minutes and solicited to recall their dream mentation.

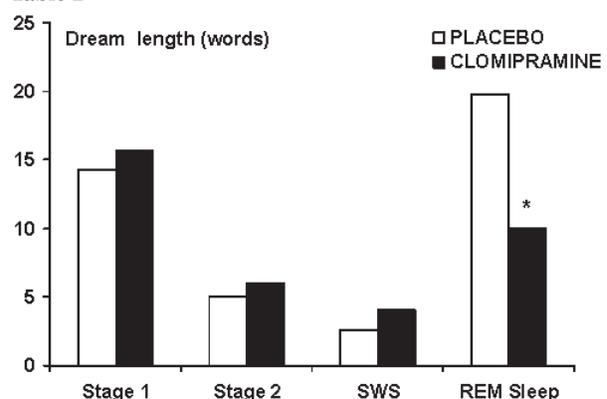
Table 1

Sleep characteristics	Baseline	Placebo	Clomipramine
Total sleep time	408 ± 62	391 ± 43	381 ± 90
REM sleep latency	120 ± 48	118 ± 54	222 ± 96*
REM sleep duration	64 ± 21	65 ± 30	17 ± 15*
REM sleep %	15.6 ± 4.8	16 ± 6	5 ± 4*
REM sleep without atonia %	16 ± 29	13 ± 27	83 ± 32*
REM N/min	3.2 ± 1.3	3.5 ± 1.1	3.1 ± 1.3
REM %	23 ± 11	24 ± 12	16 ± 15

\*P<0.0001

**Results:** REM sleep was suppressed in 2 subjects (duration: 1 min) and postponed and decreased 66% in the other 12 subjects (Table). Reports of dream mentations including images and scenario were obtained during the clomipramine night, even in the two REM sleep deprived subjects. There were no differences between placebo and clomipramine in the percentage of recall and length of dream obtained during NREM sleep (figure). During REM sleep, the length of dream report was shorter with clomipramine than with placebo. In 9 subjects, dream reports (Foulkes score >1) were obtained even before the first REM sleep episode.

Table 2



**Conclusions:** The persistence of dreaming activity when REM sleep is decreased or suppressed strongly suggests that dreaming mechanisms are not exclusively dependent on REM sleep mechanisms.

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**Oral Presentation**  
**Assessment of Sleepiness: Methodology**

**193.I**

**HABITUAL SLEEP TIME PREDICTS ACCURACY OF SELF-REPORTED ALERTNESS**

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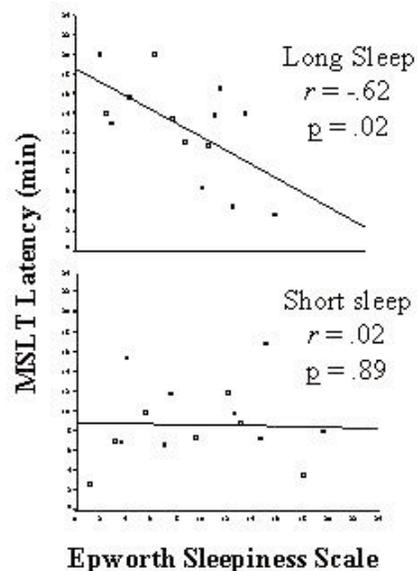
**Introduction:** The identification of factors that affect one's ability to detect physiological variations in sleep tendency is an important question. Knowledge of one's own level of alertness can affect decisions to refrain from dangerous tasks (e.g., driving) or seek treatment for sleep-related complaint. Previous studies have documented a poor correlation between "subjective" and "objective" measures of sleepiness in normal sleepers, during pharmacological manipulations, and in sleep disorder populations (1). The relationship may also be altered by a variety of other factors. For example, chronic sleep loss may attenuate the perception of sleepiness over time as one becomes accustomed to a lower level of alertness (2). A common definition of a "short sleeper" is a relatively short sleep time with no associated report of daytime sleepiness. To assess the relationship between reduced sleep time and the ability to detect sleepiness we assessed physiological and "subjective" sleepiness in individuals with long and short habitual sleep time.

**Methods:** Previous studies have used less than ~6 hours and greater than ~9 hours to denote short and long sleepers, respectively (3). Thirty individuals (17 women and 13 men) with long (>9 hrs, n = 15) or short (<6 hrs weekday and < 7 weekend, n = 15) average habitual sleep duration (2-week sleep diary) were studied as part of a larger epidemiological study. Each participant was studied in the laboratory for ~24 hours. The protocol included an 8.5-hour overnight polysomnogram, subjective assessments of sleepiness (Epworth [ESS] and Visual analog scales [VAS]), a multiple sleep latency test (MSLT) and individuals predicted their subsequent latency to sleep prior to each MSLT nap.

**Results:** Individuals with short sleep had significantly lower MSLT scores  $8.90 \pm 3.88$  vs  $12.93 \pm 4.95$  minutes, respectively ( $t_{28} = -2.48$ ,  $p = .02$ ), but importantly did not have subjectively different scores on any of the standard subjective measures (ESS short = 9.7, long = 8.9,  $t_{27} = .44$ ,  $p = .68$ ) (VASmm short = 58.45, long = 54.22,  $t_{28} = .59$ ,  $p = .56$ ). In the long-sleeper group, subjective-objective correlations were significant and robust for ESS and VAS ( $r = -.62$  and  $.57$   $p < .03$ ),

while short-sleepers showed no evidence of subjective-objective correlations ( $r = .02$ , and  $.28$ ,  $p > .10$ ) (Figure). When looking at actual latency on the MSLT versus predicted latency using ANOVA, a Latency (subjective, objective) X Group (short sleeper, long sleeper) interaction was found ( $F_{1,28} = 6.78$ ,  $p = .02$ ). Specifically, habitual short sleepers overestimated their actual sleep latency by an average of +17.33 minutes ( $t_{14} = 5.16$ ,  $p < .001$ ) whereas long sleepers did not overestimate sleep latency +4.38 minutes ( $t_{14} = .81$ ,  $p = .43$ ).

Figure 1



**Conclusions:** Short habitual sleep duration is associated with a reduced capacity to accurately assess physiological sleep tendency. Habitual short sleepers underestimate sleepiness, predicting greater sleep latency than actually observed. In contrast, individuals who regularly obtain more than 9 hours of sleep per night accurately assessed their level of alertness both in an absolute sense (predicted latency) and in relation to other individuals (high intersubject correlation). These results suggest that habitual sleep duration may be an important factor mediating the accuracy of introspective judgments of sleepiness.

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## 194.I

## EVIDENCE FOR POOR PERCEPTION OF SLEEPINESS IN PROFESSIONAL DRIVERS

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**Introduction:** Whilst drivers appear to recognise increasing sleepiness there is little data to show how sleepy they become before they decide to stop driving. The aims of this study were to compare the decision to continue driving, and specific sleepiness symptoms, with objective measures of sleepiness in professional drivers during simulated driving.

**Methods:** Seven professional drivers undertook a 24 hour period of total sleep deprivation. Performance was monitored with the AusEd driving simulator (seven, thirty minute sessions) and psychomotor vigilance task (PVT)(twelve, ten minute sessions). Sleepiness was measured objectively using video monitoring for slow eye closure (greater than one second) and EEG to calculate spectral power whilst on the driving simulator. Both of these measures predict performance impairment in sleepy subjects. After each driving session subjects were asked to rate the frequency of specific sleepiness symptoms and whether they would stop driving because of sleepiness.

Table 1

Symptom	Correlation with eye closure		Correlation with speed variation	
	R	P	R	P
Struggling to keep eyes open	0.65	<0.01	0.51	<0.01
Vision becoming blurred	0.54	<0.01	0.36	0.01
Nodding off to sleep	0.70	<0.01	0.53	<0.01
Difficulty keeping to middle of road	0.28	0.06	0.65	<0.01
Difficulty maintaining correct speed	0.51	<0.01	0.57	<0.01
Mind wandering	0.18	0.23	0.07	0.64
Reactions slow	0.61	<0.01	0.69	<0.01
Head dropping down	0.75	<0.01	0.50	<0.01

**Results:** There was a significant increase in variability of speed and steering on the driving simulation with increasing hours awake (n=47, p<0.05), as well as reaction time and lapses (reaction times greater than 500 ms) on the PVT (n=80, p<0.05 for both). The number of episodes of slow eye closure per session was related to speed variation (r = 0.51, n = 46, p<0.05) and steering variation (r = 0.35, n = 46, p<0.05). Slow eye closure also increased after 17 hours awake, but this was not statistically significant. Subjects were more likely to state that they would stop driving if slow eye closure was present during the test session (n=47, p<0.05). However, slow eye closure was present during 24.3% of episodes when subjects stated that they would continue driving on a short drive (n=37, 95%CI 11.7-41.2%) and 21.2% of episodes when they stated that they would continue driving on a long drive (n=33, 95%CI 9.0-38.9%). Head dropping down, nodding off to sleep

and struggling to keep eyes open were the symptoms which correlated most highly with the number of episodes of eye closure per driving session. Difficulty keeping to the middle of the road and reactions were slow correlated most highly with speed variation (see table).

**Conclusions:** Performance on simulated driving deteriorated during 24 hours of sleep deprivation in professional drivers and was associated with an increase in episodes of slow eye closure. The decision to continue driving was related to increased slow eye closure and reduced driving performance. In 24% of sessions, following which subjects felt able to continue driving, slow eye closure had occurred. This suggests that poor driver recognition of excessive sleepiness is a common problem. Education of drivers about specific sleepiness symptoms may aid in the recognition of excessive sleepiness and enable them to utilise countermeasures appropriately.

**Research supported by NHMRC, Vicroads. AusEd driving simulator provided by Professor Ron Grunstein, Dr David Joffe, Dr Heather Engleman, Mr Ben Constable**

## 195.I

## COMPARING THE IMPAIRMENT ASSOCIATED WITH SLEEP DEPRIVATION AND ALCOHOL INTOXICATION: SUMMARIZED VALIDATIONS OF A WORK-RELATED FATIGUE MODEL

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**Introduction:** The authors have previously published a work-related fatigue model that uses hours-of-work as the input. This model produces a fatigue score based on duration and time-of-day of shifts, prior seven-day work history and the biological limitations on recovery sleep (Dawson and Fletcher, 2001). In laboratory experiments, fatigue has been shown to have performance consequences comparable to alcohol intoxication (Dawson and Reid, 1997; Lamond and Dawson, 1999). This paper collates comparisons of fatigue scores from the model with data from these experiments to provide fatigue score/blood alcohol concentration equivalents.

**Methods:** In study one, Dawson and Reid (1997) used forty subjects in two counterbalanced experiments. In one they were allowed to sleep from 0000h to 0800h and were then kept awake from 0800h until 1200h the following day. In the other experiment they consumed 10-15 g alcohol at 30-min intervals from 0800h until their blood alcohol concentration (BAC) reached 0.10%. Neurobehavioral performance was measured at 30-min intervals using an unpredictable tracking task. In study two, Lamond and Dawson (1999) twenty-two subjects participated in two counterbalanced conditions. In one they were allowed to sleep from 2300h to 0700h and were then kept awake from 0700h until 1100h the following day. In the other condition they consumed 10-15 g alcohol at 30-min intervals from 0800h until their BAC reached 0.10%. Neurobehavioral performance was measured at 1-hr intervals using simple reaction time, vigilance, grammatical reasoning, and unpredictable tracking tasks. For each hour of the experiments, performance changes were predicted using the fatigue model. Predicted performance change was then compared against actual perform-

ance changes for all measures. Regression equations were determined for each performance measure using both fatigue scores and BAC as the dependent measure. These equations were then simultaneously solved so that fatigue could be expressed as a blood alcohol equivalent.

**Results:** The comparison using data from study one indicated that impairment at a fatigue score of 80 is comparable to the impairment observed in an individual who has experienced 21-22 hours of sleep deprivation or has a BAC of 0.05% or greater. In study two, vigilance score most highly correlated with fatigue score; the fatigue score accounted for greater than 70% of the variance. For vigilance score, performance decrements observed at a fatigue level of 80 are also associated with decrements seen in individuals with a BAC of 0.05% or greater. This observation was also supported by the other measures.

**Conclusions:** The results suggest that individual with a fatigue score of 80 is at least as impaired as someone with a BAC of 0.05%. In most countries around the world, there are legally prescribed maximums for alcohol intoxication whilst driving: most commonly 0.05% or 0.08% BAC. It would be reasonable to suggest that similar impairment due to fatigue or drugs could be used as a limit within workplaces or vehicles. Further studies are currently being undertaken using locomotive and flight simulators, which may further clarify the potential use for the fatigue model and also for blood alcohol equivalents.

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Research supported by The Australian Research Council

## 196.I

### VALIDATION OF AUTOMATED EEG QUANTIFICATION OF ALERTNESS: METHODS FOR EARLY IDENTIFICATION OF INDIVIDUALS MOST SUSCEPTIBLE TO SLEEP DEPRIVATION

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**Introduction:** Electroencephalographic (EEG) indices and neurobehavioral measures were simultaneously acquired to quantify alertness during a 44-hour sleep deprivation study. Psychomotor vigilance (PVT) and paired associate learning/memory (PAL) performance, modified Maintenance of Wakefulness Test (MWT), technician observations of drowsiness (i.e., inspection of video for eye-closures and head nods and EEG slowing) were quantified to validate the B-Alert

EEG classification system [1].

**Methods:** Twenty-four healthy subjects (18 males, 6 females, age 21-38) completed baseline (beginning ~09:00 on Friday) and nine, three-hour batteries between 19:00 Friday and 05:00 Sunday, with one-hour breaks between batteries and a 40-minute nap at 19:00 Saturday. Continuous EEG (CzOz-differential) and EOG recordings were acquired during: PVT, PAL and a modified MWT. EEG B-Alert classifications, technician observations of drowsiness (available for 18/24 subjects), reaction times (RT) and percentage of correct responses were averaged across each of the PVT and PAL sessions. MWT was terminated following 90 consecutive seconds of EEG evidence of sleep and absence of finger-tapping.

**Results:** Repeated measures ANOVA across the 10 time-points revealed progressively increasing drowsiness in all indices as a result of sleep deprivation (B-Alert classifications, technician observations and performance) during PVT and PAL (all  $p$ 's < 0.001). Pearson product-moment correlations for each subject across time-points showed good agreement. Box plots (Fig. 1) display the median of the correlations, with ~50% of the data represented by the shaded area (fourth-spread), and ~99% of the data within horizontal bars (outlier cutoff points). Since the four subjects identified as outliers exhibited strong performance across all time points, a further examination was conducted. Thresholds were applied across time-points to the PVT, PAL and MWT measures in an effort to stratify individuals into three groups (good, fair, poor performers) based on vulnerability to sleep deprivation [2,3]. A 3(group) X 10(time-points) repeated measures ANOVA revealed significant effects between groups during the PVT for B-Alert %Sleepy ( $p$ <0.001) and %Drowsy ( $p$ <0.002), %Correct and RT ( $p$ <0.001). The ANOVA during the PAL revealed significant effects between groups for Technician Observation-Drowsy and -Asleep ( $p$ <0.004), B-Alert %Drowsy ( $p$ <0.032) and %Sleepy ( $p$ <0.003), %Correct and RT ( $p$ <0.001). Pair-wise comparisons between groups showed that the RT and B-Alert %Drowsy discriminated Good and Fair groups from the Poor group ( $p$ < 0.01) beginning at 23:00 (See Fig. 2). The B-Alert %Sleepy discriminated the Poor group at baseline ( $p$ <0.01). None of the measures discriminated the Good from Fair groups.

Figure 1

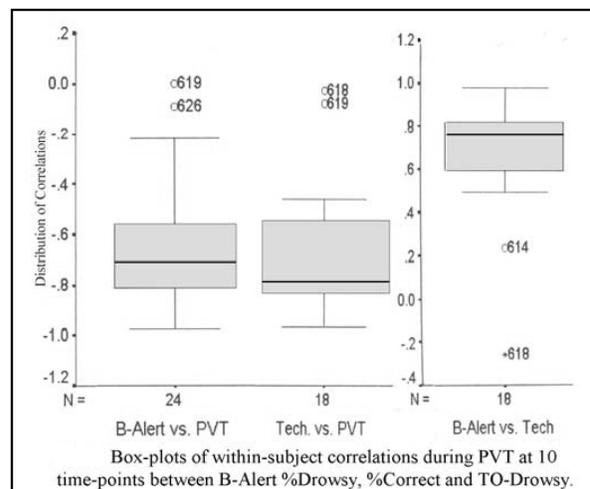
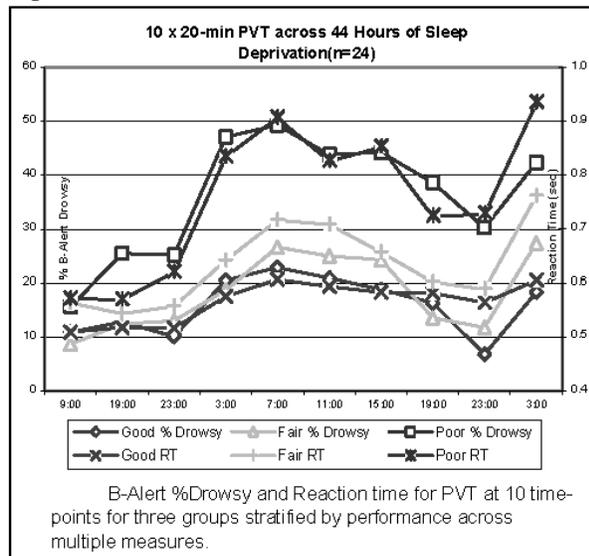


Figure 2



**Conclusions:** The B-Alert classification system correlated with technician observations and electrophysiological and performance measures of alertness. The combination of the B-Alert classifications and neuro-behavioral measures suggest an approach that can identify individuals whose performance is most susceptible to sleep deprivation. Additional research is required to determine whether these objective measures can provide a “biobehavioral assay” to identify individuals most susceptible to sleep deprivation.

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### 197.I

#### ALPHA AND THETA ACTIVITY AND SLOW EYE CLOSURE ARE RELATED TO DRIVING PERFORMANCE IN PROFESSIONAL DRIVERS

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**Introduction:** Brief periods of alpha and theta activity on EEG and monitoring for slow eye closure, have been used to assess sleepiness in awake subjects. Only a small number of studies have assessed the relationship between these parameters and performance measures, however. The aims of this study were 1. To assess changes in slow eye closure and brief

periods of alpha and theta activity on EEG over a 24 hour period of sleep deprivation in professional drivers and 2. To assess the relationship between these changes and performance on a simulated driving task and reaction time task.

**Methods:** Seven professional drivers undertook a 24 hour period of total sleep deprivation. Performance was monitored with the AusEd driving simulator (seven, thirty minute sessions) and psychomotor vigilance task (PVT)(twelve, ten minute sessions). Sleepiness was measured objectively using video monitoring for slow eye closure (greater than one second) and EEG whilst on the driving simulator. Manual EEG analysis was undertaken to look for periods of alpha and theta activity of 3 seconds or more and to calculate spectral power for 10 second epochs. Changes in the EEG measures and eye closure over the 24 hour period were assessed using Friedman's repeated measures ANOVA.

**Results:** There was a significant increase in variability of speed and steering on the driving simulation with increasing hours awake ( $n=47$ ,  $p<0.05$ ), as well as reaction time and lapses (reaction times greater than 500 ms) on the PVT ( $n=80$ ,  $p<0.05$  for both). Slow eye closure and the number of EEG epochs with elevated alpha and theta activity also increased significantly after 17 hours awake ( $P<0.01$  for both). The number of episodes of slow eye closure per session was related to speed variation ( $r = 0.51$ ,  $n = 46$ ,  $p<0.05$ ) and steering variation ( $r = 0.35$ ,  $n = 46$ ,  $p<0.05$ ). Manually scored alpha and theta activity was related to lapses (reaction times > 500 ms) on the PVT ( $r = 0.57$ ,  $p<0.01$ ) and steering variation on the driving simulator ( $r = 0.56$ ,  $p<0.01$ ).

**Conclusions:** Our study demonstrated an increase in episodes of slow eye closure and alpha and theta activity during 24 hours of sleep deprivation in a group of professional drivers. Few studies have demonstrated these abnormalities whilst performing a driving task. These changes were related to deterioration in performance on the driving task and vigilance task. Measurement of slow eye closure and brief periods of alpha and theta activity appear to be a reasonable way of objectively monitoring sleepiness in subjects whilst performing tasks.

Research supported by NHMRC, Vicroads. AusEd driving simulator provided by Professor Ron Grunstein, Dr David Joffe, Dr Heather Engleman, Mr Ben Constable

### 198.I

#### EVENT-RELATED POTENTIAL MEASURES OF FRONTAL LOBE ACTIVITY FOLLOWING TOTAL SLEEP DEPRIVATION

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**Introduction:** Increasing evidence suggests that the frontal lobes are particularly vulnerable to the effects of sleep deprivation (SD)<sup>1</sup>. Unfortunately, tasks that are thought to require frontal lobe activity also tend to be complex. Thus, it is not clear whether the effect of SD is due to impairment of the frontal lobes or to task complexity<sup>2</sup>. Event-related potentials (ERP) can be employed to monitor the activity of various brain regions. A late positive wave, P3b, is elicited whenever subjects consciously detect the occurrence of rare target stim-

uli. This P3b is at a maximum level over parietal areas. If subjects are presented with rare, highly novel stimuli, an earlier positive wave called P3a is elicited, which maximizes over anterior regions of the scalp. Detection of novelty, a non-complex behavior, is known to involve frontal lobes. It is hypothesized that SD impairs the novelty detection, which will result in smaller amplitude of the frontal component of the P3a.

**Methods:** 22 right-handed participants volunteered for the study. Two men and 8 women (age range 18 to 26) were tested after 36 h of SD. Four men and 8 women (age range 18 to 25) were tested after 12 h of normal daytime activities. The EEG was recorded from Fz, Cz and Pz. EOG was also recorded to monitor blink artifacts. An auditory oddball task was administered at 8 pm. Subjects were asked to detect (button press) rare high pitch tones ( $p=0.10$ ) that occurred among more frequently presented low pitch tones ( $p=0.80$ ). Unexpected environmental sounds ( $p=0.10$ ) were also presented at random. Participants were told to ignore the unexpected (novel) stimuli. ERPs were averaged separately for each stimulus type.

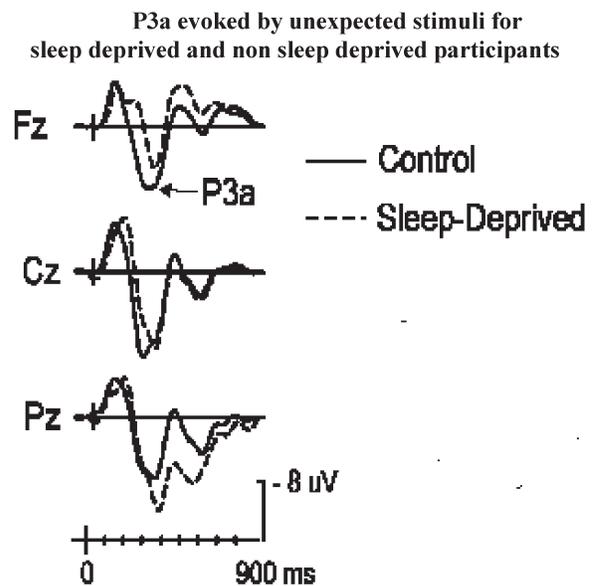
**Results:** The auditory novel stimuli elicited a positive wave that ranged from 250-450 ms. There was a significant group X electrode placement interaction ( $F(2,40)=9.55, p=0.0004$ ) for P3a amplitude. P3a was smaller at Fz (0.04), and marginally larger ( $p=0.06$ ) at Pz for the SD group (see Table 1 and Figure 1).

**Table 1**  
**P3a amplitude in different regions of the scalp for SD and non-SD participants**

ELECTRODE PLACEMENT	36 H SD (UV) (MEAN ± SD)	NO SD (UV) (MEAN ± SD)
FZ	*6.9 ± 3.5	12.1 ± 7.6
CZ	12.8 ± 5.4	14.6 ± 6.0
PZ	14.5 ± 3.9	10.6 ± 4.9

\* $p < 0.05$

**Figure 1**



**Conclusions:** P3a amplitude was reduced in the frontal region in the SD group, commensurate with observations of frontal lobe injury patients<sup>3</sup>. Sleep deprivation therefore appeared to compromise frontal detection of novel stimuli in an easy task. However, P3a was moderately larger at the parietal site in the SD group. The possibility that SD subjects must overtly detect the novel stimulus in order to discriminate it from the target might explain this finding. The target required an overt response while the novel stimulus required the withholding of a response. Thus, the usual frontal, passive detection of novelty that occurs under normal circumstances may require more effort following sleep deprivation, which the larger parietal amplitude would reflect. Further studies could increase our understanding of this phenomenon.

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**199.I**

**OBJECTIVE MEASUREMENT OF THE EFFECTS OF PARTIAL SLEEP DEPRIVATION IN CHILDREN**

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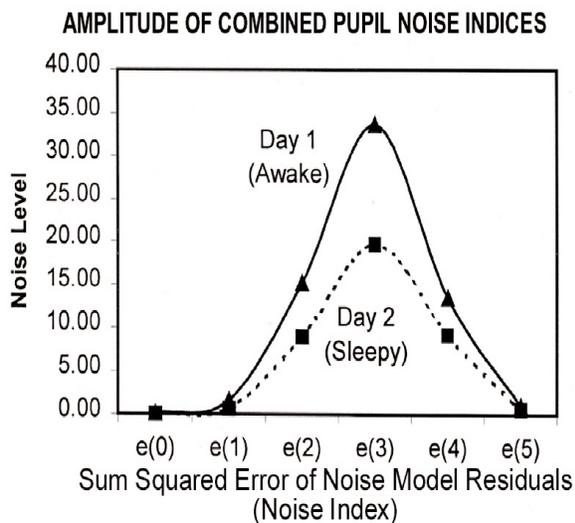
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**Introduction:** The sleepy child often goes undetected for a long time in contrast to the sleepless child. A number of stud-

ies have reported that children with obstructive sleep apnea and other sleep disorders (who are thought to be sleepy) have more difficulty in school work.(1). However, traditional methods of measuring sleepiness have not been standardized or validated for young children. There is a need to develop a rapid objective measure of sleepiness and problem sleepiness in childhood. In a prospective manner, in this study we measured the changes in pupillary stability in a group of children on two successive days, one after they had a full night's sleep and on the next day after they had been partially sleep deprived.

**Methods:** Eight children, mean age of 7.12 yr (S.D. 2.03), who had no known sleep or medical disorders were studied on two successive days, Day 1 following > 9 hours of sleep at home and Day 2 following 6 hours overnight sleep. Total sleep time each night was recorded by actigraphy and sleep logs. The research assistants monitored subjects and kept participants awake during the day and evening of sleep deprivation with games and other activities. At 10 a.m. and 2 p.m. each day, participants completed a Sleepy-Face Visual Analog Scale. Pupillometry measurements followed. After 5 minutes dark adaptation, participants were asked to look into the tube of the pupillometer for 18 seconds, at which time they were presented with multiple 2-second LED variable light stimuli. Pupillary dynamics in response to the light stimuli were recorded and pupillary noise estimates from subsequent models were used as a test statistic to discriminate between a child on the day following usual rest and the day after partial sleep deprivation.

Figure 1



**Results:** Mean Total Sleep Time on Night 1 was 10.84 hours (S.D. > 1.13) and on Night 2 was 6.06 hours (S.D. 0.18). Mean scores on the SVAS decreased in the afternoon and on Day 2, but all were above the midpoint. Each subject had a 6 element pupillary noise vector estimated and the 8 subject average of these were significantly different between Day 1 and Day 2, as tested by a runs test ( $p < 0.02$ ). The covariance matrix of these vectors were highly different ( $p < 0.001$ ) by a Kullback discrimination statistic and noise autocorrelation estimates con-

firmed the noise differences between subjects on the "rested" day (Day1) and the "partial sleep deprivation day" (Day2). Figure 1.

**Conclusions:** Previous research using pupillometry to measure sleepiness or vigilance has yielded confusing, contradictory or quantitatively elusive results. O'Neill et al.(2) have developed an algorithm that filters out direct pupillary response to complicated inputs such as light and sound, and analyzes pupillary noise. This provides a more physiologically pure assessment of alertness or sleepiness. Pupillary noise has been shown to be a robust discriminator between unmedicated persons with narcolepsy and matched control participants. In addition, Kotsos found pupillary noise decreased in college students with increased number of hours of sleep deprivation. These results comparing pupillary noise of 8 children, after their usual night's sleep (>9 hours) at home and after a night of partial sleep deprivation (6 hours sleep) are entirely consistent with the findings for adults who were sleepy and non-sleepy. Pupillary noise measurement provides a quick, non-invasive discriminator between children in their rested state and partially sleep deprived state.

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## 200.I

### SPECTROSCOPY AFTER TOTAL SLEEP DEPRIVATION IN HEALTHY ADULT MEN

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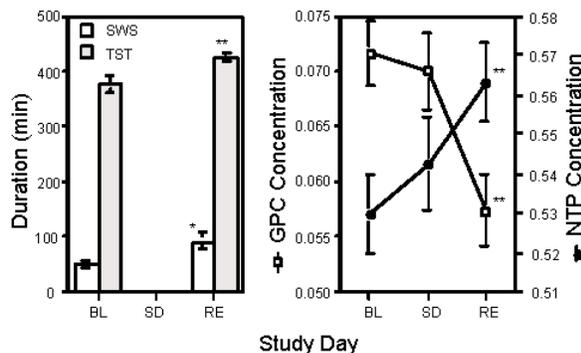
**Introduction:** The antidepressant effect of sleep deprivation has been widely reported (1). Phosphorous (31P) magnetic resonance spectroscopy (MRS) is a technique that can be used to measure global and region-specific changes in high energy phosphates alpha-, beta-, and gamma-NTP (Nucleoside triphosphate). As it has been shown that beta-NTP is lower in the basal ganglia of depressed subjects (2), it is possible that 31P MRS might permit us to detect chemical changes in the brain that are related to the antidepressant effect of sleep deprivation. A recent study using 31P MRS showed no changes in phosphomonoesters (PME), phosphocreatine (PCr), and intracellular pH in the frontal lobe of normal subjects the morning after sleep deprivation (3). An important limitation of using 31P MRS is the high signal to noise ratio in localized spectra. In the present study, MRS data were acquired from a relatively large brain region (a 5 cm slice centered on the basal ganglia and anterior cingulate), to allow more sensitive detection of metabolite changes after both sleep deprivation and recovery sleep.

**Methods:** Ten healthy, adult men (26±3.3 yrs) participated in a baseline night (BL), a supervised night of total sleep deprivation (SD) and a night of recovery sleep (RE). Sleep was

recorded polysomnographically on BL and RE nights for all subjects. Proton decoupled phosphorous spectra were acquired using a short echo time (TE = 3 ms) at 7-8 a.m., after the three nights, using a GE Signa 1.5T MR scanner (5.4 operating system). Spectra were fit using the VARPRO/MRUI time domain technique and mole percent values for PME, PCr, inorganic phosphate (Pi), glycerophosphoethanolamine (GPE), glycerylphosphorylcholine (GPC), and alpha, beta, and gamma-NTP were calculated.

**Results:** Repeated measures ANOVAs showed significant differences across the three nights for beta-NTP ( $p < .01$ ), total NTP ( $p < .01$ ), and GPC ( $p < .001$ ). Increases in beta-NTP and total NTP were found after RE vs. BL ( $p < .01$ ) and RE vs. SD ( $p < .05$ ). GPC decreased after RE vs. BL ( $p < .01$ ) and SD ( $p < .01$ ) (Figure). Significant changes in PCr, PME, Pi, GPE, and gamma-NTP were not observed. Expected changes in sleep measures were observed on the RE night, including increased slow-wave sleep (SWS) ( $p < .05$ ), sleep efficiency (SE) ( $p < .01$ ), total sleep time (TST) ( $p < .01$ ). There was a negative correlation between change in GPC and change in total NTP from BL to RE ( $r = -.74$ ;  $p < .05$ ) and a positive correlation between change in total NTP and change in SE ( $r = .82$ ;  $p < .05$ ). Changes in beta-NTP and SWS were negatively correlated ( $r = -.84$ ;  $p < .01$ ).

Figure 1



Sleep and MRS measures during baseline (BL) and after sleep deprivation (SD) and recovery (RE). SWS = slow-wave sleep; TST = total sleep time; GPC = glycerylphosphorylcholine; NTP = nucleoside triphosphate. \*  $p < 0.05$ , \*\*  $p < 0.01$  compared to baseline.

**Conclusions:** Surprisingly, significant increases in NTP and decreases in phospholipid catabolite production were observed after recovery sleep, rather than after the sleep deprivation night. These findings were related to sleep variables and are consistent with previously reported increases in adenosine in the basal forebrain as a result of sleep deprivation. Our results may indicate that sleep is promoted as adenosine levels are increased globally in the brain. SWS increase may decrease the need for further production of adenosine. Decreases in GPC, a phospholipid catabolite, are consistent with animal studies that have shown that phospholipid catabolism decreases during sleep. These data suggest that the more salient changes in the brain after sleep deprivation in non-depressed individuals may occur as a result of the recovery process

rather than after the deprivation.

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**Oral Presentation**  
**Sleep Co-Morbidity in Pediatric Disease**

**201.G****INCREASE SLEEP SPINDLES DURATION AND FREQUENCY IN CHILDREN WITH SICKLE CELL DISEASE**

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**Introduction:** It has been shown that children with sickle cell disease have high prevalence of asymptomatic brain ischemia (silent stroke)(1). These ischemia/infarction in the brain can be demonstrated by MRI especially in the area of cortex and deep white matter (2). Since the presence of cerebral ischemia in both animal models and human is associated with alternation in sleep architecture and sleep spindles (3), we investigate whether there are any changes in sleep spindles of children with sickle cell disease.

**Methods:** We retrospectively reviewed recordings of polysomnographic studies in children with sickle cell disease and african american aged-matched control. These children were referred to sleep center for evaluation of sleep-disordered breathing and underwent a formal overnight polysomnographic evaluation with monitoring of the following parameters: body position, EOG, 3 channel EEG, chin EMG, leg EMG, tracheal microphone, EKG, pulse oximetry and pulse waveform, thoracic and abdominal inductance plethysmography, oronasal airflow and end-tidal pCO<sub>2</sub>. Sleep staging and sleep spindles were scored according to the Standard Rechtschaffen and Kales. The sleep spindles were visually detected and were manually measured for duration in seconds. The total number of sleep spindles, number of spindles per minute (Spindle index) and mean spindles duration were calculated. Children who had significant central apnea, obstructive apnea, hypoventilation, periodic leg movement disorders or children who were on medications that may affect sleep sleep spindles were excluded from the study.

**Results:** Fifteen patients met the criteria to entry into analysis, 7 control [C] and 8 sickle cell disease [S]. No significant difference in the age ( $11.3 \pm 4.5$ [S] vs.  $8.3 \pm 4.1$  [C], p=NS) and sex was observed between the two groups. Children with sickle cell disease had a significant increase number of sleep spindles as demonstrated by an increase in sleep spindles index ( $2.32 \pm 1.77$  /min [S] vs.  $0.64 \pm 0.48$  /min [C]; p=0.03). In addition, the mean sleep spindles duration was significantly longer in sickle cell disease group ( $1.21 \pm 0.14$  seconds [S] vs.  $1.48 \pm 0.30$  seconds [C]; p=0.04). There was no significance difference in sleep efficiency, sleep stage distribution or arousal index between sickle cell disease and control group.

**Conclusions:** Children with sickle cell disease have a significant increase in the number and duration of sleep spindles. It is speculated that these alternations in the sleep spindles may be associated with silent brain ischemia/infarction in sickle cell disease and may represent the neurophysiologic changes

secondary to brain ischemia in these populations.

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**Research supported by AHA #0160230B and Constance Kaufman Fund.**

**202.G****ROLE OF HORMONAL BALANCE, OBESITY AND OREXIN IN SEVERE HYPERSOMNOLENCE DEVELOPING AFTER PITUITARY SURGERY.**

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**Introduction:** Following resection of hypothalamic/pituitary tumors children are at risk for development of hormonal deficiency, obesity, and hypersomnolence. However, their incidence and pathophysiology are very poorly understood. The purpose of the current study was to assess the prevalence and severity of hypersomnolence in children following resection of pituitary tumors, and to study the potential factors contributing to this sleepiness if present. Some data suggest an association between narcolepsy and pituitary disease. Thus, we further hypothesized decrements in orexin levels secreted from the lateral hypothalamus may contribute to the sleepiness.

**Methods:** All charts of children who underwent resection of pituitary tumors in the last 10 years at Rambam Medical Center were reviewed. Five age-matched healthy children served as controls. All participants underwent a full-night in-lab polysomnography, followed by MSLT modified for children (30-minute nap trials). Children who were found to have a primary sleep disorder (e.g. OSA) underwent treatment and were re-studied thereafter. Blood was drawn for measurements of thyroid hormone, prolactin, and cortisol. All children from the study group, and 3 control children underwent blood and CSF measurements of orexin levels in a blinded fashion. Probands and controls were compared using unpaired Student t-tests.

**Results:** Six potential patients were identified and 5 agreed to participate in the study. Their sleep and MSLT characteristics are shown for both patients and controls in the Table. Although patients slept longer with similar efficiency than controls, all 5 demonstrated relatively severe daytime somno-

lence. In the 2 patients with OSA, compliant CPAP therapy did not modify their daytime somnolence. Patients were euthyroid and were given adequate steroid replacement. Serum and CSF orexin levels did not differ between patients and controls.

**Table 1**

	n	Age (y)	BMI (Kg/m <sup>2</sup> )	Time In Bed (min)
Patients	5	15±3	28±6	503±31
Controls	5	15±3	19±2*	433±23 *

	(%) Sleep Effic.	No. sleep episodes in MSLT	Average MSLT sleep latency (min)
Patients	82±14	4.4±0.5	10.3±5.3
Controls	80±7	1.6±0.5 *	26.2±1.1 *

\* P<0.05

**Conclusions:** We conclude that severe hypersomnolence is very frequent among children undergoing pituitary surgery, which can not be explained by inappropriate cortisol or thyroxin replacement, disturbed nocturnal sleep, OSA, or by low levels of orexin in the serum or CSF. We speculate that unidentified neuro-hormones or cytokines may mediate this sleepiness.

**203.G**

**SLEEP IN CHILDREN WITH BRAIN TUMORS**

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**Introduction:** Sleep is generated by and primarily for the benefit of the brain; and though some of the anatomic locations and physiologic mechanisms by which the brain accomplishes these tasks are known, many are not. The clinical assessment of children who have sustained brain trauma has demonstrated that any significant brain trauma may affect sleep. This has been described across a wide range of brain injury including traumatic, infectious, metabolic, ionizing radiation, vascular, embolic, chemotherapy, and malignant. The study of children with brain tumors provide's some unique insights into the mechanisms by which brain trauma results in sleep symptoms, because the area of the brain which has been injured is well established. These children have sustained a variety of significant brain trauma which may include the tumor itself, neurosurgical removal of the tumor, if surgery is involved, cranial irradiation, and intrathecal administered medication. The most frequent case reports have been of sleep disordered breathing in individuals with brainstem tumors(1);and hypersomnolence in individuals with hypothalamic tumors. Malik (2) recently described 18 cases of symptomatic narcolepsy, 7 of whom had brain tumors. However, there have been no case series reports

of PSG and MSLT'S in children with brain tumors. This report describes the clinical presentation, PSG and MSLT of 12 consecutive children with brain tumors seen over the past 8 years at the Mn Regional Sleep Center and Childrens Hospital and Clinics.

**Methods:** Clinic records for all children with brain tumors seen at the Minnesota Regional Sleep Disorder Center and the St Paul Children's sleep center for the past 8 years were reviewed. Twelve children were evaluated, most were seen by the author(GR). All clinical information was reviewed. This included: clinical sleep history, oncology notes, PSG , and MSLT.

**Results:** Table 1 summarizes the types of tumors and their treatments. The sleep problems in this referral population of children with tumors were: excessive daytime sleepiness 8/12, long sleepers 2/12, nocturnal seizures 2/12, respiratory insufficiency 2/12, nocturnal hypoxemia 1/12, nocturnal enuresis 1/12. continuous movements during sleep 1/12. Six of the children with complaints of EDS had mean MSLT's less than 10.6 minutes, 4/5 had 2 or more SOREMS on the MSLT, consistent with the diagnosis of symptomatic narcolepsy. The shortest mean MSLT'S were in children with hypothalamic-pituitary injury and SOREMS. The MSLT data is summarized in Table 2.

**Table 1**

Tumor	#	Initial Treatment
Astrocytoma	3	surgery, chemotherapy, radiation
Medulloblastoma	3	surgery, chemotherapy, radiation
brain stem glioma	2	surgery, chemotherapy
craniopharyngyoma	1	surgery, chemotherapy
langerhans cell histiocytosis	1	chemotherapy
hypothalamic hamartoma	1	surgery, radiation
Pineal blastoma	1	surgery ,chemotherapy radiation

**Table 2**

patient	nap #1	nap #2	nap #3	nap #4	nap #5	mean
*AD (16yr)	5	+1.5	0	+1	-	2
*DG (20yr)	+0.5	1	+1	1	+1	0.87
*AP (14 yr)	+6	+11	+13	7	+15	7.9
R.C (10yr)	+4.5	11	13	8.5	-	9
*MY (7 yr)	5.5	+8.5	+7	+6.5	-	6.4
*JA (12 yr)	1.5	19.5	11.5	10	14	10.6
TM (7 yr)	14.5	+10.5	15	20	14	14.8
GD (15yr)	20	20	20	20	-	20
*AB (16yr)	20	20	20	20	-	20

(\*denotes hypothalamic injury, + denotes REM on naps)

**Conclusions:** Children with brain tumors may present with a variety of sleep problems, most commonly excessive daytime sleepiness and respiratory failure. Children who have sustained hypothalamic-pituitary injury as a result of their tumor, or surgery commonly show the most severe daytime sleepiness and often have the polysomnographic findings of symptomatic narcolepsy .

**References:**

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stem gliomas with predominant symptom of sleep apnea. *Int J Pediatr Otorhinolaryngology* 1996;37:53-64  
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## 204.G

### POLYSOMNOGRAPHY AND CONTINUOUS GLUCOSE MONITORING IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS.

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**Introduction:** Adult patients with diabetes mellitus often have signs of abnormal ventilation during sleep as well as cardiovascular dysfunction. Impairment of respiratory control during sleep in children with type 1 diabetes has been recently reported (1, 2). However the influence of blood glucose levels on respiratory control during sleep has not been well established yet. Aim of this study was to assess the relation between respiratory changes and blood glucose levels during sleep in children and adolescents with type 1 diabetes.

**Methods:** Ten patients (7 M, 3 F), mean age  $13.4 \pm 3.3$  yrs, with a mean duration of the disease of  $63.2 \pm 34.5$  months, were evaluated. All patients were in treatment with 2-4 daily subcutaneous injections of short- and intermediate-acting human insulin. The metabolic control was assessed by daily monitoring of blood glucose and by measurement of HbA1c: mean HbA1c in the last 12 months was  $7.7 \pm 0.5$  % (range 8.3% to 6.8%) and HbA1c at the time of evaluation was  $8.6 \pm 1.1$  % (range 10.3-7.1%). The mean insulin requirements per day was  $0.84 \pm 0.14$  U/Kg. All patients underwent a full nocturnal polysomnography (12 channels, Alice 3) as well as blood glucose continuous monitoring by means of CGMS, Minimed. All recordings were scored in terms of sleep stages according to Rechtschaffen and Kales criteria and in terms of respiration according to the ATS criteria for cardiopulmonary sleep studies in children (3). Patients were divided into two groups according to their mean HbA1c values during sleep: those with good metabolic control (HbA1c less/equal 7.9%) and those with poor control (HbA1c greater 7.9%).

**Results:** No difference was found in terms of sleep architecture (total sleep time, stages 1-4 NREM %, REM %, fragmentation and arousals) between the two groups. Moreover no significant difference was found in the two groups in terms of apnea index (AI), central apnea index (CAI), apnea/hypopnea index (AHI), mean apnea duration (MAD), maximal apnea duration (MaxAD), minimal SaO2 and mean SaO2 (Tab 1). Concerning the relation between glucose levels and respiratory pattern we only found that patients with a good metabolic control showed significant ( $p < .05$ ) lower blood glucose levels during central apnea periods compared to blood glucose levels during non-apneic sleep periods ( $86 \pm 58$  vs  $106 \pm 60$ ).

**Table 1**

	HbA1c $\leq$ 7.9%	HbA1c $>$ 8.0%
CA	1.9 $\pm$ 0.5	1.6 $\pm$ 1.3
CAI	1.5 $\pm$ 0.8	1.5 $\pm$ 1.3
AHI	3.3 $\pm$ 0.9	2.8 $\pm$ 1.7
MAD	19.9 $\pm$ 2.0	19.4 $\pm$ 3.4
MaxAD	27.1 $\pm$ 2.4	24.9 $\pm$ 6.8
MinSaO2	93.5 $\pm$ 2.5	92.2 $\pm$ 2.0
Mean SaO2	93.3 $\pm$ 4.1	93.3 $\pm$ 1.6

Values are mean  $\pm$  1SD

**Conclusions:** Our results suggests that a drop of blood glucose levels during sleep can influence the respiratory control during sleep in patients with type 1 diabetes with a good metabolic control.

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- (3) American Thoracic Society: Standards and indications for cardiopulmonary sleep studies in children. *Am J Respir Crit Care Med* 1995; 153: 866-878.

## Oral Presentation Circadian Rhythms: Shift Work

## 205.E

### CIRCADIAN ADAPTATION TO NIGHT SHIFT WORK: DAYTIME DARK IS GOOD, ADDING LIGHT DURING THE NIGHT SHIFT IS BETTER

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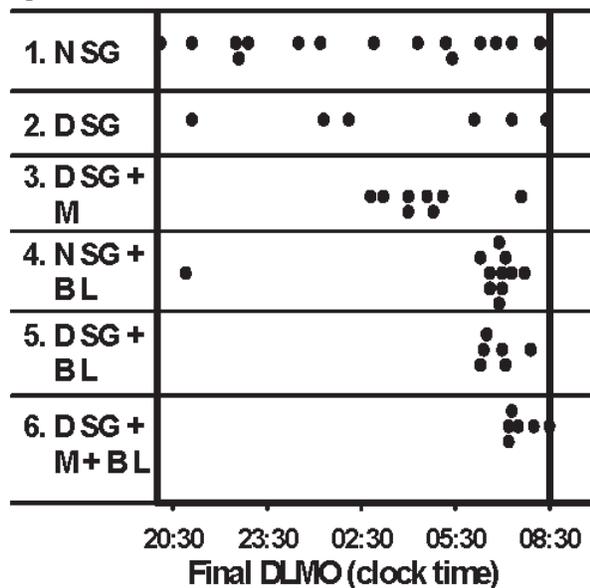
**Introduction:** Various interventions have been tested to help phase shift the circadian clock and promote adjustment to night work and day sleep schedules (1). Our ongoing study tests various combinations of interventions.

**Methods:** Thus far, 52 healthy young adults have participated. The subjects work 5 consecutive simulated night shifts (23:00 to 07:00) and sleep at home (08:30 to 15:30). Subjects are required to stay in bed, in the dark for the full 7 hours. This daily dark sleep episode is the building block for all combinations of interventions, and others are added in order of the least amount of effort for the night worker. There are 6 intervention groups (see Figure). While traveling home, subjects wear normal sunglasses (N SG) or dark sunglasses (D SG) (transmit 15% or 2% of light respectively). Subjects take a placebo or melatonin (M) pill (1.8 mg sustained release) before daytime sleep. During the night shifts, subjects are exposed to a moving pattern of intermittent bright light (BL) (~5000 lux, 20 min of some hours) or dim light (~200 lux). There is a circadian phase assessment before the first and after the last night shift in which subjects give saliva samples every half hour for determination of the dim light melatonin onset (DLMO). Sub-

jects fill out sleep logs. They also complete computerized mood and performance batteries during the night shifts.

**Results:** The Figure shows the final DLMO in all subjects. The more interventions that were added, the more likely the final DLMO was phase delayed enough to have been in a normal phase relationship with the preceding daytime sleep episodes (2-3 hours before 8:30am). The groups that received BL shifted the most. Other studies have shown that the temperature minimum occurs about 7 hours after the DLMO. Thus, we estimate that subjects whose DLMO occurred after 1:30am had temperature minima that fell within daytime sleep. This amount of re-alignment should reduce symptoms of night shift work. Subjects who shifted their final DLMO past 1:30am felt significantly more alert (Stanford Sleepiness Scale) and showed significantly less decrement in performance (lapses on a psychomotor vigilance task) during the night shifts than those who did not. However, there was no difference among groups in daytime sleep duration. Subjects reported sleeping for almost the full 7 hours.

Figure 1



**Conclusions:** These data suggest that a regular dark daytime sleep opportunity and normal sunglasses are enough to produce circadian adaptation in some subjects, but more interventions are needed in others. Bright light during the night shift increases the likelihood of circadian adaptation. We need to run more subjects to determine whether melatonin produces an additional advantage.

**References:**

(1) Burgess HJ, Sharkey KM, Eastman CI. Bright light, dark and melatonin can promote circadian adaptation in night shift workers. *Sleep Medicine Reviews* (in press).

Research supported by NIOSH grant R01 OH03954, light boxes donated by Apollo Light Systems, melatonin and matching placebo donated by Ecological Formulas, Concord, CA.

**206.E**

**IMPROVEMENT OF DAYTIME SLEEP IN SHIFT WORKERS BY JUDICIOUS LIGHT EXPOSURE**

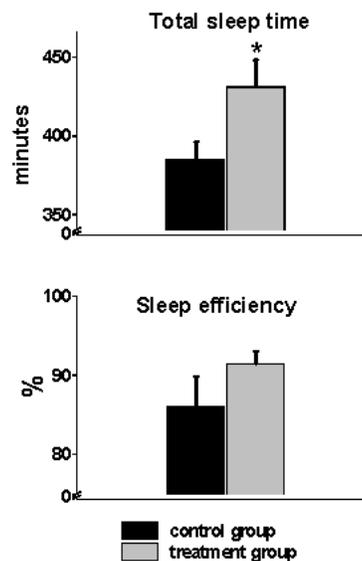
James FO,<sup>1,2</sup> Chevrier E,<sup>1,2</sup> Boivin DB<sup>1,2</sup>

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**Introduction:** Night shift workers typically experience difficulty sustaining diurnal sleep for longer than 6 hours (1), and may be particularly vulnerable to the repercussions of acute and chronic sleep deprivation (2). Where the quality of sleep is in part governed by circadian phase (3), we implemented an intervention designed to shift circadian phase and increase the length of daytime sleep in shift workers.

**Methods:** Following a vacation period including  $\geq 10$  days on a regular daytime schedule, 15 nurses returned to their regular schedule of full-time night shifts for ( $\pm$  SD)  $\geq 12.1 \pm 0.7$  shifts. Ten workers ( $41.7 \pm 8.8$  years) were observed under the treatment condition. They were given an intervention regimen consisting of a 6-hour exposure to bright light ( $\sim 2000$  lux) at the beginning of their shifts and shielding from morning sunlight with tinted goggles. Nine workers ( $41.98 \pm 7.2$  years) were observed under the control condition in their habitual lighting environments. Both groups maintained regular sleep habits following night shifts that consisted of a single 8-hour darkness period during which they attempted to sleep. This period was scheduled 2 hours after the end of night shifts. Diurnal sleep was objectively measured by portable polysomnography or the NightCap device. Total sleep time and sleep efficiency were significantly correlated between recording methods ( $r=0.623$ ,  $p<0.001$  and  $r=0.681$ ,  $p<0.001$ , respectively). The endogenous circadian temperature minimum was assessed before and after the series of night shifts using a 36-hour constant routine. The phase angle between the temperature minimum and the time of awakening was calculated.

Figure 1



**Results:** Mean diurnal total sleep time ( $\pm$  S.E.M.) of treatment group workers was  $7:12 \pm 0:17$  hours with a sleep efficiency of  $91.5 \pm 1.56$  %. Total sleep time in the control group was  $6:25 \pm 0:11$  with a mean sleep efficiency of  $86.1 \pm 3.7$ %. Differences in total sleep time were statistically significant ( $P=0.04$ ) while those of sleep efficiency were not ( $P=0.2$ ). Following the intervention, only the treatment group workers displayed phase shifts conducive to phase angles comparable to those of the initial condition ( $F_{s,1,15} = 0.02, p=0.9$ ).

**Conclusions:** In the treatment group, the intervention resulted in a proper relationship between circadian phase and the sleep-wake cycle as well as a 46-minute extension of the diurnal sleep episode. Circadian adaptation to night shifts was incomplete in the control group, which resulted in abbreviated diurnal sleep. These results further support the importance of promoting circadian adaptation in shift workers.

#### References:

- (1) Foret J, Benoit O. Structure du sommeil chez des travailleurs à horaires alternants. *Electroencephalogr Clin Neurophysiol* 1974;37:337-344.
- (2) Rosekind MR, Hurd S, Buccino KR. Relationship of day versus night sleep to physician performance and mood. *Ann Emerg Med* 1994;24:928-934.
- (3) Czeisler CA, Weitzman ED, Moore-Ede MC, Zimmerman JC, Knauer RS. Human sleep: Its duration and organization depend on its circadian phase. *Science* 1980;210:1264-1267.

Research supported by Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail du Québec

## 207.E

### EVENING NAPS AND/OR CAFFEINE AS COUNTER-MEASURES FOR SLEEPINESS DURING SIMULATED NIGHT SHIFTS

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**Introduction:** We previously reported a modest positive effect of evening naps on alertness and neurobehavioral performance, limited to the first of five consecutive simulated night shifts. (1) The minimal effect of naps on night shift alertness and performance during subsequent consecutive nights probably accounted for the failure of evening naps to represent additional sleep during the prior 24 hours. (2) Practical countermeasures to enhance alertness and performance on the night shift are needed, particularly for those occupations key to public safety. The present study systematically examines the effects of a) napping before the first two of four consecutive simulated night shifts (NAP), b) 4mg/kg caffeine before all four simulated night shifts (CAF), c) the combination of the NAP and CAF conditions (NAP+CAF), and d) placebo before all four simulated night shifts (PBO).

**Methods:** 57 subjects (26 m, 31 f; mean age  $32.5 \pm 12.8$ ) were randomly assigned to one of the four experimental conditions. Sex representation was similar and mean age did not differ among groups. Each subject participated during four consecu-

tive nights and the following four days. The simulated night shift began at 2300 and ended at 0700, during which time the Maintenance of Wakefulness Test (MWT; 2345, 0145, 0345 and 0630), a Neurobehavioral Assessment Battery (NAB; 2300, 0100, 0300, 0545), and various cognitive tests (0215 and ~0440) were administered. Daytime sleep was recorded each day beginning at 0830 (*ad lib* with a minimum of six hours in bed). A 4 groups X 4 nights X 4 time points ANOVA was the primary statistical model used for all performance and alertness variables, followed by paired comparisons. Results from the MWT, the psychomotor vigilance task (PVT, a subtest of the NAB), and daytime sleep and nap data are reported here.

**Results:** Mean minutes of nap sleep on nights 1 and 2 were 101.6 and 71.9 for NAP and 94.1 and 91.2 for NAP+CAF (NS). Mean total sleep time (minutes) over the 4 days were: 373 (range 357.5 to 389.2) for CAF, 338 (316.4 to 368.8) for NAP+CAF, 344 (317.3 to 332.1) for NAP, and 341 (303.2 to 361.0) for PBO (NS). MWT analysis indicated a night x group interaction ( $p=.006$ ; see Fig 1) and main effects for night ( $p=.028$ ), and time-of-night ( $p<.001$ ), with latencies becoming much shorter as the night shift progressed. On night 1, NAP, NAP+CAF, and CAF all had longer latencies compared to PBO ( $p<.025$ ). In addition, NAP+CAF was more alert than NAP ( $p=.031$ ) and tended to be more alert than CAF ( $p=.099$ ). On night 2, only NAP+CAF was more alert than PBO ( $p=.019$ ). No group difference in MWT were present on nights 3 and 4. PVT square root-transformed lapses showed a trend for a main effect for group ( $p=.09$ ; see Fig 2). Performance decreased as the night shift progressed ( $p<.001$ ) and worsened slightly across the 4 nights ( $p<.001$ ). A significant group by time interaction ( $p<.004$ ) was accounted for by improved performance in the early morning hours for NAP, NAP+CAF, and CAF compared to PBO during nights 1 and 2, and for NAP+CAF and CAF vs PBO on nights 3 and 4. There were no differences among NAP, NAP+CAF, and CAF groups on any night. Data were similar for PVT slowest 10% of responses

Figure 1

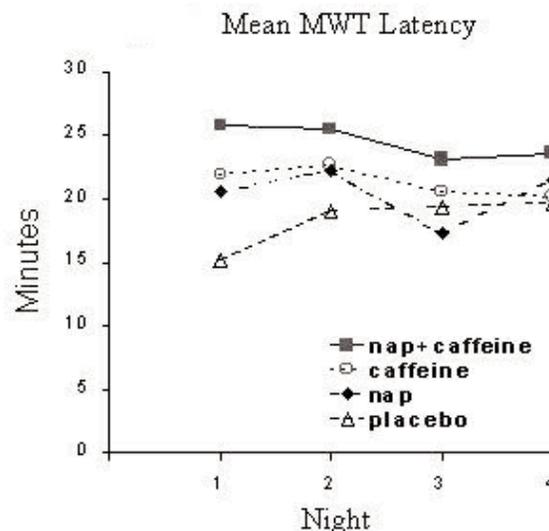
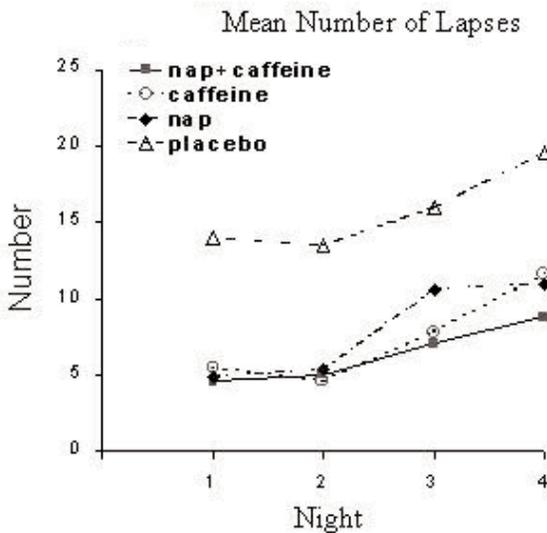


Figure 2



**Conclusions:** These data indicate that caffeine and/or napping improve both alertness and performance during 4 simulated night shifts. Improvements in alertness were maximal on the first night shift with slight differences among the 3 active treatments. NAP+CAF appears to be a slightly more alerting manipulation as its effect persisted into the second night. Performance improvements were also maximal on the first night shift and persisted across subsequent shifts. However there were no differences among the active treatment groups. Alertness and neurobehavioral performance during usual night shift hours are enhanced by pre-shift naps, caffeine, and the combination of these countermeasures.

**References:**

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- (2) Schweitzer PK, Walsh JK: Evening naps reduce daytime sleep time on simulated night shifts; *Sleep* 2001; 24(suppl):A124.

Research supported by R01 OH03966 from the Centers for Disease Control and Prevention/National Institute For Occupational Safety and Health

**208.E**

**MODAFINIL ENHANCES ALERTNESS AND PERFORMANCE DURING FOUR CONSECUTIVE SIMULATED NIGHT SHIFTS**

Schweitzer PK,<sup>1</sup> Kader GA,<sup>1</sup> Walsh JK<sup>1</sup>

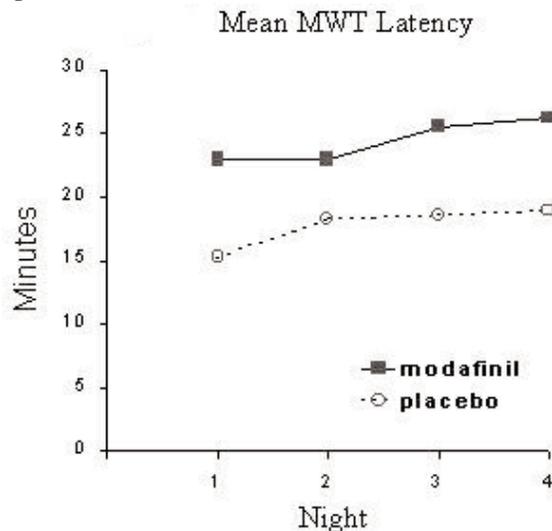
(1) Sleep Medicine and Research Center, St. John's Mercy Medical Center/St. Luke's Hospital, (2) Department of Psychiatry, St. Louis University Health Sciences Center,

**Introduction:** Reduced alertness during night shift, and the associated risk of errors and impaired performance, remains an intractable problem for many industries and occupations. Therefore, we studied the effects of the alerting drug, modafinil (MOD), on alertness and performance during usual

night shift hours in a simulated shift work protocol.

**Methods:** Twenty-six males and females (age range: 18-52 yrs) participated in a parallel groups, double-blind, repeated-measures design. Written informed consent was obtained. All were free of medical and psychiatric disorders, kept a regular sleep schedule, habitually consumed < 10 alcoholic drinks/week and < 400 mg caffeine/day), and did not take CNS active medications. A standard PSG adapted subjects to laboratory procedures and excluded those with sleep disorders. A daytime MSLT excluded individuals with a mean latency ≤ 5 minutes. Prior to randomization, subjects were trained on performance tests and maintained a regular sleep-wake schedule. Either MOD 200 mg or placebo (PBO) was given at 2200 hr each night during a 4 night/4 day simulated night shift schedule. From 2300 until approximately 0700 each night subjects engaged in a variety of performance tests and alertness measures. This report includes results for the maintenance of wakefulness test (MWT), psychomotor vigilance task (PVT), and digit symbol substitution test (DSST). Daytime sleep was recorded each day beginning at 0830 (*ad lib* with a minimum of six hours in bed). A 2 groups X 4 nights X 4 time points ANOVA was the primary statistical model used for all performance and alertness variables, followed by paired comparisons.

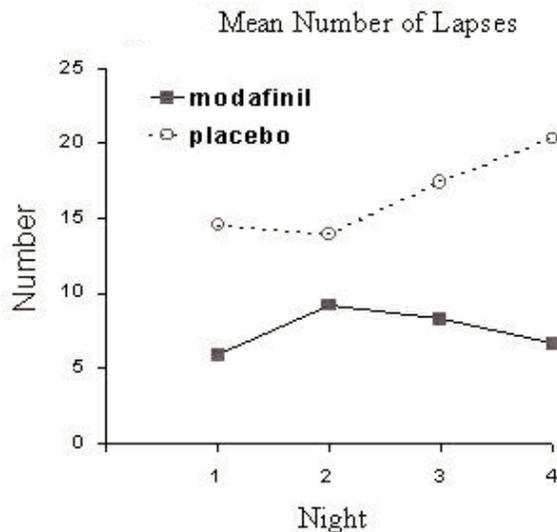
Figure 1



**Results:** The MOD group had higher levels of alertness than PBO as evidenced by a significant main group effect on the MWT ( $p=.027$ ; see fig.1). MWT main effects for night and time were also significant ( $p<.02$ ). The enhanced difference between MOD and PBO during the last three time points of the night was reflected in a trend ( $p=.057$ ) for a time X group interaction. Improved performance with MOD vs PBO in the early morning hours was indicated by significant time X group interactions for PVT square root-transformed lapses ( $p=.007$ ) and slowest 10% of responses ( $p=.002$ ). The beneficial effects of MOD on these measures was also greater later in the week of night shifts ( $p=.016$  and  $p=.04$ , respectively). Figure 2 shows the mean number of PVT lapses averaged across each night for each group. The DSST showed beneficial effects of

MOD essentially identical to those seen on the PVT. There were no significant group, or group X day, differences in PSG measures of daytime sleep.

Figure 2



**Conclusions:** Modafinil 200mg significantly improved physiological alertness and performance during four consecutive, 8hr simulated night shifts. No side effects were reported or detected, including an absence of significant effects on daytime sleep. The role of modafinil for the treatment of night shift-related sleepiness and impaired performance should be examined, particularly for workers in occupations known to be susceptible to early morning accidents.

Research supported by CDC/NIOSH R01 OH03966 and Cephalon, Inc., West Chester, PA.

### Oral Presentation Sleep and Phylogeny

#### 209.F

##### POLYGRAPHIC AND NEURONAL CORRELATES OF SLEEP IN FREELY MOVING TURTLES

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**Introduction:** Previously we reported that 95% of neurons located in the caudal pons and rostral medullary reticular formation in freely-moving turtles displayed decreased firing rates and variability as turtles moved from wakefulness to quiescence (Eiland et al., 2001). Here we present further data on the pattern of neuronal discharge throughout the brain and its relationship to behavioral states in the turtle.

**Methods:** We recorded EEG, EMG, EKG, EOG and unit activity from 13 freely-moving turtles of the species *T. carolina* and *P. scripta*. Units were recorded from the midbrain (n=11), pontine (n=39) and medullary (n=18) reticular formation, dorsal

cortex (n=7), the diencephalon (n=5), cerebellum (n=18), optic tectum and pretectal area (n=11). Neuronal discharge rates were correlated with accompanying polygraphic data.

**Results:** As in previous studies (e.g., Flanigan et al., 1974) we recorded EEG spikes in most of the turtles studied here. Unlike those studies, however, we did not observe an increase in the number and amplitude of EEG spikes with lengthening of quiescence as measured by gradually decreasing neck and leg muscle tone, slowing of the heart rate and eye closure. The number of EEG spikes in quiescent turtles was not associated with postural changes (number of limbs extended, position of the head) and the occurrence of EEG spikes did not depend on the environmental temperature in the range of 23-28° C. EEG spikes usually occurred symmetrically in the two hemispheres irrespective of eye state. 67% of all units recorded in the quiescent turtle fired at rates of less than 1 Hz and 35% fell virtually silent (<0.1 Hz). All optic tectum units discharged in response to visual stimulation and did not noticeably modify their firing rates across behavioral stages. Most brainstem reticular, cerebellar and cortical cells showed progressively decreasing firing rates (63-75%, 77% and 57%, respectively) and/or increased regularity of discharge (69-88%, 100%, and 57%, respectively) as turtles moved from wakefulness to quiescence. Other cells showed no state specific discharge. Several cells (3 of 26 or 12%) located between the roots of nerve V and VII showed increased irregularity of discharge in quiescence. 3 of 7 (40%) cortical and 1 of 5 (20%) diencephalic cells showed a burst-pause discharge pattern in quiescence. In only one cortical unit, the appearance of bursts clearly correlated with EEG spikes and the firing rate and the number of EEG spikes per epoch showed parallel increases.

**Conclusions:** The results confirm our previous data that the discharge of most units throughout the turtle brain is movement, muscle tone or stimulus-response related. However, some cells recorded in midbrain and forebrain showed changes in firing pattern (bursting-pause discharge, increased variability of discharge) with lengthening quiescence not related to changes in muscle tone. Both polygraphic and neuronal data favor the idea that sleep in turtles is a single homogeneous state, not subdivided into distinct REM and non REM states.

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#### 210.F

##### SLEEP IN THE CUTLEFISH SEPIA PHARAONIS

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**Introduction:** Sleep is ubiquitous, however an unequivocal

nonREM-REM sleep cycle has been documented only in mammals and birds where it may have evolved from a common precursor. REM sleep is proposed to play a role in learning, and since cephalopods are highly intelligent invertebrates that perform comparably to mammals on many learning tasks, a state analogous to REM sleep may have evolved independently in cephalopods, having important implications for our understanding of the function of REM sleep. In this study, the cuttlefish *Sepia pharaonis* was studied with continuous video recording to characterize behavioral sleep. The cuttlefish was chosen because it has a bony mantle allowing implantation of telemetry equipment for electrophysiological recording in future experiments.

**Methods:** Five sub-adult cuttlefish were adapted to a 12 hour bright light-dim light cycle in individual aquariums. Each animal was recorded continuously for three days and behavior was scored in one minute epochs. Arousal threshold was tested with 1/2 second voltage pulses applied across two stainless steel plates immersed at opposite ends of the aquarium. Voltage was increased in 1/2 volt increments until a clear escape response (rapid darting) was elicited. Homeostasis was studied by manually preventing behavioral quiescence during a 12 hour light cycle and measuring subsequent dark period quiescence.

**Results:** Cuttlefish spent much time either swimming about the aquarium or hovering near the bottom with nearly continuous postural adjustments and tentacle movements. During periods of quiescence, cuttlefish would lie motionless on the gravel with invariant coloration, often in a shallow depression with tentacles retracted. Postural adjustments were absent except for occasional brief movements in which the rear end would "bob" upward. Quiescent periods ranged from one to 63 minutes, and commonly occurred in 10 to 15 minute periods interrupted by several minutes of hovering behavior. An average of 391.4±28.1 minutes was spent quiescent in the dark period compared to 596±18.6 minutes in the light period. A simple paired T-test demonstrated a significant difference,  $t=12.8, p>.001$ . Quiescent periods tended to be more consolidated in the light period. In hovering or swimming cuttlefish, 9.2±.27V was required for a clear escape response; during behavioral quiescence a clear escape response occurred at an average of 10.8±.22 V ( $t=7.5, p>.01$ ). When deprived of quiescence during the light period, dark period quiescence increased from an average of 391.4±28.1 to 521.3 minutes. During quiescence, cuttlefish exhibited periods of complex color changes lasting from several seconds to two minutes, occasionally occurring cyclically in 5-15 minute intervals.

**Conclusions:** This study provides evidence that the cuttlefish *Sepia pharaonis* exhibits behavioral sleep having: 1) a rapidly reversible species specific resting posture, 2) a circadian pattern of consolidated rest periods, 3) an elevated arousal threshold during rest and 4) homeostatic regulation, with rest deprivation leading to rest rebound. The intriguing possibility that periods of color changes during behavioral quiescence may represent an active state of sleep analogous to mammalian and avian REM sleep warrants further investigation with more extensive behavioral observations and electrophysiological monitoring.

## 211.F

### HYPOCRETIN IMMUNOREACTIVE NEURONS IN NORMAL AND ROLLER PIGEONS (COLUMBIA LIVIA)

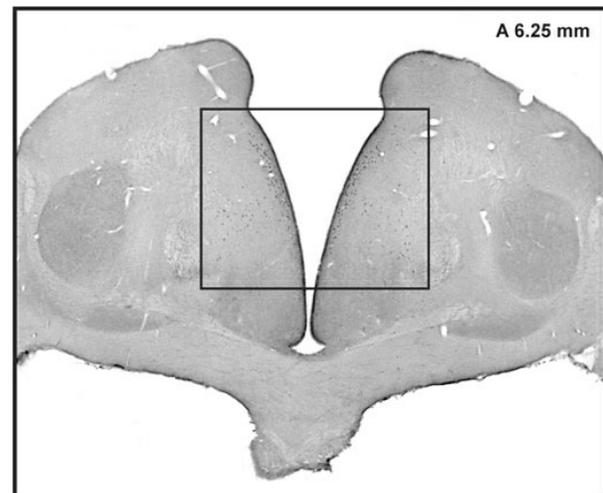
Rattenborg NC,<sup>1</sup> Gerstner JR,<sup>1</sup> Landry CF,<sup>1</sup> Obermeyer WH,<sup>1</sup> Benca RM<sup>1</sup>

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**Introduction:** The hypocretin (orexin) receptor-ligand system is involved in the pathophysiology of narcolepsy<sup>1</sup>. Given their regulatory role in mammalian REM sleep, hypocretins may also be involved in sleep regulation in birds, the only non-mammalian class to show REM sleep<sup>2</sup>. We determined the distribution of hypocretin neurons and fibers in normal and roller pigeons. Roller pigeons are of particular interest since they intermittently roll or tumble toward the ground during flight, an idiopathic behavior that may reflect cataplexy.

**Methods:** Adult normal and roller pigeons were purchased from private breeders. The roller pigeons were from a proven line of show-quality birds. The pigeons were housed under a 12:12 LD photoperiod. Brains were collected 1-h after lights on. Immunocytochemistry was performed on adjacent 50 /μm sections using polyclonal antibodies for mammalian hypocretin-1 and hypocretin-2 (Oncogene™).

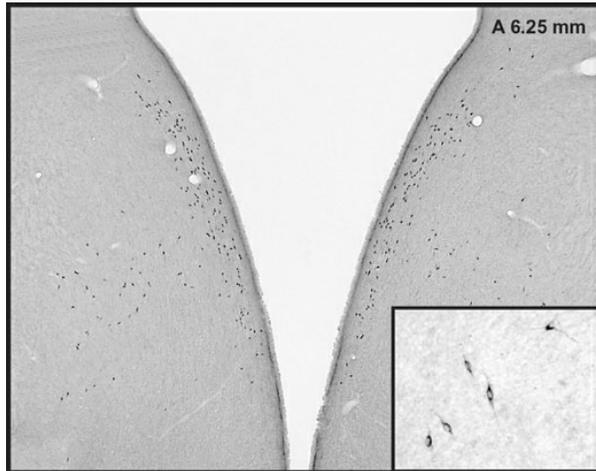
Figure 1



**Results:** The distribution of immunoreactive (IR) staining for neurons and fibers was similar for both strains of pigeons and hypocretin antibodies. Control sections in which the antibody was preincubated with the antigen did not show staining for neurons or fibers, suggesting that the staining was specific to hypocretins. IR staining was restricted to the soma of fusiform neurons and thick varicose fibers. IR neurons were distributed densely along the third ventricle in a region corresponding to the *n. periventricular hypothalami* and *n. paraventricularis hypothalami*, and diffusely in the *regio lateralis hypothalami* and *stratum cellulare externum* (Fig.1,2). Hypocretin IR fibers were widely distributed throughout the brain. The density of fibers was low in the *hyperstriatum accessorium*, an area

homologous to the mammalian cortex<sup>3</sup>. Fibers were moderately dense in the hippocampus and *archistriatum*, a structure homologous to the mammalian amygdala. Fiber density was high in the septal region, n. accumbens, locus ceruleus, and portions of the thalamus and hypothalamus. Finally, hypocretin fiber density varied across different laminae of the optic tectum.

Figure 2



**Conclusions:** Hypocretin immunoreactive neurons and fibers were distributed throughout the pigeon brain in a pattern similar to mammals. The pattern of hypocretin neurons and fibers was similar in normal and roller pigeons, suggesting that gross deficiencies in hypocretin producing neurons or their projections do not account for this idiopathic behavior. Ongoing studies will determine whether roller pigeons exhibit mutations in genes encoding for the prepro-hypocretin neuropeptide or hypocretin receptors. It is also possible that rolling in pigeons is not equivalent to mammalian cataplexy. Finally, future studies will determine whether hypocretins play a role in regulating sleep and wakefulness in birds. Comparisons between the role of hypocretins in avian and mammalian sleep may provide insight into the evolution of sleep mechanisms and function.

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## Oral Presentation

### Impact of Neurologic Disorders on Sleep

#### 212.O

#### GILLIAN BARRÉ SYNDROME AND LOW CSF HYPOCRETIN/OREXIN LEVELS

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**Introduction:** Although undetectably low CSF hypocretin/orexin levels are highly specific for narcolepsy-cataplexy among various sleep disorders (Mignot et al, this issue) and neurological conditions (1), we have observed that 3 Gillian Barré syndrome (GBS) patients (among 11 subjects) exhibited undetectably low CSF hypocretin levels (1). All 3 GBS cases were severely affected and exhibited tetraplegia. Thus, low CSF hypocretin levels in GBS does not confound diagnostic values of low CSF hypocretin levels for narcolepsy. These results, however, suggest a possible involvement of the hypocretin system in the pathophysiology of GBS and immune mediated polyneuropathies. In the current study, we therefore assessed CSF hypocretin levels and clinical symptoms in a larger GBS sample population and in other immune mediated polyneuropathies.

**Methods:** Twenty-three GBS (41±25 [mean±SD] yrs, 14 male), 5 Fisher syndrome (50±17 yrs, 4 male), and 12 chronic inflammatory demyelinating polyneuropathy (CIDP) (51±25 yrs, 4 male) were included. CSF samples collected by lumbar punctures between 9:00 and 17:00 were immediately frozen, and stored at -80C until the measurements were done. CSF hypocretin-1 levels were measured with direct radioimmunoassay (1). In 7 patients, CSF taps were repeated 2-3 times within a 2 month period.

**Results:** CSF hypocretin levels of 4 GBS subjects (3 previous cases and one new case) are undetectably low (<100pg/ml) and those of 7 additional subjects were significantly low compared to controls (<196 pg/ml, the means [345 pg/ml] minus 2SD of 48 healthy controls). Significantly low hypocretin CSF levels were also observed in 3 out of 5 patients with Fisher syndrome, while hypocretin levels were not altered in most CIDP subjects (11/12). These GBS cases whose CSF hypocretins were undetectable exhibited tetraplegia (n=4) and respiratory failure (n=3). In one case (a 69 yr. old man), hypocretin-1 was already undetectable before tetraplegia and respiratory failure occurred. Furthermore, no treatment was initiated and no increase in CSF protein was observed when undetectable hypocretin levels were observed at the first CSF tap. While most patients with undetectably low (1 case) and significantly low (5 cases) stayed in the similar levels during repeated taps, one patient with low levels showed recovery of hypocretin levels, with levels increasing from 156 pg/ml to 274 pg/ml after 24 days, and reaching a level of 317 pg/ml after 44 days.

Although sleep abnormalities were difficult to be noted in severe GBS cases, shortened sleep latency (40 sec in 2 nap test, done at 18 month after the GBS onset) was recorded in one patient (a 28 yr. old man) who had the undetectable level, 1 month after the disease onset.

**Conclusions:** About half of the patients with GBS and Fisher syndrome showed significantly low CSF hypocretin levels. Although low hypocretin levels are likely to be associated with acute inflammatory polyneuropathy and with severity of the disease, changes are not likely to be iatrogenic or secondary to severely impaired health conditions, since one case of hypocretin-1 was already undetectable before any treatments were initiated and before any severe symptoms, no increase in CSF protein appeared. The pathophysiological mechanism of low hypocretin levels in GBS is not known, but hypothalamic dysfunction may be involved in some GBS cases. In fact, a syndrome of inappropriate secretion of antidiuretic hormone or diabetes insipidus that suggests a global hypothalamic dysregulation, has been reported in some severe GBS cases. Similarly, links between low hypocretin levels and occurrences of sleep abnormalities are not certain in our subjects. Interestingly, however, Guilleminault had reported 2 cases (with Epstein-Barr viral infections) (2) and Mukai (3) has reported one case of GBS associated with excessive daytime sleepiness. Further investigations of whether abnormal sleep symptoms exist in hypocretin deficient GBS patients and associations between low levels and types of preceding infections, and the existence (and types) of auto-antibodies are warranted.

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## 213.O

### ARE PATIENTS WITH PARKINSON'S DISEASE AWARE THAT THEY FALL ASLEEP DURING THE DAY ?

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**Introduction:** It has been suggested that motor vehicle mishaps in drivers with Parkinson's disease (PD) may sometimes be due to the sudden onset of sleep (1). It has also been suggested that dopamine agonists may be associated with these sleep attacks. However, evidence is accumulating that PD patients have inherently poor perception of sleep-wakefulness transition. We therefore studied PD patients referred to our sleep clinic to determine whether they were aware of having fallen asleep during the day.

**Methods:** Fifty-six moderately disabled PD patients (Hoehn and Yahr score:  $2.7 \pm 9$ ), aged 53-85 years, underwent night polysomnography and multiple sleep latency tests. Mini-mental score ranged 16-30 and mean Epworth sleepiness score was  $14 \pm 4$ . They were all treated with levodopa for  $10 \pm 6$  years, and 26 patients took a dopaminergic agonist as adjunct thera-

py. At the end of each daily nap, they were asked if they believed they had slept or napped.

**Results:** A total of 241 sleep episodes occurred during 277 tests. In 34 of the sleep episodes, the patients concerned (n=21, 38% of the group) were not aware of having slept or napped. Overall, sleep episodes that were not perceived had a similar duration to those that were perceived (mean  $\pm$  SD:  $12.0 \pm 6.3$  min versus  $11.9 \pm 6.3$  min, respectively), and comprised similar proportions of slow wave (mean: 21% versus 34%, respectively) and REM sleep (mean: 26% versus 28%, respectively). The clinical (age, duration and severity of PD, cognitive impairment) and treatment characteristics (dose of levodopa, presence and dose of dopaminergic agonists) of patients perceiving their sleep episodes were similar to those of patients not perceiving their sleep episodes. Although the daytime sleep latency was similar across the whole group, patients who did not perceive sleep episodes tended to underestimate their sleepiness with the Epworth sleepiness scale compared with those who did perceive ( $12 \pm 3$  versus  $15 \pm 4$ , respectively;  $p=0.06$ ).

**Conclusions:** One-third of PD patients in this study were unaware of having daytime sleep episodes of a mean duration of 12 minutes. The impaired sleep perception may relate to subtle cognitive defects. This study suggests that daytime sleepiness, associated with a poor recollection of daytime sleep, is a characteristic of a subset of PD patients and that this is not associated with dopamine-agonist treatment.

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## 214.O

### CHRONIC VAGUS NERVE STIMULATION IN PATIENTS AFFECTED BY REFRACTORY EPILEPSY: MODIFICATIONS OF SLEEP EEG STRUCTURE.

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**Introduction:** Vagus nerve stimulation at low intensities reduces daytime sleepiness in epilepsy patients and enhances daytime REM sleep, with no changes on overnight polygraphic parameters (Malow et al 2001). High intensity stimulations seem to reduce overnight REM sleep (Vaughn and D'Cruz 1999). Sleep EEG rhythms strength and amplitude have been reported to increase (Armitage et al 2001). Our study aims to evaluate the existence and entity of changes in the sleep structure and in the sleep EEG power following high intensity vagus nerve stimulation (VNS) in patients with refractory epilepsy.

**Methods:** a polysomnographic study has been carried out on the nocturnal sleep of 10 subjects with refractory epilepsy. Subjects have been recorded in basal conditions and during chronic VNS. The intensity of VNS stimulus was  $>1.5$  mA in

all patient but one. We have evaluated sleep parameters (R&K)of the entire night, and the incidence of both interictal and ictal epileptogenic activity. The digitized EEG was assessed by a Fast Fourier Transform for 2-second consecutive epochs and averaged every 1 minute. Power spectra were divided into four segments corresponding to delta [SWA, 0.5-4.0 Hz], theta [TB, 4.5-8 Hz], alpha [AB, 8.5-12 Hz], sigma [SA, 12.5-16 Hz]. Mean absolute and relative power values of the four spectral bands were computed for wakefulness, the first NREM sleep cycle and REM Sleep. Epochs containing artefacts, arousals and wakefulness after sleep-onset were discharged. The differences between the two conditions have been subjected to parametric and non-parametric statistical evaluation.

**Results:** VNS determines a significative reduction of REM sleep, along with an increase of number of awakenings, % WASO and S1 sleep (Table 1). Such a modification is coherent in all the subjects with VNS stimulus intensity >1.5 mA, and absent in the only patient with a stimulus intensity < 1.5 mA. The incidence of interictal epileptogenic activity is diminished, although not significantly; the length of electrical discharges is significantly reduced. Spectral analysis showed an enhancement of alpha power during wakefulness and REM sleep and of delta power during NREM sleep (Table 2).

**Table 1**  
VNS effects on sleep parameters

Sleep parameters	Baseline: mean ±SD	Treatment: mean ±SD	p
Sleep latency min	12.44 ± 8.97	10.33 ± 6.22	0.489
REM Latency min	97.11 ± 38.41	124.78 ± 58.48	0.353
WASO min	23.78 ± 25.32	89.78 ± 84.29	0.036
%WASO	5.33 ± 6.06	22.89 ± 22.17	0.038
Total sleepTime min	415.22 ± 41.05	315.22 ± 140.72	0.071
Sleep Efficiency	88.78 ± 6.91	70.11 ± 24.60	0.066
REM min	77.33 ± 36.24	27.33 ± 19.81	0.006
% REM	18.44 ± 7.65	7.56 ± 3.91	0.004
S1 min	14.89 ± 11.71	27.11 ± 14.81	0.001
% S1	3.67 ± 3.04	11.22 ± 12.05	0.054
S2 min	225.55 ± 64.90	191.67 ± 98.47	0.191
% S2	54.78 ± 15.47	55.22 ± 15.55	0.900
S3+4 min	96.67 ± 60.55	79.44 ± 50.39	0.488
% S3+4	22.89 ± 13.40	25.78 ± 15.59	0.573
Awakenings	9.89 ± 7.77	21.11 ± 11.43	0.007
Phase shifts	107.44 ± 87.77	130.22 ± 76.15	0.526

**Table 2**  
Spectral power values (µV<sup>2</sup>/min, mean ± Standard deviation)

		REM	NREM	wakefulness
Delta	preVNS±DS	14,57 ± 4,29	33,65 ± 28,23	14,57 ± 5,51
	postVNS±DS	13,03 ± 7,17	48,93 ± 35,23	30,11 ± 39,83
	p	0,04	0,01	0,52
theta	preVNS±DS	10,63 ± 5,93	19,34 ± 19,17	20,39 ± 13,53
	postVNS±DS	11,03 ± 9,19	24,4 ± 19,63	34,23 ± 25,23
	p	0,12	0,18	0,05
alpha	preVNS±DS	3,56 ± 2,75	8,94 ± 9,65	5,59 ± 4,28
	postVNS±DS	4,03 ± 2,34	11,16 ± 7,56	12,35 ± 9,23
	p	0,03	0,13	0,01
sigma	preVNS±DS	2,19 ± 1,01	4,24 ± 3,45	2,93 ± 1,64
	postVNS±DS	2,56 ± 1,64	6,08 ± 2,22	4,72 ± 2,47
	p	0,15	0,97	0,96

**Conclusions:** Our data seem to be in agreement with previously reported improvement of EEG rhythms after VNS. Similarly we confirm the decrease of REM sleep in subjects with high intensity stimulation while low intensity ones leaves

REM sleep unchanged or increased. This reduction of REM sleep could also explain the improvement of mood and quality of life in these patients; the REM-suppressor effect could represent a rationale to the empirical use of VNS in refractory mood disorders.

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**215.O**

**THE EFFECTS OF VAGAL NERVE STIMULATION ON RESPIRATION DURING SLEEP IN PEDIATRIC PATIENTS WITH EPILEPSY**

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**Introduction:** Left vagus nerve stimulation (VNS) is a promising new treatment for epilepsy. In 1997, VNS was approved in the U. S. as an adjunctive treatment for medically refractory partial-onset seizures in adult and adolescents. VNS entails implantation of a programmable signal generator-the Neurocybernetic Prosthesis (NCP)-in the chest cavity. The stimulating electrodes of the NCP carry electrical signals from the generator to the left vagus nerve. Although the mechanism of action of VNS is not known, controlled studies have shown that it is safe and well tolerated by patients with long-standing partial-onset epilepsy. Side effects, which are generally of mild to moderate severity, almost always disappear after the stimulation settings are adjusted. Mild respiratory impairments during variable intensities of VNS in adult patients with epilepsy have been documented. This analysis uses polysomnographic evaluation on 4 pediatric patients following NCP implantation to further document the respiratory consequences, if any, mediated by vagal nerve stimulation.

**Methods:** 4 patients were evaluated using full polysomnography. Patients included in this study ranged in age from 8-15 years and all were referred for concerns regarding sleep apnea. There were 3 boys and 1 girl. All 4 patients were being treated for refractory seizure disorders using VNS. A standard polysomnographic montage was used in addition to two channels devoted to monitoring the output of the VNS. 2 leads were placed over the posterior aspect of the left sternocleidomastoid and 2 leads were placed more medially over the anterior aspect of this muscle. In all cases both channels showed VNS activity appropriately.

**Results:** 3 of 4 patients studied showed very mild respiratory changes associated with firing of the NCP in a fixed relationship to NCP firing. In 1 patient, there were no respiratory changes associated with the firing or quiescence of the NCP though parental reports indicated that choking and gasping decreased or ceased with recent setting alterations. For those patients whose respiratory patterns did change, there was a

slight diminution in airflow and oxygen saturation as well as slight evidence of partial respiratory paradox associated with the firing of the NCP. During VNS breathing remained quiet, there was no sign of respiratory difficulty and respiratory rates often increased. However, usually no decrement in intercostal activity and a paradoxical component was noted suggesting these events were obstructive in nature.

**Conclusions:** This analysis further supports the previous literature documenting mild respiratory impairments during VNS. While the impact of these events ultimately appeared to be of little clinical significance in these children, these findings may be significant in other individuals already at risk for obstructive sleep apnea (OSA). Considering the increasing popularity of VNS as a treatment for epilepsy, this analysis supports polysomnographic evaluation of some individuals prior to NCP implantation to identify and treat preexisting OSA.

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Monday, June 10

## 216.A

**LOCAL ADMINISTRATION OF SEROTONIN INTO THE PHASIC PONTINE-WAVE (P-WAVE) GENERATOR OF THE FREELY MOVING RAT SUPPRESSES P-WAVE ACTIVITY BUT NOT REM SLEEP**Mavanji VK,<sup>1</sup> Spoley EE,<sup>1</sup> Patterson EH,<sup>1</sup> Datta S<sup>1</sup>

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**Introduction:** Field potentials in the pontine tegmentum, known as PGO- and P-waves, which begin just prior to the onset of REM sleep and continue throughout that state, are prominent phasic signs of REM sleep. Based on a number of indirect studies, it is commonly believed that the P-wave generator is held in inhibitory restraint during wakefulness and slow-wave sleep (SWS) by the serotonergic dorsal raphe neurons (1), though the exact mechanism of action is not known. It has been known for a long-time that the P-wave generator is located in the pons, however it is only recently that the P-wave generator has been mapped in the cat and rat (2, 3). The aim of this study was to test the hypothesis that serotonin inhibits P-wave activity by its direct action on the P-wave generator. To test this hypothesis, serotonin (5-HT) or saline was microinjected unilaterally into the P-wave generator while the effects on wakefulness, sleep, and P-wave activities were quantified in freely moving chronically instrumented rats.

**Methods:** Experiments were performed on 12 male Sprague-Dawley rats weighing between 250 and 350 g. With the use of sterile procedures, cortical electroencephalogram (EEG), dorsal neck muscle electromyogram (EMG), electrooculogram (EOG), hippocampal EEG (to record theta wave), and bilateral pontine EEG (to record P-waves in both sides of the brain) recording electrodes were chronically implanted. In addition, bilateral stainless steel guide tubes were stereotaxically implanted for the microinjection of serotonin and control vehicle into the P-wave generator. Following a post-surgical recovery period of 3-7 days, rats were habituated to a sound attenuated recording cage and free moving polygraphic recording conditions for 7 days. All recording sessions were performed between 10:00 and 16:00 h, when rats are normally sleeping. After the adaptation recording sessions, microinjection sessions began. Six-hour microinjection recording sessions began after a single, unilateral microinjection of 100 nl control saline (control vehicle) or 5-HT (1.0 nmol) into the P-wave generator. To determine the effects of 5-HT, sleep-wake and P-wave variables were compared between post-control saline (n=6) and post-5-HT (n=6) injections into the P-wave generator.

**Results:** In the six-hour post-injection recording sessions, P-wave density analysis showed that the P-wave density in the injection site was significantly reduced after 5-HT application (70.18% reduction,  $p < 0.001$ ) compared to after control saline. However, the P-wave density in the P-wave generator contralateral to the injection side, after 5-HT injection, was minimally reduced (8.42%) and was not significantly different compared to the P-wave density in the contralateral P-wave generator after control injection. Surprisingly, the total per-

centages of W, SWS, and REM sleep in the 6-hour post-injection recording sessions after 5-HT were not significantly different compared with control saline. The results also showed that there were no significant changes in the latency between microinjection and the first episode of REM sleep, total number of REM sleep episodes, and mean duration of REM sleep episodes after injections of 5-HT compared to after control vehicle injections.

**Conclusions:** These results presented here provide direct evidence for the first time that the direct application of 5-HT into the P-wave generator of freely moving rats inhibits P-wave activity. These results also demonstrated that the inhibition of the P-wave generator by 5-HT is unable to change the REM sleep in the rat. We suggest that during W and SWS the P-wave generator remains inhibited due to the increased availability of serotonin within the P-wave generator.

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## 217.A

**WAKE-SLEEP CYCLE EFFECTS OF GABA-A RECEPTOR AGONIST MICROINJECTION INTO THE LATERAL HYPOTHALAMUS OF THE FREELY MOVING RAT**Spoley EE,<sup>1</sup> Mavanji VK,<sup>1</sup> Patterson EH,<sup>1</sup> Datta S<sup>1</sup>

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**Introduction:** Hypocretin, also known as orexin, is a recently discovered neuropeptide that has been implicated in the etiology of narcolepsy and the general arousal system of the brain. Hypocretin/orexin producing cells in the brain are produced exclusively by neurons located in the lateral hypothalamus (1, 2). Hypocretin/orexin producing cells project to almost the entire brain and spinal cord (2). More recently, it has been shown that the GABA-ergic sleep promoting cells in the pre-optic area project to the perifornical region of the lateral hypothalamus (Pf-LH) where those hypocretin/orexin cells are located (3). However, to date, very little is known about how these hypocretin/orexin cells are regulated to influence the normal sleep-wake cycle. The aim of this study was to examine the influence of GABA within the hypocretin/orexin cell area on the normal sleep-wake cycle of freely moving rats.

**Methods:** Experiments were performed on adult male Sprague-Dawley rats weighing between 250 and 350 g. With the use of sterile procedures, cortical electroencephalogram (EEG), dorsal neck muscle electromyogram (EMG), elec-

troculogram (EOG), hippocampal EEG (to record theta wave), and pontine EEG (to record P-waves) recording electrodes were chronically implanted. In addition, bilateral stainless steel guide tubes were stereotaxically implanted for the microinjection of a specific GABA-A receptor agonist (Isoguvacine) and control saline into the Pf-LH. Following a post-surgical recovery period of 3-7 days, rats were habituated to a sound attenuated recording cage and free moving polygraphic recording conditions for 7 days. All recording sessions were performed between 10:00 and 16:00 h, when rats are normally sleeping. After the adaptation recording sessions, microinjection sessions began. Six-hour microinjection recording sessions began after bilateral microinjections (one in each side) of 100 nl control saline (control vehicle) or Isoguvacine (1.5 nmol in 100 nl/injection) into the Pf-LH. To determine the effects of GABA-A receptor agonist, sleep-wake variables were compared between post-control saline and post-Isoguvacine injections into the perifornical area of the LH.

**Results:** In the six-hour post-injection recording sessions, Isoguvacine and saline treated rats had similar amounts of wakefulness. However, Isoguvacine treated rats spent less time (35.23% less) in slow-wave sleep (SWS)-1 and more time in SWS-2 (28.42% more) compared to control saline treated rats. Surprisingly, these Isoguvacine treated rats also spent less time in REM sleep (73.13% less) and in transitional sleep (between SWS and REM sleep) (22.99% less) compared to control saline treated rats.

**Conclusions:** Results presented here provide evidence for the first time that the activation of GABA-A receptors within the Pf-LH increase deep SWS and decrease REM sleep. These preliminary results show that the function of the hypocretin/orexin system may not be as simple as previously suggested. Further studies are being carried out to understand the mechanisms of hypocretin/orexin system modulation of normal REM sleep.

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**Research supported by NIH research grants MH59839 and NS34004.**

## 218.A

### REGULATION OF PEDUNCULOPONTINE TEGMENTAL NEURONAL ACTIVITY AND REM SLEEP: ROLE OF GABA-ERGIC NEUROTRANSMISSION IN THE FREELY MOVING RAT

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**Introduction:** Excitation and inhibition of brainstem pedunculo-pontine tegmentum (PPT) cells are important processes for the regulation of REM sleep (1). Activation of PPT cells caused by activating glutamate receptors induces REM sleep (2). It has long been suggested that neurotransmitters like norepinephrine (NE), serotonin (5-HT), and adenosine (AD) are involved in the regulation of REM sleep by inhibiting PPT cell activity. More recently, another inhibitory neurotransmitter, GABA, in the brainstem has been implicated for the regulation of REM sleep (3). In the present study we examined the sleep-wake responses of freely moving rats following microinjections of 1) Arterenal Bitartrate (NE), 2) 5-hydroxytryptamine (5-HT), 3) Adenosine (AD), 4) Isoguvacine (GABA-A receptor agonist), 5) Baclofen (GABA-B receptor agonist), and 6) Cis-4-Aminocrotonic acid (GABA-C receptor agonist) into the cholinergic cell compartment of the PPT.

**Methods:** Experiments were performed on 31 male Sprague-Dawley rats weighing between 250 and 350 g. With the use of sterile procedures, cortical electroencephalogram (EEG), dorsal neck muscle electromyogram (EMG), electrooculogram (EOG), hippocampal EEG (to record theta wave), and bilateral pontine EEG (to record P-waves in both sides of the brain) recording electrodes were chronically implanted. In addition, bilateral stainless steel guide tubes were stereotaxically implanted for the microinjection of drugs and control vehicle into the PPT. Following a post-surgical recovery period of 3-7 days, rats were habituated to a sound attenuated recording cage and free moving polygraphic recording conditions for 7 days. All recording sessions were performed between 10:00 and 16:00 h, when rats are normally sleeping. After the adaptation recording sessions, microinjection sessions began. Six-hour microinjection recording sessions began after a single, unilateral microinjection of 100 nl control saline (control vehicle) or one of the three different doses (0.5, 1.5, and 3.0 nmol/100 nl saline) of any one of the following six different drugs: 1) NE, 2) 5-HT, 3) AD, 4) GABA-A receptor agonist, 5) GABA-B receptor agonist, or 6) GABA-C receptor agonist into the PPT.

**Results:** In the six-hour post-injection recording sessions, GABA-B receptor agonist suppressed REM sleep dose-dependently. These dose-dependent results showed that 1.5 nmol induced the maximum reduction of REM sleep compared to control saline (no drug) injection ( $p < 0.001$ ). After injection of GABA-B receptor agonist, within 3-5 minutes, animals went back to deep slow-wave sleep (SWS) and spent most of the time (>80%) in that state for about 60-90 minutes. Following SWS, animals remained mostly wake for another 90-120 minutes. During the first three hours following injection of the optimum dose of GABA-B receptor agonist (1.5

nmol in 100 nl), 80% of REM sleep was suppressed compared to results after control saline injection. None of the NE, 5-HT, AD, GABA-A receptor agonist, or GABA-C receptor agonist injections into the cholinergic cell compartment of the PPT caused any significant behavioral state changes compared to results after control vehicle injection.

**Conclusions:** The results presented here provide direct evidence for the first time that the activation of GABA-B receptor in the cholinergic cell compartment of the PPT suppresses REM sleep in the freely moving rat. These results suggest that the GABA-ergic mechanisms in the brainstem may be involved in the regulation of REM sleep. The results of this study do not support the notion that NE, 5-HT, or AD in the PPT inhibit REM sleep in the freely moving rat.

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## 219.A

### TRANSCRIPTIONAL REGULATION OF THE MOUSE FATTY ACID AMIDE HYDROLASE GENE

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**Introduction:** Fatty acid amide hydrolase (FAAH) is a membrane-bound enzyme that inactivates a family of fatty acid amide molecules that are implicated in physiological processes such as pain and sleep. These bioactive molecules include lipids such as oleamide, a sleep-inducing agent originally isolated from the cerebrospinal fluid of sleep-deprived cats, and anandamide, an endogenous ligand for the brain CB1 cannabinoid receptor. It has been proposed that the metabolic activity of FAAH coupled with endogenous neuromodulatory lipid molecules play important roles in the CNS by ensuring rapid termination of specific signaling processes. Mice lacking FAAH are severely impaired in their ability to degrade endogenous anandamide and when treated with this compound, exhibit CB1-dependent behavioral responses, including analgesia, catalepsy, hypomotility and hypothermia. Here, we report the cloning and characterization of FAAH promoter and show that this sequence has activity in vitro.

**Methods:** The 1.9 kb fragment of the 5'-flanking region of the mouse FAAH gene (Genbank Accession No. AF432907) was

cloned into the KpnI and XmaI sites of pGL3-Basic plasmid (Promega) for expression studies. This plasmid, designated pMP-FAAH, carries 110 bp of the coding sequence including the ATG start codon. The luciferase activities of transfected cells were assayed using a Dual-Luciferase™ Reporter system (Promega). The cells were transfected with pMP-FAAH, ER or GR and allowed to recover in growth medium for 24 h before treatment. The transcription start site for pMP-FAAH was determined by primer extension method using whole brain poly (A+) RNA and a 32P-labeled primer complementary to positions +47 to +64 of the FAAH transcript.

**Results:** The cloned fragment had the ability to promote luciferase expression in SY5Y, COS-7, and CHO cells. Based on the expression levels, SY5Y cells were selected for further studies. Primer extension analysis revealed a transcription start site 212 bases upstream from the putative translation start site. This sequence contained seven AP-1, three AP-3, seven AP-4, one AP-5, three Sp1, and five E4TF1 sites. It also contained one Ets-1 box, one CCAAT box, and an upstream regulatory element (URE). The sequence also contained six imperfect EREs and five imperfect GREs. The addition of 17(beta)-estradiol (E2) had no significant effect on the promoter activity. However, the introduction of ER(alpha) or ER(beta) into the cells, in the absence of external E2, significantly suppressed the luciferase activity by about 45%. The addition of E2 did not affect the reduced luciferase activity. Tamoxifen and ICI 182,780 did not significantly affect promoter activity beyond that observed in cultures transfected with any of the ERs alone. Similar results were obtained when GR was used in the co-transfections with pMP-FAAH.

**Conclusions:** Our studies demonstrate that 1.9 kb from the 5'-flanking region of the FAAH gene is sufficient to promote gene expression in vitro. We have identified a number of EREs and GREs in this region and shown that the ER and GR down-regulate the expression of FAAH independent of their ligands. This regulatory mechanism provides a system for pharmacological intervention of the physiological pathways that are affected by this family of fatty-acid amide molecules, such as pain and sleep.

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## 220.A

### FOS ACTIVATION IN AMYGDALA AND LOCUS COERULEUS: IMPLICATIONS FOR FEAR-CONDITIONED SUPPRESSION OF REM SLEEP

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**Introduction:** Fear-conditioning has a pronounced suppressing effect on REM sleep. Shock training and later presentation of fear-conditioned cues alone can suppress REM sleep for up to 6 h post-exposure in BALB/cJ mice, which show greater reactivity to environmental stimuli (1). The amygdala is critical for fear conditioning, and the central nucleus of the amygdala (CNA) is the source of descending projections to brainstem regions responsible for generating REM sleep (e.g., locus

coeruleus (LC)). We examined Fos expression in the amygdala and LC over 6 h after shock training and after presentation of a fear-conditioned cue to assess the possibility they could have a role in fear-conditioned REM suppression.

**Methods:** A total of 60 BALB/cJ mice were examined (3 groups (naïve, shock and cue) at 3-4 time points and 6 animals in each time point). The shock group received 15 tone-shock pairings at 9:00 AM. The cue group was given 15 tone-shock pairings at 9:00 AM for 4 days, and 3 days later were presented 15 tones alone at 11:00 AM. The mice were perfused at two h intervals after shock training or cue presentation and naïve animals were perfused at intervals to match both groups. Brains were post-fixed, 50- $\mu$ m coronal sections were cut, and every fifth section was collected. The sections were processed for Fos and CRH immunohistochemistry. Fos-positive nuclei were counted and expressed as number of nuclei per mm<sup>2</sup>.

**Results:** In both shock and cue groups, there was a significant increase of Fos-positive nuclei in the amygdala and LC compared with naïve controls, and this increase lasted for up to 6 hours after shock and 2 hours after cue (Table 1). With CRH staining, we could clearly distinguish CNA. Activation in the amygdala was mainly limited to the basolateral nucleus (BLA), with less in the lateral (LA) and basomedial nuclei (BMA), and virtually no Fos-positive neurons in CNA (Figure 1).

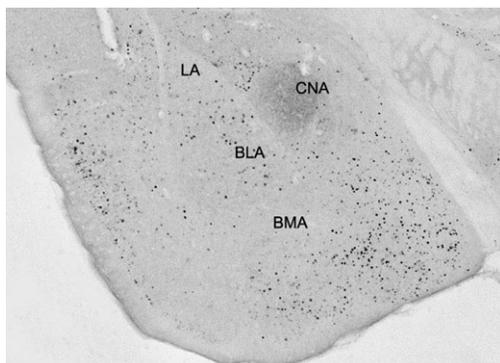
**Table 1**

Number of Fos-positive neurons (per mm<sup>2</sup>) in amygdala and LC at 2, 4, 6 h following shock or fear-conditioned cue presentation.

Time	1100	1300	1500	1700
<b>Amygdala</b>				
Naïve	16.6 (4.7)	22.8 (6.3)	17.7 (5.8)	31.1 (12.0)
Shock	276.7 (9.5) c	97.0 (18.8) b	56.4 (7.9) b	-
Cue	-	109.1 (23.0) a	37.4 (5.9)	56.2 (12.5)
<b>LC</b>				
Naïve	19.8 (15.9)	12.0 (7.2)	33.2 (14.1)	3.4 (2.1)
Shock	810.4 (117.5) c	642.2 (53.3) c	442.8 (116.8) c	-
Cue	-	156.3 (25.0) c	23.1 (22.0)	28.1 (13.0)

a, P < .05; b, P < .01; c, P < .001. compared to naïve mice.

**Figure 1**



Fos staining in the amygdala two h after shock training.

**Conclusions:** The amygdala plays a role in sleep regulation (2) and LC may play a permissive role in REM sleep. Fos activation in the amygdala and LC after shock-training and fear-conditioned cues suggests that these regions could be involved in REM suppression produced by conditioned fear. Interestingly, Fos-activity was relatively absent in CNA. We have found that inactivating CNA with the GABAA agonist, muscimol, produces a selective suppression of REM much like that seen with conditioned fear (3). This suggests that inhibition of CNA output may be involved in the suppression of REM produced by shock and fear-conditioned cues.

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**221.A**

**SLEEP/WAKE BEHAVIOR IN MCH OVEREXPRESSION MICE**

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**Introduction:** The lateral hypothalamus (LH) is a key integrator of homeostatic mechanisms, regulating feeding, energy balance, and arousal states. Two peptidergic systems, melanin-concentrating hormone (MCH) and orexin, have cell bodies in the LH, and these neurons innervate brain regions involved in sleep/wake regulation (1). MCH-overexpressing (MCH-OE) mice are prone to obesity when fed a standard diet (2), while MCH knockout mice have reduced body weight due to hypophagia and an inappropriately increased metabolic rate. To determine the role of MCH in feeding and arousal states, we examined sleep/wake behavior in MCH-OE and wild-type (WT) mice during baseline conditions, 54 hours of food deprivation, and 24 hours of recovery.

**Methods:** Mice on a C57BL/6J background were maintained for at least 2 weeks prior to study under constant conditions (12:12 LD cycle) and fed a standard rodent diet ad libitum. Mice were implanted with EEG and EMG electrodes for polysomnographic recording and recovered for 7-10 days before 3 days of habituation. Recordings were done over five consecutive days: Baseline 1 & 2 (B1 & B2); Food Deprivation 1 & 2 (FD1 & FD2); and Recovery (Rec). Food deprivation began at 13:00 (CT6) during B2 and continued through two 24-hour recording periods until 19:00 (end of FD2). Data was scored for wake, NREM, and REM in 10 second epochs using an automated sleep scoring system (Sleep Sign, Kissei Comtec, Matsumoto, Japan) followed by manual correction.

One week after the recordings, the mice were killed following another 54-hour period of food deprivation. Brains were immunostained for MCH.

**Results:** MCH-OE mice had clear increases in the density and thickness of the MCH fibers throughout the brain, but the distribution of MCH projections was similar to that of the WT mice. During the baseline day (B1), MCH-OE and WT mice spent similar amounts of time in NREM, REM, and wake states. After 54 hours of food deprivation, both groups had increased wakefulness during the first 6 hours of the dark period, with more wakefulness in WT mice. During the food deprivation days, WT mice had a marked increase in the amount of wakefulness mainly through an increase in the duration of wake bouts and a proportional loss of NREM and REM sleep. There was no change in spectral power during NREM sleep across the four days of recordings.

**Conclusions:** We found that food deprivation increased wakefulness during the first half of the dark period in both WT and MCH-OE mice. These results are consistent with past reports of nocturnal increases in wakefulness in food deprived rats (3). Although MCH neurons innervate many state regulatory regions, we did not find substantial differences in the sleep/wake behavior of our MCH-OE mice. Thus, the increase in wakefulness seen with food deprivation may be due to the action of other systems such as orexin/hypocretin.

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## 222.A

### SLEEP DEPRIVATION INDUCES SPATIAL MEMORY DEFICIT AND DOWN-REGULATES EXTRACELLULAR SIGNAL-REGULATED KINASE PHOSPHORYLATION IN THE HIPPOCAMPUS

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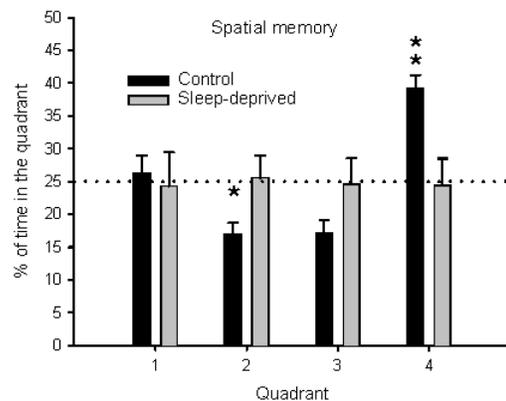
**Introduction:** Increasing evidence indicates that loss of sleep may result in memory impairment. However, little is known about the biochemical basis for memory deficits induced by sleep deprivation. Extracellular signal-regulated kinase (ERK) is involved in memory consolidation in different tasks, including spatial memory (Blum et al, 1999). Phosphorylation of ERK is necessary for its activation and is an important step in

mediating neuronal responses to synaptic activities. The aim of the present study was to determine the effects of sleep deprivation on spatial memory (Experiment #1) and ERK phosphorylation in the brain (Experiment #2).

**Methods:** Adult male Sprague-Dawley rats were used in the experiments. Rats were housed on a 12:12 h light-dark cycle. In Experiment #1, rats were trained in Morris water maze for 12 trials on a single day after 6 h total sleep deprivation (n=10) or spontaneous sleep (n=10). Training started 6 h after light onset and lasted for about 30 minutes. In Experiment #2, ERK phosphorylation and total ERK in the hippocampus and cortex were determined by Western blot in rat receiving 3 h, 6 h sleep deprivation or 6 h sleep deprivation plus 2 h recovery and in control rats sacrificed at the same time points (10 rats in each group at each time point).

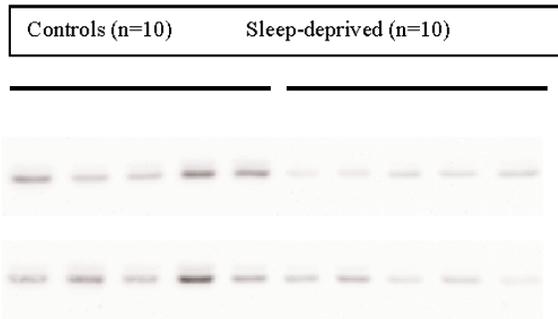
**Results:** Experiment #1. Sleep deprivation had no effect on learning, but significantly impaired memory tested 24 h after training (Fig. 1) as indicated by the time spent in the target quadrant ( $39.18 \pm 2.02$  seconds in controls vs.  $24.20 \pm 4.11$  seconds in sleep-deprived rats,  $p < 0.005$ ). Experiment #2. Phospho-ERK levels in the hippocampus were not altered after 3 h sleep deprivation, were significantly reduced to about 30% of the control levels after 6 h sleep deprivation ( $p < 0.0001$ ) (Fig. 2), and returned to the control levels after 2 h recovery sleep. Total ERK1 and ERK2 were slightly increased after 6 h sleep deprivation and returned to control levels after 2-h recovery sleep. In the cortex, phospho-ERK, total ERK1 and total ERK2 were not altered by sleep deprivation. Protein phosphatase-1 (PP1) and mitogen-activated protein kinase phosphatase-2 (MKP-2), which dephosphorylate phospho-ERK, were also measured in the second experiment, but they were not altered by sleep deprivation.

Figure 1



Effects of 6 h sleep deprivation on spatial memory. Sleep-deprived rats spent significantly less time in the target quadrant (quadrant 4) compared to the controls ( $p < 0.01$ ).

Figure 2



Effects of 6 h total sleep deprivation on ERK Phosphorylation.

**Conclusions:** These results indicate that: 1) short period (6 h) of total sleep deprivation significantly impairs spatial memory but not spatial learning; 2) sleep deprivation selectively reduces ERK phosphorylation in the hippocampus but not in the cortex; and 3) MKP-2 and PP1 are not involved in sleep deprivation-induced reduction in ERK phosphorylation. We suggest that decreased ERK activation in the hippocampus is involved in sleep loss-induced memory impairment.

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**223.A**

**SPONTANEOUS SLEEP IN NEURONAL AND INDUCIBLE NITRIC OXIDE SYNTHASE KNOCKOUT MICE**

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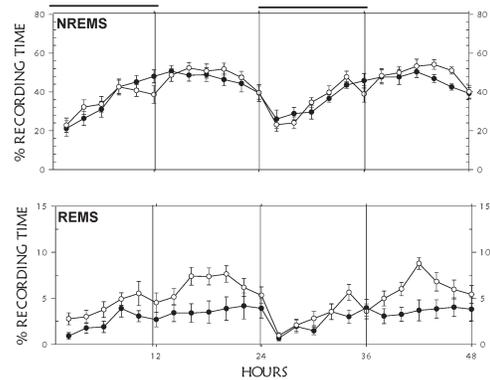
**Introduction:** Nitric oxide has multiple functions, including the regulation of sleep (1). NO plays an important role in rapid eye movement sleep (REMS) regulation. For example, the cholinergic projections from pedunclopontine tegmental nuclei and the laterodorsal tegmental nucleus to the medial pontine reticular formation (mPRF) are crucial in REMS generation. Local NOS inhibition within the mPRF reduces acetylcholine release and decreases the amount of REMS (2). To investigate the role of NO in spontaneous sleep we characterized sleep in mice with targeted mutations in the NOS-1 or NOS-2 genes, commonly referred to as NOS-1 or NOS-2 knockouts (KO).

**Methods:** The gene KO mice and their control mice were acquired from Jackson Labs. NOS-1 KO mice (B6;129-Nos1tm1plh) were compared with suitable control mice (B6;129SF2/J), and NOS-2 KO mice (B6.129 P2- Nos2tm1Lau) were compared to their controls (C57BL/6J). Sixty males, 6-8

weeks old (N=15 for each strain), were implanted with EMG and EEG electrodes. The mice were housed individually at 29°C on a 12:12 L/D cycle. Sleep-wakefulness status was scored visually offline. Data were analyzed by two-way analysis of variance followed by the Student-Newman-Keuls test.

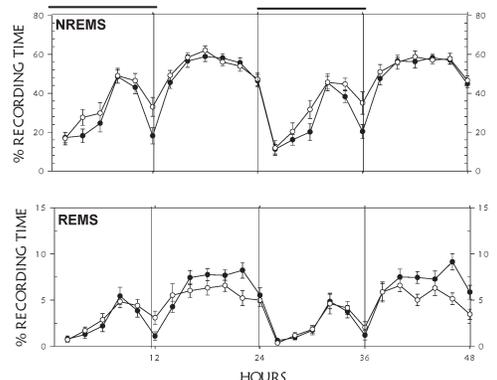
**Results:** NOS-1 KO mice and their controls had similar amounts of NREMS. In contrast, during the 12 h light period, the duration of REMS in NOS-1 KO mice was significantly less than that observed in control mice (Fig. 1) (P<0.05). This difference was due to a significantly lower number of REMS episodes (12 vs. 26). EEG slow wave activity (SWA) during NREMS and EEG spectral analysis failed to reveal differences between NOS-1 KOs and their controls. NOS-2 KO mice and their controls had similar amounts of NREMS. However, during the 12 h light period, the duration of REMS in NOS-2 KO mice was significantly more than that observed in controls (Fig. 2) (P<0.05). This difference resulted primarily from a higher number of REMS episodes (34 vs 27). NOS-2 KO mice also had less NREMS and REMS during the dark-light transition period. In addition, EEG SWA of NOS-2 KO mice was 10% less than that of their C57BL/6J controls (P<0.05) and EEG spectral analysis showed a decrease of power density is across all bands (0.5 -25 Hz) during NREMS in the NOS-2 KO mice.

Figure 1



Spontaneous sleep of nNOS KO mice (represented by close circle) and their controls (open circles) and their controls (open circles). N=15

Figure 2



Spontaneous sleep of iNOS KO mice (represented by close circle) and their controls (open circles) and their controls (open circles). N=15

**Conclusions:** Results suggest that nNOS and iNOS play opposite roles in REMS regulation. Thus the inhibition of REMS observed during infection could result from the up-regulation of iNOS since iNOS KO mice have more REMS. In contrast, nNOS seems likely to be involved in physiological REMS regulation because, if it is removed, the mice had less REMS.

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**Research supported by NIH, Grants HD 36520 and NS 25378.**

## 224.A

### GABAERGIC PROCESSES CONTROLLING ACTIVE SLEEP AND WAKEFULNESS IN THE NUCLEUS PONTIS ORALIS OF THE GUINEA PIG

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**Introduction:** The nucleus pontis oralis (NPO) is critical in the generation and maintenance of active sleep (AS) and wakefulness [1] and microinjections of cholinergic agonists in this area produce short latency long duration episodes of AS in the cat [2]. On the other hand, microinjections of GABA agonists into this nucleus in the cat result in wakefulness, whereas GABA receptor antagonists induce active sleep [1]. In the present study, we examined the NPO in the guinea pig with respect to the effect of GABAergic agonists and antagonists on sleep and waking states.

**Methods:** Eight adult guinea pigs (500-800 g) were anesthetized with urethane (1.3 g/kg, i.p.). EEG, hippocampus and neck EMG recording electrodes were implanted. The effect of the microinjection of 0,05 to 0,1 µl of carbachol (4 µg/µl in saline), muscimol (20 mM) or bicuculline (15mM) via a glass micropipette attached to a Hamilton syringe was determined. Thereafter, 0.1 µl of Sky-blue was microinjected into the most effective area of injection of carbachol, muscimol or bicuculline. Subsequently, an overdose of pentobarbital was administered and the animal was perfused with fixatives; the sites of microinjection were determined with standard histological techniques.

**Results:** An area in the nucleus pontis oralis, approximately centered on the stereotaxic coordinates of A:1.0, L:1.5, H: 9.0 was found where carbachol produced EEG desynchronization, theta rhythm in the hippocampus and muscle atonia. Dissociate states were also induced which consisted of some but not all of the preceding indices of active sleep (e.g. either EEG desynchronization and theta rhythm or atonia). In the region in which carbachol was most effective, the microinjection of GABA was found to produce EEG desynchronization, an increase in muscle tone, and hippocampus theta activity. These electrophysiological patterns of activity were similar to those

observed in the guinea pig during wakefulness. On the other hand, the microinjection of bicuculline into this area produced a state similar to that which arose following the microinjection of carbachol, i.e., EEG desynchronization, hippocampus theta and most importantly, a decrease in muscle tone; all of the preceding patterns of activity were similar to those which are present during naturally-occurring AS. These data indicate that GABA plays a key role in promoting wakefulness in the NPO, and suppressing AS. We suggest that this action of GABA is part of the mechanisms that underlie the phenomenon of reticular response-reversal.

**Conclusions:** In the guinea pig, the NPO appears to be a cholinceptive executive area that is responsible for the generation of active sleep as well as wakefulness. In addition, in this area of the brainstem, there is a GABAergic system that actively promotes wakefulness while suppressing active sleep.

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## 225.A

### CALCIUM RESPONSES TO GROWTH HORMONE-RELEASING HORMONE AND INTERLEUKIN 1β IN CULTURED HYPOTHALAMIC NEURONS IS DEVELOPMENTALLY REGULATED

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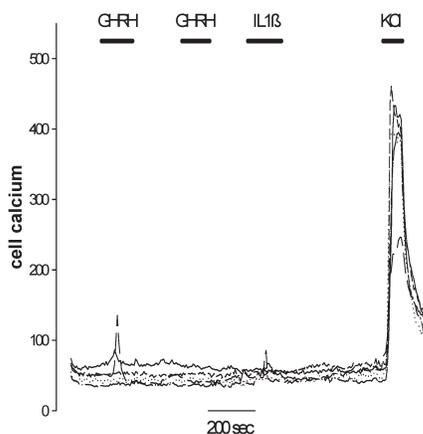
**Introduction:** Central or systemic growth hormone releasing hormone (GHRH) and the cytokine interleukin 1β (IL1β) are involved in non-rapid eye movement sleep (NREMS) regulation (reviewed Krueger *et al.*, 2000). Microinjection of GHRH into the preoptic area promotes NREMS activity in rats. Injection of IL1β into the third ventricle area increases NREMS in rats. Administration of anti-IL1β antibodies or the IL1β receptor antagonist or the soluble IL1β receptor causes inhibition of spontaneous sleep or sleep induced by sleep deprivation. Sleep induced by IL1β is greatly attenuated by an anti-GHRH antibody. Thus GHRH and IL1β responsive neurons in the preoptic area are hypothesized to play a role in the regulation of sleep. The cellular mechanism by which GHRH and IL1β activate neurons is not clearly understood. The literature suggests that GHRH causes an increase in cytosolic Ca<sup>2+</sup> in pituitary somatotropes in a dose dependent manner. This effect of GHRH is blocked by removing extracellular Ca<sup>2+</sup> (Cuttler *et al* 1992). In the present study we focused on identifying GHRH and IL1β responsive neurons in primary cultures of fetal hypothalamic tissues using a single cell imaging technique with the calcium indicator fura-2.

**Methods:** *Primary culture of fetal hypothalamic neurons:* Primary cultures of fetal hypothalamic neurons were prepared using poly-l-ornithine coated coverslips. Cells were grown in

Dulbecco's Modified Eagle's Medium (DMEM) with 10% fetal calf serum. The medium was replaced every 2 days with serum-free DMEM containing a defined serum substitute until used for experiments. *Measurements of Cytosolic Calcium:* Cells were loaded with 2  $\mu$ M fura-2-AM and washed in physiological saline at room temperature. Coverslips were placed in a closed chamber (~0.5 ml) which was exposed to a constant bath perfusion (~2 ml/min) of physiological saline or physiological saline containing the test substance. Experiments were performed at room temperature on the stage of an inverted microscope.

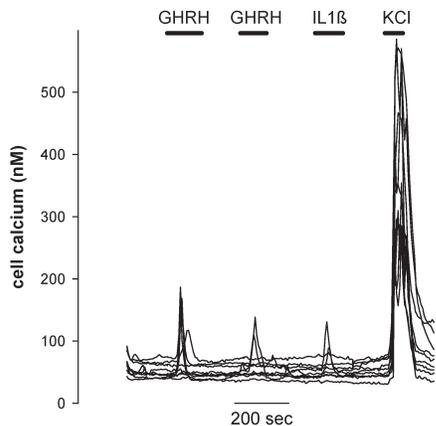
**Results:** When using neurons isolated from 18 day-old fetuses, 1.4% of the neurons examined responded to GHRH, 1.4% responded to IL1 $\beta$ , and 0.6% responded to both. In neurons isolated from 21 day-old fetuses, 11.1% of the neurons examined responded to GHRH, 4.7% responded to IL $\beta$ , and 1.9% to both. The calcium responses to both GHRH and IL1 $\beta$  completely desensitized in neurons isolated from day 18 fetus (fig 1) but some neurons from 21-day-old fetus can respond to a second GHRH challenge (fig 2).

Figure 1



Calcium responses to GHRH and IL1 $\beta$  in neurons isolated from 18 day-old fetuses.

Figure 2



Calcium responses to GHRH and IL1 $\beta$  in neurons isolated from 21 day-old fetuses.

**Conclusions:** In primary cultures of hypothalamic neurons, calcium responses to GHRH and IL1 $\beta$  are dependent on the age of animals at the time of tissue collection. This may reflect a maturation of brain responsiveness to GHRH and IL1 $\beta$ .

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Research supported by NIH NS25378 and NS27250.

**226.A**

**THE EFFECT OF JUXTACELLULAR APPLICATION OF HYPOCRETIN-1 ON NEURONS OF THE NUCLEUS PONTIS ORALIS: AN INTRACELLULAR STUDY**

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**Introduction:** We recently reported that microinjections of hypocretin (orexin) into the nucleus pontis oralis (NPO) of the chronic cat induce, with a short latency, a behavioral state that appeared identical to naturally occurring active (REM) sleep (1). These data indicate that hypocretinergic processes in the NPO may be involved in the generation of active sleep. To further understand the functional significance of hypocretinergic projections onto neurons in the NPO vis-à-vis the behavioral states of active sleep and wakefulness, we examined the effects of the juxtacellular application of hypocretin-1 on the electrical activity of intracellularly recorded NPO neurons in acute, anesthetized cats.

**Methods:** Three adult cats were used in the present study. Surgical procedures, which were carried out under halothane anesthesia, have been described, in detail, previously (2). After the completion of all surgical procedures the animals were anesthetized with  $\alpha$ -chloralose (60 mg/kg, i.v.). Intracellular recordings in conjunction with the juxtacellular application of hypocretin were obtained from NPO neurons with an electrode assembly composed of a single-barrel recording micropipette and a multibarrel drug ejection micropipette. The intracellular recording micropipette was filled with 2 M K-citrate or 3 M KCl. One barrel of the micropipette assembly was filled with hypocretin-1 (100  $\mu$  M in saline; American Peptide Co., CA) and another barrel was filled with saline. Hypocretin-1 was ejected by pressure using a two-channel picoinjector (PLI-100, Medical Systems). The injection pressure was varied from 5 to 30 PSI (pounds per square inch) for a duration of 5-30 seconds. At the end of the experiments, the site of recordings was marked with a 2% solution of Chicago sky blue dye in 0.5 M Na-acetate. Subsequent histological studies revealed that recording sites were located within the NPO.

**Results:** Following the application of hypocretin-1, neurons in the NPO exhibited membrane depolarization (i.e., a reduction in the resting membrane potential) and an increase in the frequency of spontaneous discharge. In all NPO neurons examined, the application of hypocretin-1 (10-12.5 PSI, 30 s) pro-

duced a depolarization in the resting membrane potential ( $6.1 \pm 1.2$  mV, 9 cells) and a significant increase in the mean frequency of discharge (control:  $0.7 \pm 0.2$  spikes/s vs. hypocretin:  $20.8 \pm 4.4$  spikes/s, 9 cells,  $P < 0.01$ ). The application of hypocretin-1 also produced an increase in the excitability of NPO neurons. Rheobase (Rh, which is defined as the minimum stimulus intensity of a 50-msec duration intracellular depolarizing current pulse that constantly elicited an action potential and reflects the excitability of a neuron) was significantly reduced by 43.8% from  $1.6 \pm 0.4$  nA before to  $0.9 \pm 0.3$  nA during the application of hypocretin (7 cells,  $P < 0.05$ ).

**Conclusions:** The present electrophysiological data clearly demonstrate that hypocretin in vivo excites neurons of the NPO. We therefore suggest that the changes in behavioral state induced by the injection of hypocretin into the NPO results from the effects of this substance on populations of NPO neurons that are involved in the generation of active sleep and the epiphenomena which comprise this state.

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## 227.B

### EFFECTS OF ROTATION ON THE SLEEP STATE-DEPENDENT MIDLATENCY AUDITORY EVOKED P50 POTENTIAL IN THE HUMAN.

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**Introduction:** Motion sickness (MS) produces, among other symptoms, attentional and cognitive deficits, and is believed to be due to a neural mismatch caused by unweighting of the otolith organs. Conversely, vertigo appears due to under- or overstimulation of the semicircular canals. We used overstimulation of the semicircular canals via the rotary chair as a paradigm for MS and tested its effects on the manifestation of the P50 midlatency auditory evoked potential. The P50 potential is sleep state-dependent, characterized by rapid habituation and blockade by the cholinergic antagonist scopolamine, and is thought to be a measure of the output of the reticular activating system.

**Methods:** Recordings were carried out as previously described using a paired stimulus paradigm with a 250 msec interstimulus interval (1). The amplitude of the response following the first stimulus is considered a measure of arousal, while the ratio of the response to the second stimulus as a percent of the response to the first is considered a measure of sen-

sory gating or distractability. Following control recordings, subjects were blindfolded and spun to the point of nausea in the rotary chair. A second P50 recording was made within 10 min post-rotation. Rotation was initiated at 5 rpm (0.5 rad/sec) and incremented by 2 rpm (0.2 rad/sec) every 5 min, with rotational velocity kept constant during each 5 min interval. The maximum velocity was 30 rpm (3.1 rad/sec). At 2 sec intervals throughout each 5 min period, the subject was prompted to make head movements at 45° from the vertical in 4 directions (left, right, front, back).

**Results:** For the 8 subjects tested, rotation time was  $33 \pm 8$  min (Mean $\pm$ SE). P50 potential amplitude following the first stimulus was  $2.0 \pm 0.3$   $\mu$ V before and  $2.2 \pm 0.3$   $\mu$ V after rotation, i.e. not statistically different. The ratio of the second response as a percent of the first (sensory gating) was  $7.5 \pm 5.5$  % before and  $39.0 \pm 9.0$  % after rotation. There was a statistically significant difference in sensory gating using a t-test ( $df=7,7$ ,  $F=2.69$ ,  $p < 0.01$ ) and one way ANOVA ( $df=14$ ,  $F=8.78$ ,  $p < 0.01$ , post hoc Newman-Keuls  $p < 0.05$ ).

**Conclusions:** Rotation-induced MS produced no change in the level of arousal as measured by P50 potential amplitude following the first stimulus, but did produce a significant deficit in sensory gating as measured by the ratio of the two responses. These findings suggest that some of the attentional deficits observed in MS may be due to distractability induced by decreased habituation to repetitive stimuli, and these can be detected using the P50 potential. The ideal pharmacological countermeasures for MS should not reduce P50 potential amplitude (arousal) while normalizing sensory gating (decreasing distractability).

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**Research supported by (NSBRI) NSBRI-00-081 (JD) and (NIH) NS20246 (EGR)**

## 228.B

### INFRARED THERMAL IMAGING AS A MEASURE OF PERIPHERAL TEMPERATURE CHANGE AT SLEEP ONSET: A PILOT STUDY.

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(1) Centre for Sleep Research, University of South Australia,

**Introduction:** Thermoregulation and sleep are interrelated processes. Traditionally, peripheral temperature measurements have been made using contact thermometry. The technique has limitations in that measurements can only be made at discrete points on the body, and from these whole body changes must be inferred. Further, insulation of the area of measurement by the thermistor may itself produce erroneous results. The current study will use digital infrared thermal imaging (DITI) technology to examine the dynamic, whole-body changes in peripheral temperature around the time of sleep onset in real-time. The technology will allow us to assess the normal patterns of heat transfer that occur around the time of sleep onset.

**Methods:** Sixteen healthy male participants, aged 18-30 were recruited to the study. Participants spent an adaptation night and a recording night in the laboratory. We recorded sleep using conventional PSG and temperature using both contact thermometry (core and feet) and DITI (whole upper body). Participants were lying supine in bed with their hands by their sides at least 90 minutes prior to their normal lights out. At the time of lights out they were requested to try and fall asleep in the same position. From 60 minutes prior to lights out thermal images were captured every 30 seconds. Splicing the images together into a continuous animation sequence allowed qualitative assessment of the peripheral temperature changes. Quantitative measurements were taken from regions of interest (hands, forearms, face, neck, chest and torso).

**Results:** 1. Infrared thermal images can be captured from participants around the time of sleep onset with minimal loss of data due to movement (fig 1). 2. The patterns of heat exchange across the period of sleep onset can be readily visualised in normal sleepers. 3. Preliminary data analysis indicates that significant peripheral temperature changes occur in the forearms and hands, in addition to the lower torso region.

**Figure 2**—Digital infrared thermal images taken from a subject prior to sleep (top panel) and at sleep onset (bottom panel). The images are grayscale for better visualisation in black and white. The change in peripheral temperature is most evident in the forearms and hands, and the face and neck, with the darker shade indicating higher temperature. (An animation of the coloured images can be found at [www.unisa.edu.au/sleep/research/default.htm](http://www.unisa.edu.au/sleep/research/default.htm))



**Conclusions:** The results indicate that digital infrared thermal imaging is a technique that can be readily applied to the investigation of sleep initiation processes. Patterns of heat exchange around sleep onset, particularly in the arms and hands, and face and neck can be clearly visualised. Images from the present study will be compared with thermal images collected from sleep-onset insomniacs, with the aim of qualifying the differences in temperature exchange between normal sleepers and insomniacs.

## 229.B

### ALTERATIONS IN BLOOD PRESSURE ACROSS THE SLEEP ONSET PERIOD

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**Introduction:** Blood Pressure (BP) has a 24-hr variation that is dependent on the sleep-wake cycle, with a reduction occurring during sleep. Recent evidence suggests that BP falls rapidly during sleep onset, reaching its lowest level once stable sleep is attained. The aim of this study was to characterise the pattern of change in BP, Heart Rate (HR) and baroreflex activity during the period from relaxed pre-sleep wakefulness to stable sleep.

**Methods:** Continuous BP and HR recordings were collected beginning 2 hrs before lights out until the end of the first NREM sleep period in 9 young, healthy, male and female subjects maintained in a supine position. The data was analysed as a function of 5 consecutive phases: 1) 30 minutes before lights out; 2) lights out to stage 1 sleep; 3) stage 1 to stage 2 sleep; 4) stage 2 sleep to the last micro-arousal before stable sleep; and 5) the first 30 minutes of undisturbed stable sleep. Data was analysed on a beat-by-beat basis and reported as 2 min periods for phases 1 and 5, and as 10% epochs for phases 2, 3 and 4 (as subjects had variable time periods in these phases). The level of baroreflex activity was assessed by the number of 3 beat inverse sequences between BP and HR, while baroreflex sensitivity (BRS) was assessed by the average slope within sequences. During phases 3 and 4, the BP and HR response to arousal from sleep was determined.

**Results:** A combination of inferential and descriptive statistics were applied to the data. From relaxed wakefulness to stable sleep, HR fell by 7 b/min, whilst systolic blood pressure (SBP) fell by 13 mmHg and diastolic blood pressure (DBP) by 10 mmHg, with the minimum values occurring 15 minutes into stable sleep. The fall in BP occurred during phase 2 (following lights out - SBP fell 8 mmHg) and phase 5 (following the attainment of stable sleep - SBP fell 5 mmHg). There were no significant differences in the number of sequences generated, while BRS increased by 3 msec/mmHg during phase 3, but otherwise was unchanged. During phases 3 (stage 1) and 4 (stage 2 with micro-arousals), BP did not change during periods of sleep, while arousals were associated with transient, high frequency increases in activity that returned BP and HR back to the pre-lights out wakefulness levels (average response amplitude of 13 mmHg).

**Conclusions:** Data suggest that the fall in BP during sleep onset is due to a rapid downward resetting of the baroreflex, a process that is retarded, and may be reversed, by arousals occurring during periods of sleep-wake instability. This phenomenon may contribute to the “non-dipping” BP profile seen in some sleep and cardiovascular disordered patients.

**Research supported by an ARC grant.**

## 230.B

## INCREASED SLEEPINESS AND FINGER SKIN TEMPERATURE AFTER MELATONIN ADMINISTRATION: A TOPOGRAPHICAL INFRARED THERMOMETRY ANALYSIS

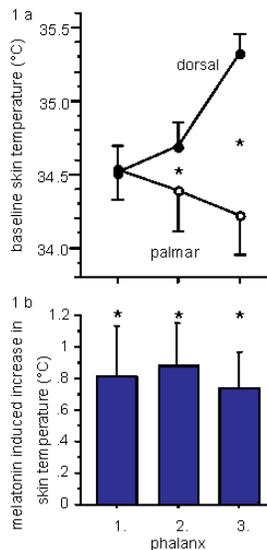
Kräuchi K,<sup>1</sup> Pache M,<sup>1</sup> von Arb M,<sup>2</sup> Wirz-Justice A,<sup>1</sup> Flammer J<sup>1</sup>

(1) Center for Chronobiology, Psychiatric University Clinic; (2) University Eye Clinic, Basel, Switzerland,

**Introduction:** Recent studies have shown a close relationship between sleepiness and the thermolytic effects of melatonin, which induces heat loss via distal skin regions and hence heat loss in the body core (1). Because of the selective increase in distal, but not proximal skin temperatures after melatonin administration, we suggested a specific vasodilatory action of melatonin in skin regions containing arteriovenous anastomoses (AVAs) (2). However, we previously measured distal skin temperatures on the back of the hand, a region containing no AVAs (2). It is the fingertip, and especially the nail bed, which contains the majority of AVAs in the hand (2). Thus, the fingers provide a good model to study the specificity of action of melatonin on blood flow and skin temperature.

**Methods:** In a double-blind placebo-controlled 1-week crossover study, 11 healthy men (mean age  $26y \pm 2$  SD, BMI  $22.2 \pm 1.7$ ) received melatonin (mel, 5 mg p.o.) or placebo (plac) at 14:00h in a balanced order. Skin temperatures of the fingers were measured by means of an infrared detector (TH3100mr Thermo Tracer; NEC San-ei Instruments Ltd., Tokyo, Japan) 30 min before and 60 min after pill intake (room temperature:  $26 \pm 1^\circ\text{C}$ ). Subjective ratings of sleepiness (mm VAS) and core body temperature (CBT, sublingual) were measured in parallel. Subjects remained in a sitting position 30min before and during the measurements. Here we report mean skin temperature of distal and planar skin regions of the first, second and third phalanx of the middle finger (ANOVA for repeated measures, significance level  $p < 0.05$ ).

Figure 1



**Results:** Melatonin showed a soporific and thermolytic effect (mm VAS sleepiness:  $+15.4 \pm 6.8$  mm; CBT:  $-0.07 \pm 0.03^\circ\text{C}$ ), confirming previous findings under supine constant routine conditions (1). Baseline skin temperatures (Figure 1a) were highest on the fingernail and lowest on the palmar side of the third phalanx. No dorsal-palmar differences in the first phalanx could be observed. Melatonin uniformly increased skin temperature independent of skin region (Figure 1b, mean temperature of palmar and dorsal skin regions).

**Conclusions:** To achieve a skin temperature increase of similar magnitude at both proximal and distal regions a much larger increase of blood flow in the latter is required. Therefore, our results indicate a higher skin blood flow elevation by melatonin in the fingertip than in the proximal finger, most probably by opening of AVAs.

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## 231.B

## GH REPLACEMENT FAILS TO NORMALIZE SLEEP RESPONSES TO VIRAL INFLUENZA INFECTION IN GHRH-RECEPTOR DEFICIENT MICE.

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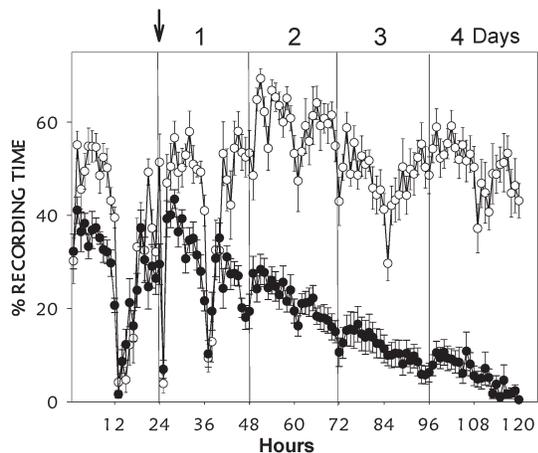
**Introduction:** Viral infections induce excess non-rapid eye movement sleep (NREMS) and somnogenic cytokines, including interleukin- $1\beta$  (IL- $1\beta$ ). IL- $1\beta$  stimulates growth hormone-releasing hormone (GHRH), a peptide also implicated in NREMS regulation. Via QTL analysis, the GHRH-receptor (GHRH-R) was identified as a candidate gene responsible for NREMS responses of mice to influenza challenge (1). We found that the dwarf *lit/lit* mouse with a point mutation in the GHRH-R gene (2), responded to influenza with decreased NREMS (3). GH might be necessary for normal function of the immune system and sleep. We determined therefore, whether GH replacement can normalize the sleep response in the *lit/lit* mice to influenza infection.

**Methods:** Mice (control C57BL/6,  $n=12$ ; *lit/lit*,  $n=12$ ) were implanted with EEG and EMG electrodes. Animals were on a 12:12-h light-dark cycle at  $29^\circ\text{C}$ . Alzet minipumps were implanted ip in *lit/lit* mice to release 11  $\mu\text{g}$  mouse GH per day ( $n=4$ ) or 24  $\mu\text{g}$  rat GH per day ( $n=8$ ). Findings in the 2 groups did not differ and were pooled. Controls received saline. Weights were taken to determine if the GH therapy was effective. We recorded spontaneous sleep for 48 h, 8-9 days after surgery. Mice were then intranasally infected on postoperative day 10, with A/PR/8/34 (H1N1) influenza virus ( $2.5 \times 10^6$  TCID<sub>50</sub>s in 50  $\mu\text{l}$ ) at light onset. Changes in NREMS and

REMS were compared by means of two-way ANOVA.

**Results:** After 1 week of GH infusion, the weight gain in the *lit/lit* mice was significantly higher ( $+1.9 \pm 0.2$  g) than in the controls ( $+0.8 \pm 0.2$  g) though the body weight of the *lit/lit* mice remained less than that of controls ( $13.4 \pm 0.2$  vs.  $23.9 \pm 0.5$  g). The *lit/lit* mice had less NREMS than controls on the baseline day (figure). In control mice, influenza virus induced increases in NREMS and suppression of REMS. GH replacement did not alter the pathological sleep response in the *lit/lit* mice. These mice decreased NREMS after infection. The GH replacement therapy in *lit/lit* mice restored REMS close to values obtained from control mice on the baseline day, but it did not affect the REMS responses to influenza challenge. The GH-treated *lit/lit* mice exhibited pathological EEG slow wave and spike activity after infection as previously reported (3). Five out of 12 GH-treated *lit/lit* mice died compared to 1 of 12 controls.

**Figure 1**



After influenza challenge (arrow), NREMS in GH-treated *lit/lit* mice decreased (closed circle) compared to the increased NREMS observed in control mice (open circles).

**Conclusions:** Results suggest that GH is not involved in the NREMS response to influenza infection. The pathological alterations in sleep and, perhaps, the high death rate of the *lit/lit* mice might be due to the defect in GHRH signaling.

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Research supported by NIH HD36520, NS27250, and NS25378.

## 232.C

### EFFECTS OF YOKU-KAN-SAN-KA-CHIMPI-HANGE ON THE SLEEP OF NORMAL ADULT SUBJECTS

Aizawa R,<sup>1</sup> Kanbayashi T,<sup>1</sup> Saito Y,<sup>2</sup> Ogawa Y,<sup>2</sup> Sugiyama T,<sup>2</sup> Kitajima T,<sup>2</sup> Kaneko Y,<sup>3</sup> Abe M,<sup>2</sup> Natsui E,<sup>2</sup> Shimizu T<sup>2,3,2C</sup>

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**Introduction:** Yoku-kan-san-ka-chimpi-hange (YKCH), a Japanese traditional herbal medicine (JTHM) is known to be effective for the treatment of insomnia (1). Regarding the therapeutic effects of a Japanese traditional herbal medicine (JTHM) on insomnia, all studies previously reported was based on subjective evaluation of the sleep. In the present study, with the purpose of evaluating the effects of YKCH on the sleep, we performed the double blind cross over objective study using all night polysomnography (PSG) with Anchu-San as control drug.

**Methods:** It is known that the effects of JTHM differ in each case according to "Sho" of each individual. "Sho" is equivalent to a syndrome, but it comprises not only psychic and somatic symptoms but also signs obtained by a traditional physical examination that focuses on the patient's constitution, general physical condition, pulse, and abdominal signs. Including an examination of the tongue (1). We have given YKCH (7.5 g/day; for 3 days and 3 times a day)(2) to 20 healthy male adults without considering "Sho" (mean  $\pm$  SD: 27.1 years  $\pm$  6.8) in advance to the PSG study(mean  $\pm$  SD: 27.1 years  $\pm$  6.8). All subjects gave informed consent about the study. Seven subjects (23.9 years  $\pm$  2.0), who reported the easiness to get to sleep or the feeling better sleep, were selected from twenty subjects. The all night PSG was performed in these selected subjects. The experiment was carried out by double blind method, using YKCH and Anchu-San. The latter medicine, is a drug for gastroenteropathy without effects on the sleep. @The interval between two experiments was set to one week. Subjects took either medication for succeeding three days before the experiment night. @The night before the experiment night was set as a adaptation night. All night PSGs were recorded from 23:00 to the next morning when the subject spontaneously woke up or up to 7:00 in the morning if the subject did not spontaneously wake up. On the sleep variables in each experiment, statistical analysis was performed by paired t-test. The level of significance was set to:  $p < 0.05$ .

**Results:** Table 1 summarizes the sleep variables when YKCH and Anchu-san are given. Compared with Anchu-san, YKCH significantly increased the total sleep time ( $p=0.04$ ). Although it was not statistically significant, the following trends were observed: decrease of sleep latency, increase of sleep efficiency, increase of stage2, and decrease of stage3+4. There was no apparent influence on REM sleep. Also, no subject complained of any side effects.

**Table 1**

Sleep parameters in the night with Yoku-kan-san-ka-chimpi-hange (YKCH) or Anchu-san.

	YKCH	Anchu-san
time in bed (min)	474 (18)	453 (19)
sleep period time	462 (17)*	425 (14)
total sleep time	438 (13)*	371 (19)
sleep latency	4.66 (1.3)	10.4(2.7)
sleep efficiency index	0.95 (0.0)	0.88 (0.1)
wake (min)	23.9 (4.6)	54.3 (28)
stage1	47.6 (6.4)	50.6 (8.8)
stage2	123 (46.1)	50.6 (8.8)
stage3+4	39 (18)	52 (18)
REM sleep	64.6 (11)	48.6 (9.2)

Figures in the table are mean values with SEM. \*p < 0.05

**Conclusions:** Benzodiazepines (BDZs) is now used as the drug for improving sleep. It is reported that BDZs have the effects such as shortening of sleep latency, extension of total sleep time and the increase of stage2 and the decrease of stage3+4 (3). Compared with Anchu-san, YKCH significantly extended the total sleep time, it have no influence on REM sleep and have the following trends: increase of stage2 and decrease of stage3+4. Regarding the non-REM sleep, the effect of YKCH exhibits a profile similar to that of BDZs. Since we selected the seven responders from twenty subjects using self reports in this study, further study should be carried out on "Sho", and to identify the factors, by which we would be able to predict the responders of YKCH.

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### 233.C

#### EFFECTS OF DONEPEZIL (ARICEPT) ON THE REM SLEEP OF NORMAL SUBJECTS

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**Introduction:** Donepezil (Aricept) is a therapeutic drug for the treatment of Alzheimer diseases (AD). Dysfunction of cholinergic neurons is attributed to cognitive impairment in AD (1). Donepezil effects via activation of cholinergic neurons by inhibiting acetylcholin-esterase (ACh-E)(1). Animal studies indicated that ACh-E inhibitors increased REM sleep (2), however these compound had also peripheral side effects, such as difficulties of urination and mouth dryness, so the human study was not easy. Since donepezil has been clinically used in Europe and USA, there have been only two reports

which described the effects of donepezil on sleep using nocturnal polysomnography (PSG)(3). In this respect, we evaluated the effects of donepezil on the sleep of normal subjects using PSG.

**Methods:** The study was performed on 8 healthy male subjects. Age distribution was  $28 \pm 2$  years (mean  $\pm$  SD). Double blind cross over method was adopted using donepezil (5 mg) and placebo. Time interval between the experiments was set to one week. Each subject was instructed to sleep in the recording room for two consecutive nights. First night was regarded as the night for adaptation, and the second night was the experiment night. All subjects gave informed consent. The drug or placebo was given at 22:30 of the experiment night. Overnight PSG was recorded from 23:00 to the next morning when the subject spontaneously woke up or up to 8:00 in the morning if the subject did not spontaneously wake up. On the next morning of the experiment night, the inquiry was made on: sleepiness, dizziness, feeling of muscle weakness, digestive organ symptoms, and whether the subject dreamed or not. Sleep variables in each experiment was statistical analyzed by paired t-test. The level of significance was set to:  $p < 0.05$ .

**Results:** Table1 summarizes the sleep variables when donepezil and placebo are given. Compared with the placebo, donepezil significantly increased the percentage of REM sleep to the total sleep time (TST). Also, a tendency of extension of sleep latency was found although it was not statistically significant. Regarding the REM sleep latency and other sleep parameters, there was no significant difference. No subject complained of sleepiness, dizziness or feeling of muscle weakness in the next morning of the experiment night, but some subjects reported the difficulty in falling a sleep and increased dreams.

**Table 1**

Sleep parameters in the night with Donepezil or Placebo.

	Donepezil	Placebo
time in bed (min)	464 (15)	453 (16)
sleep period time	419 (11)	429 (13)
total sleep time	379 (20)	398 (16)
sleep latency	23 (10)	9 (3)
REM latency	125 ( 15 )	98 ( 7 )
sleep efficiency index	0.9 (0.04)	0.93 (0.02)
wake (min)	39(14)	31(8)
stage1	52 (7)	57(88)
stage2	213(18)	234 (9)
stage3+4	45 (10)	53(16)
REM sleep	68 (7)*	54(7)

Figures in the table are mean values with SEM. \*p < 0.05

**Conclusions:** It has been reported in animal studies that ACh-E inhibitor increases the percentage of REM sleep to TST and it shortens REM sleep latency (2). In our present study on healthy subjects, there was no change in REM sleep latency, but the increase of the percentage of REM sleep to TST was found. There have been many reports describing the decrease

of REM sleep in the cases of AD. Schredl et al. described that there was a significant positive correlation between the increase of REM sleep by donepezil and the improvement of cognitive function in normal elderly subjects (3). Recently, Moraes et al reported that this compound increased REM sleep in the patients with AD compared to that of placebo group patients with AD and the amount of REM sleep was reached to the level of normal elderly controls. In these previous studies, the administration of drugs was at the morning and continued one week or more (3). While in the present study, the significant increase of REM sleep was observed even in a single administration of 5mg donepezil to normal subjects immediately before retiring. This result indicated that the effect of donepezil is direct and immediate to nocturnal sleep. The reason was unknown why the REM sleep latency did not change, however a tendency of extension of sleep latency by donepezil might be involved. Regarding the question as to whether or not the increase of REM sleep may have direct causal relationship with the improvement of cognitive function in the treatment of patients with AD, further study should be necessary including the experiments on other types of ACh-E inhibitors and choline stimulants.

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**234.C**

**METHYLPHENIDATE'S ALERTING EFFECTS: TIME-IN-BED AND DOSE**

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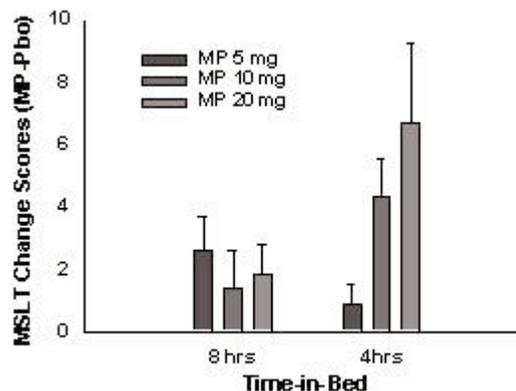
**Introduction:** Previous studies have found that methylphenidate's alerting effects depend on the prior amount of nocturnal sleep and consequent daytime sleepiness. This study was done to determine how dose range might interact with prior sleep amount in altering the alerting and reinforcing effects of methylphenidate.

**Methods:** Eighteen healthy, normal adults, 21-45 yrs old, participated. All were in good medical and psychiatric health with no history of alcoholism or drug abuse. All underwent a standard screening 8-hr polysomnogram and MSLT the following day. To qualify subjects were required to have a >85% sleep efficiency, no evidence of primary sleep disorders, and an average daily sleep latency of >8 min on the MSLT. Those subjects qualifying were randomly assigned to a methylphenidate dose (5, 10, or 20 mg). On each of 2 days at 0900 hrs subjects received, double-blind, in a counter-bal-

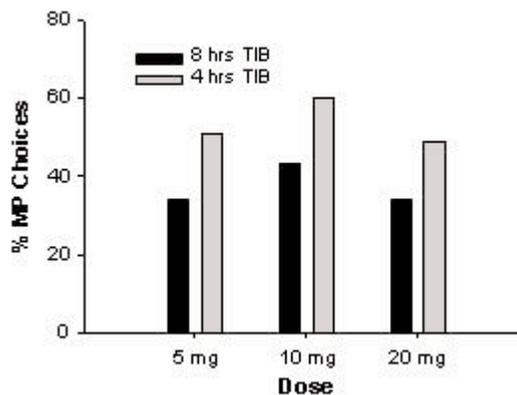
anced order, placebo or methylphenidate (at the assigned dose) capsules. For the duration of each day performance, mood, and MSLT testing was done. All completed this assessment after 8 hrs time-in-bed (TIB) and 4 hrs TIB each of the 2 nights with order of TIB counter-balanced and 1 week of recovery between TIBs. In each TIB condition on 5 subsequent choice days they choose placebo or MP based on color coding.

**Results:** On the MSLT average daily sleep latency was reduced after 4 hrs TIB compared to 8 hrs TIB [9.9 (4.9) vs 5.7 (3.9) min] ( $p<.002$ ). Methylphenidate increased average sleep latency [7.8 (4.0) vs 10.6 (5.3) min] ( $p<.001$ ). Dose response varied as a function of prior TIB( $p<.03$ ). As shown in Figure 1, in the 8 hr TIB the dose response curve was flat, while in the 4 hr TIB increasing dose increased sleep latency with the 20 mg dose producing the greatest increase in sleep latency (5.6 min). As shown in Figure 2, MP was chosen more frequently in the 4 hr TIB ( $p<.04$ ) and the 5 and 10 mg doses were clearly preferred to placebo, but not the 20 mg dose.

**Figure 1**



**Figure 2**



**Conclusions:** These data indicate that the alerting effects and the reinforcing effects of methylphenidate doses are dependent on the amount of prior sleep and consequent daytime sleepiness.

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235.D

DREAM CHARACTERISTICS IN AUTISTIC SPECTRUM DISORDERS

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**Introduction:** Autistic Spectrum Disorders (ASD) is a continuum including Asperger Syndrome and high-functioning autism. Persons with ASD have problems to verbally elaborate on their mental states and to distinguish between mental and physical entities. Furthermore, they report dreams at a later age compared to controls and they are more likely to misunderstand the concept of dreaming (1). There are no reports of dream content analysis in large groups of persons with ASD.

**Methods:** Nineteen persons with ASD and normal intelligence (17 M, 2 F, aged 22,7 ± 2,3 years) were diagnosed according to DSM IV criteria and using the Autism Diagnostic Interview. Inclusion criteria were a score above the cut-off point in the areas of social communication and restricted interest. They were compared to seventy-one healthy individuals (41 M, 30 F, aged 23,1 ± 0,7 years) who were free from sleep disorders and from a personal or a familial (first degree) history of psychiatric or neurological disorders. Subjects were asked to fill a questionnaire including fifteen questions on dream habits. Frequency of emotions in dreams was ranked from 0 (never) to 5 (always). Answers from both groups of participants were compared using Mann-Whitney U-tests and Pearson Chi-square tests for independent samples.

Table 1

Frequency reports of emotions in dreams of persons with ASD and healthy individuals (x ± s.e.m).

Emotions	ASD	Cntl	p
Joy	2.9±0.2	3.3±0.1	0.11
Fear	2.5±0.2	2.5±0.1	0.89
Sadness	2.2±0.2	2.4±0.1	0.49
Relaxation	2.5±0.3	2.6±0.1	0.75
Confusion	2.1±0.2	3.1±0.1	0.0003*
Satisfaction	2.7±0.3	3.0±0.1	0.34
Anger	2.2±0.2	2.5±0.1	0.33
Frustration	1.9±0.5	2.5±0.1	0.03*
Sexual Arousal	2.3±0.3	2.8±0.1	0.16
Apprehension	2.6±0.4	2.8±0.1	0.42
Shyness	1.9±0.2	2.4±0.1	0.04*

\*= significant at < .05

**Results:** No significant differences were found on the items related to the frequency and the number of dream recall, the

recall of content, the sharpness of dreams, the number of nightmares and bad dreams, the repetition of dream features and physical sensations in dreams. Frequency of emotions was generally lower in persons with ASD, with statistically different results for "confusion", "frustration" and "shyness" (see Table 1). When the analysis is strictly based on the presence or the absence of an emotion in dream, proportion of persons with ASD responding "never" is higher than controls for all emotions, with significant differences for "confusion", "frustration", "sexual arousal" and "shyness" (see Table 2).

Table 2

Proportion of "never" answers for emotions in dreams of persons with ASD and healthy individuals.

Emotions	% ASD	% Cntl	p
Joy	5.9	1.5	0.28
Fear	11.8	8.6	0.68
Sadness	23.5	15.7	0.44
Relaxation	25	14.3	0.29
Confusion	35.3	7.1	0.002*
Satisfaction	17.7	5.8	0.11
Anger	23.5	17.1	0.54
Frustration	41.2	16.2	0.02*
Sexual Arousal	41.2	4.3	0.00002*
Apprehension	31.3	13	0.08
Shyness	47.1	18.8	0.02*

\*= significant at < .05

**Conclusions:** Persons with ASD report similar formal dream features than controls but show differences on dream emotional contents. They tend to report a lower appearance frequency of emotions in dreams. These results are in accordance with their social and communicative impairments in the waking state. Indeed, persons with ASD are known to have difficulties to recognise and to identify emotions in photographs (2). Using the framework of Baron-Cohen, we find that persons with ASD present severe deficits in comprehension of emotions caused by beliefs (ex: deception, surprise, shyness) compared to no deficits in emotions caused by situation (ex: pleasantness) or desire (ex: satisfaction) (3).

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236.D

**YOU ARE WHAT YOU DREAM: FOOD IMAGERY IN THE DREAMS OF DEPRESSED VS. NON-DEPRESSED SUBJECTS**

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**Introduction:** Appetite disturbances are among the hallmarks of depression, so it is perhaps not surprising to find images of food or eating in the dreams of depressed subjects. The current study explores whether the spontaneous dream reports of depressed subjects more frequently contain food-related imagery than non-depressed controls.

**Methods:** This study counted the references to food, eating, and/or cooking in the spontaneous dream reports from studies of 36 depressed and 60 control volunteers. The depressed subjects had participated in studies of the effects of divorce on sleep and dreams, while the controls were a student group with no present or past episodes of major depression. Food/eating content in dreams was scored by two independent raters with 97% reliability. All differences between raters in food-related dreams were re-examined and reconciled. Chi-square analysis was computed to compare between-group differences in the frequencies of food/eating imagery in total REM periods, each of the first four REM periods, and the last REM period of the night. Differences within the night of depressed subjects were also examined using chi-square analyses.

**Results:** Figure 1 shows the percent of REM periods in which food imagery was reported in the depressed and control groups. The total frequency of food/eating imagery failed to reach significance between groups ( $X^2= 3.15, p> .05$ ). However, the difference in frequency of food dreams at the end of the night was statistically significant: depressed subjects had more frequent food-related dream imagery than controls during REM 4 ( $X^2= 7.97, p< .05$ ) and/or the last REM of the night ( $X^2= 11.39, p< .05$ ). Food-related dream imagery was also significantly more frequent during REM 4 than REM 1 ( $X^2= 4.90, p< .05$ ) in the depressed group.

**Conclusions:** The results show that depressed subjects did not experience more dreams in which food/eating imagery appeared than did non-depressed subjects. They did, however, have more frequent food-related dreams during the fourth and/or last REM period of the night, which may possibly reflect some underlying disturbed process. Leptin is involved in the initiation of hunger drive. Levels of this hormone drop before meals, and rise immediately afterward (Blundell et. al, 2001). Antonijevic et. al (1998) report significantly elevated nocturnal serum leptin levels that peak during the second half of the night in depressed patients compared with controls. Thus, it is possible that the differences observed in the present study of food imagery in depressed versus control subjects may reflect elevated leptin levels. When nocturnal leptin levels are high, the process of dreaming may connect this physiological state with past experiences in the dreamer's life, during which food or eating behavior was involved. Differences within the depressed group between REM 1st and REM 4th possibly indicate that dreams identify a significant disturbance in the state of the dreamer: a peak during the second half of the night in already elevated leptin levels.

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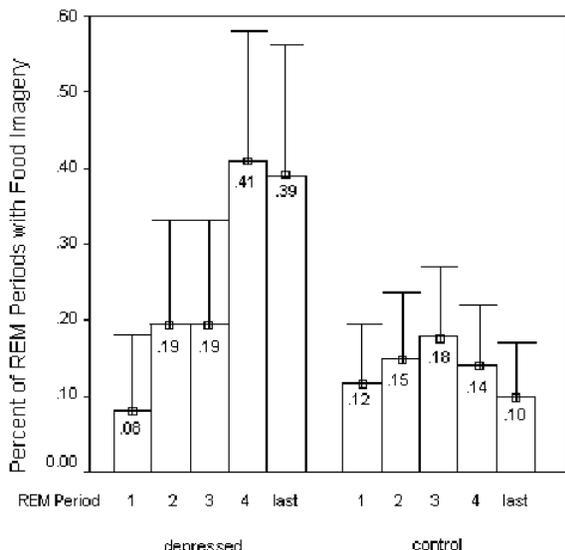
237.D

**AFFECTIVE PROCESSING BY DREAMS ACROSS THE NIGHT**

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Figure 1



**Introduction:** Change in mood across the night correlates with the content of the intervening nights' dreaming[1].The mood change may be a consequence of emotional problem solving during the intervening dream experiences. The possibility arises that pre-sleep mood correlates with with the content of the nights dreams and the nights dreams then correlates with the same aspect of mood the next morning.This would support a direct "pass-through" relationship across the night.

**Methods:** We collected dream reports from 20 college age men from the end of the first four REM periods of the night for 20 consecutive nights. Each night and morning, the subjects completed the Clyde Mood Scale. The recorded dream reports were scored "blind" using the Hall- van de Castle scoring system for three social interactions( Aggressive, Friendly, and Sexual),five emotions(Happy,Sad, Anger, Confusion, and Apprehension), and for total characters.The mean score of the six Clyde Mood Subscales(Aggressive, Friendly, Unhappy, Sleepy, Clear Thinking and Anxious) both night and morning were correlated with the mean dream content scores for the

three social interaction scales, the five emotion scales, and with the total characters in the dreams. Between subjects Pearson correlations were done. We did 108 correlations (six mood subscales x two times x nine dream content scales).

**Results:** We found ten significant positive correlations at  $p=.05$  or less. Two were with an aspect of night mood (Anxious night mood with Sexual Social Interactions and with the emotion Confusion). Eight of the significant correlations were with some aspect of morning mood and the prior nights' dreams: 1) Friendly, Unhappy, and Clear Thinking mood with Aggressive Social interactions, 2) Aggressive and Unhappy mood and the emotion Sad, 3) Friendly mood and the emotions Anger and Apprehension, and 4) Unhappy mood and the emotion Confusion. None were with total characters.

**Conclusions:** We were unable to find any direct "pass-through" relationship between mood at night, dream content and the same aspect of mood in the morning. This is in contrast to our having found a relationship between the change in mood across the night and the content of the nights' dreams. This relationship was most striking for the change in Unhappy mood across the night and the number and type of characters in the dreams. The failure to find a direct "pass-through" relationship may be a result of the relatively low dream recall percentage (63%) and/or the paucity of scoreable dream content: 343 social interactions, 224 emotions, and 1194 characters. The low frequency of dream contents precluded a within subject correlation, which may be the more appropriate level of analysis to search for a possible direct "pass-through" relationship. Clearly indirect ones were demonstrated. Three correlations were found with Unhappy, but none with characters. As more correlations were found with morning mood than night mood, dreams may be more proactive than reactive.

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## 238.D

### NIGHTMARE EXPERIENCE AND FATIGUE IN UNIVERSITY STUDENTS

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**Introduction:** Recent research and speculation suggests that nightmares may play a role in the management of stressful experience and that stressful experience may be associated with the development of fatigue. Our purpose in this study was to explore the possibility of relationships between extremes in fatigue and nightmare experiences (i.e., the frequency of three types of nightmares and nightmare distress).

**Methods:** We tested a large group of undergraduate students and identified 100 (50 men and 50 women) who scored low in fatigue, i.e., the bottom 20% on the FIS-10 and 100 (50 men and 50 women) who scored high in fatigue, i.e., the top 20% on the FIS-10. These groups were matched as closely as possible for age and ethnicity. For these Low and High Fatigue Groups, we scored their responses to frequency that they experienced the three types of Nightmares that are included in the

Spadafora and Hunt<sup>1</sup> Dream Scale and their responses to Belicki's<sup>2</sup> Nightmare Distress Scale. Then these data were organized and used to compare the differences between the nightmare experiences of the Low and High Fatigue Groups.

**Results:** The data for each nightmare parameter for each fatigue group are summarized in the table. These data indicate that there is no difference between the means of the two fatigue groups for fantastic nightmares (i.e., the typical REM Nightmare or "Bad Dream"). However, for nightmares that may be initiated by exposure to major traumatic events (Post Traumatic Nightmares and Night Terrors), the differences between the fatigue groups is both statistically significant and meaningful with the High Fatigue Group reporting experiencing 33% more Post Traumatic Nightmares and 44% more Night Terrors. Finally, these data indicate that high fatigue was associated with nightmares that were perceived as 30% more distressful than those experienced by the Low Fatigue Group.

**Table 1**

Nightmare Dimension	High Fatigue		Low Fatigue		t	p	est. $\omega^2$
	Mean	SD	Mean	SD			
Fantastic	2.34	1.08	2.21	1.58	.68	n.s.	.00
Post Traumatic	1.81	1.00	1.36	.64	3.80	<.01	.06
Night Terrors	1.83	1.04	1.27	.53	4.82	<.001	.10
Distress	17.54	6.04	13.52	2.77	6.05	<.001	.15

**Conclusions:** Collectively, these data suggest that fatigue is associated with dreaming that may reflect a prolonged attempt to cope with a major traumatic past experience.

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## 239.E

### EVENING AND MORNING DIFFERENCES IN WAKING EEG REACTIVITY IN YOUNG ADULTS

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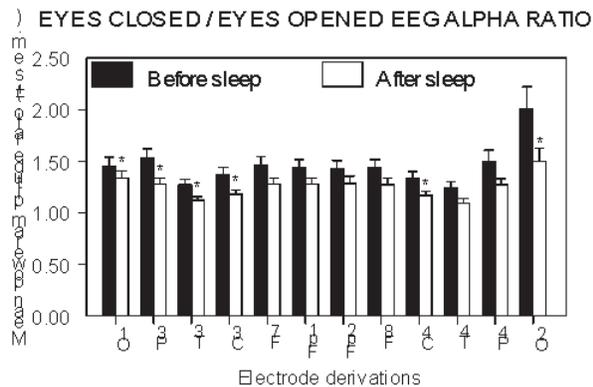
**Introduction:** A number of studies show that waking EEG power decreases in the morning, relative to evening. This is generally interpreted as reflecting the restorative functions of sleep. Such studies have used eyes closed (EC) or eyes opened (EO) recording conditions. However, it is the EC/EO ratio that is thought to best represent EEG and cortical reactivity (1). Unfortunately, the restorative function of sleep has not yet been evaluated with this measure. We investigated the topography of the evening and morning EC/EO ratio as a part of a more extensive project on sleep, EEG and performance. Efforts were devoted to control for confounding variables such as age, gender, laterality of participants, time of day, lighting

condition, napping and intervening nocturnal sleep.

**Methods:** Twenty-nine young right-handed healthy participants (15 women, 14 men, age:  $21.7 \pm 3.5$  years) spent two consecutive nights in a sleep laboratory. All were free from sleep disorders, personal or a familial (first degree) history of psychiatric or neurologic disorders, alcohol, medication, caffeine, and napping. Night 1 served as an adaptation night and screening of sleep disorders. Upon night 2, waking EEG recordings with EC and with EO were performed for five consecutive minutes each with lights on in the evening before going to bed (between 22h00 and 23h00) and on the following morning (between 07h00 and 08h00). A 12-electrode montage referred to linked ears was used: C3, C4, Fp1, Fp2, F7, F8, T3, T4, P3, P4, O1, O2. EEG amplitude power ( $\mu\text{V}/\text{Hz}$ , 0.75Hz to 19.75Hz) was determined with spectral analysis performed on 10 to 15 four-second artefact-free epochs. Frequency bands were created: Delta = 0.75-3.75 Hz; Theta = 4.00-7.75 Hz; Alpha = 8.00-12.75 Hz and Beta-1=13.00-19.75 Hz. EC/EO ratios were calculated for each frequency band. T-tests were used to compare evening and morning EC/EO ratios.

**Results:** Only alpha activity showed significant evening-morning differences. Figure 1 shows that evening values were greater for C3 ( $p=0.02$ ), C4 ( $p=0.055$ ), T3 ( $p<0.04$ ), P3 ( $p=0.03$ ), O1 ( $p=0.055$ ) and O2 ( $p=0.05$ ).

Figure 1



**Conclusions:** These results indicate that, following a night of sleep, young healthy adults show a decrease in EC/EO alpha ratio. This effect is present over most recording sites except for frontal derivations. Decreased EC/EO alpha ratios were associated to decreased cognitive performance in elderly with vascular dementia (1). However, time of day was not controlled for. Decreased EC/EO alpha ratios were also associated to sleepiness in the "Alpha Attenuation Test" protocol, a method by which multiple EC and EO daytime recordings are averaged (2-3). At first sight, our own observations seem counterintuitive as they suggest decreased cortical efficiency in the morning. On the other hand, our study is the only one controlling at the same time confounding variables such as electrode derivations, time of day, homogenous age distribution, equal distribution of genders and gaussian distribution of EEG data. We thus conclude that decreased EC/EO reflects the restorative functions of sleep.

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**240.E**

**GET A JUMP ON JET LAG**

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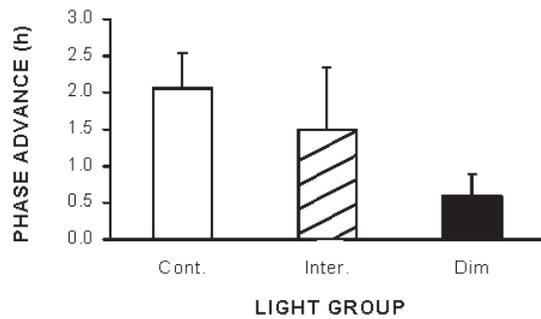
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**Introduction:** Jet lag is characterized by symptoms including fatigue, insomnia, daytime sleepiness and gastrointestinal problems. These problems are caused by the misalignment between circadian rhythms and the local destination time. As humans find it harder to phase advance than delay, jet lag is typically worse after traveling east. This ongoing study is testing the effectiveness of a treatment designed to phase advance circadian rhythms prior to eastward jet travel. With a large enough phase advance, jet lag can be completely avoided. Even smaller phase advances can be important to ensure that subsequent exposure to the destination's light/dark cycle continues to produce phase advances, rather than delays which could trigger re-entrainment in the wrong direction. Phase advances achieved before the flight can reduce the number of days of jet lag experienced after the flight.

**Methods:** To date 24 healthy adults (13 women, 11 men, age: 22-43 y) participated. They slept in the lab for 3 nights, and their sleep (dark) period was gradually advanced 1 hour per night. In the morning they experienced 1 of 3 possible light treatments: a continuous 3.5 h bright light exposure (~3000-11000 lux depending on angle of gaze), intermittent bright light (0.5 h on, 0.5 off, etc for 3.5 h) or dim ordinary room light (<60 lux). The bright light was produced by a light box (61 x 61 x 10 cm). There was a phase assessment before and after the 3 nights to determine how much their circadian rhythms advanced. During the phase assessments subjects remained awake and semi-recumbent in dim light (<10 lux) and gave saliva samples every 30 mins for later assessment of their dim light melatonin onset (DLMO).

**Results:** The Figure illustrates the mean  $\pm$  SD phase advances in each group. A one-way ANOVA indicated there was a significant group effect ( $F(2,21)=10.80$ ,  $p<0.01$ ). Post-hoc Tukey's HSD comparisons revealed that the phase advances in the continuous and intermittent groups were significantly greater than in the dim group ( $p<0.001$  and  $p<0.02$  respectively). However the continuous and intermittent groups were not significantly different ( $p=0.18$ ).

Figure 1



**Conclusions:** These results indicate that the combination of morning bright light and an advancing sleep schedule can help get a jump on jet lag. There was no significant advantage of the continuous bright light pattern compared to the intermittent pattern. This is important because intermittent light is a more feasible method of using bright light at home. The small phase advance produced in the dim light condition also reveals that advancing sleep in ordinary room light, without the use of morning bright light, can still advance circadian rhythms. More than 3 days of morning bright light exposure and advancing sleep could be used to produce even greater phase advances, and could potentially eliminate jet lag.

Research supported by NIH grant to CE: NINR RO1 NR07677. Light boxes donated by Enviro-Med, WA, USA.

## 241.E

### IDENTIFICATION OF FREE-RUNNING RHYTHMS IN TOTALLY BLIND CHILDREN

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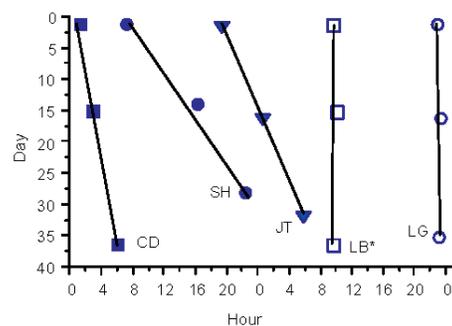
**Introduction:** Total blindness in adults is usually associated with significant sleep disturbances, daytime sleepiness and impairment in performance. The presence of free-running circadian rhythms in totally blind adults has also been well documented. Over the past 10 years there have been a handful of studies documenting circadian rhythm disturbances in totally blind children. In many of these studies, only a single circadian one-day assessment was done, and almost all of these cases were developmentally disabled children (many of them moderate to severe). Our study is the first to assess multiple 24-hour melatonin (plasma or saliva) profiles in totally blind children (who were not developmentally disabled).

**Methods:** Five children (three females, two males) between age 12-20 were recruited from the Washington State School for the Blind in Vancouver, WA. Each child was interviewed by the principal investigator prior to being enrolled in the study. During this interview, a review of their past medical history was done, and signed consent was obtained from the parent as well as the child. An eye exam was performed on each child prior to study entry. In order to accurately assess melatonin circadian phase and to predict tau, each child was admit-

ted to the OHSU General Clinical Research Center on three 24-hour occasions spaced two to three weeks apart. Each child was given the option of having hourly blood draws or collecting hourly saliva specimens.

**Results:** Plasma (JT only) and saliva samples were analyzed for melatonin using the ALPCO RIA kit. We found that three of five children had free-running melatonin circadian rhythms (see table and figure). Of the two children who were not found to be free-running, it was later discovered that one of the them (LB) had some small degree of light perception (she was previously sighted until age 5 when she was diagnosed with Type I neurofibromatosis with associated optic gliomas). The other entrained child (LG) was blind since birth, surviving a 24-week gestation and developing retinopathy of prematurity with bilateral retinal detachments. This child, however, did report a daily morning exercise routine.

Figure 1



Melatonin onsets (\*offsets for LB) are shown plotted from Day 1 for each blind child. Free-running subjects are indicated by the solid points. Since subject JT crosses midnight, a double scale for hours is shown.

Table 1

Sex	Age	Tau	Blindness Cause	
CD	F	15	24.14	Bilaterally enucleated
SH	M	17	24.56	Norrie's Disease
JT	M	20	24.35	Norrie's Disease
LB	F	12	23.99	Optic nerve compression
LG	F	14	24.01	Retinopathy of prematurity

**Conclusions:** A methodical documentation of free-running circadian rhythms in three totally blind children has now been done. It is perplexing as to why one of the children (LG) appears to be entrained. Perhaps daily exercise is a strong enough zeitgeber to maintain entrainment in this individual. However, totally blind subjects who appear to be entrained (such as LG) need to be followed longitudinally to document this with complete certainty. Accurate assessments of free-running rhythms in blind children is imperative for treatment intervention to achieve entrainment. Melatonin treatment seems practical in totally blind children given the potential risks of chronic circadian desynchrony.

Research supported by grants from Northwest Health Foundation and the Medical Research Foundation of Oregon.

## 242.E

### RECOVERY AFTER SLEEP DEPRIVATION IN SCN-LESIONED RATS

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**Introduction:** In an ongoing series of studies of baseline and post-deprivation recovery sleep, we have described a number of age-related changes. During baseline sleep, for instance, older rats manifest reduced high voltage NREM sleep ("HS2"), EEG delta power, and duration of sleep bouts (1). Following 24 hours of sleep deprivation, the older animals had smaller increases in total sleep as well as NREM and REM sleep; moreover the older animals, while starting with lower baseline HS2, had a significant rebound increase in this stage, while the younger animals did not (2). While the cause of these differences has not been established, one possibility is that they result from age-related changes in circadian regulatory mechanisms. In the current study, we have begun to explore this possibility by examining baseline and recovery sleep in young, "middle aged" and older rats following SCN lesions.

**Methods:** The study involved 54 male Fisher rats in three age groups (3, 12, and 18 months); in each group, half received a radiofrequency lesion of the SCN, while the other half underwent a sham lesion procedure. They then were given a one week recovery period in chambers with a 12:12 L:D cycle, in which lights came on at 10:00 AM. Following confirmation of the success of the lesion as manifested by 72 hour motor activity recordings, they were given a 3 day acclimatization period in continuous dim light in the sleep recording chambers, and then had a 24 hour baseline sleep recording. After 24 hours of baseline sleep recordings, they underwent 24 hours of sleep deprivation using the disk-over-water technique, followed by a 24 hour recovery sleep recording. All recordings, and the sleep deprivation period, began at 10:00 AM. All lesions and sham-lesions were histologically confirmed at the completion of the study.

**Results:** An assessment of the amplitude of the sleep/wake circadian rhythm in the baseline recordings was carried out using 3 methods (cosine fit, the "A" statistic, and day/night ratio), and revealed greatly reduced amplitude in the SCN-lesioned animals ( $p < 0.001$ ). One of the methods (day/night ratio) showed a greater reduction in the 18 month old animals. Lesioned animals, independent of age, manifested a 4% increase in NREM sleep ( $p < 0.05$ ) and 15% increase in NREM delta power ( $p < 0.05$ ), as well as a 10% decrease in REM ( $p < 0.05$ ). SCN lesions had no significant effects on the amount of NREM or REM during recovery sleep. Delta EEG power in NREM sleep, however, was 85% higher in the lesioned animals ( $p < 0.01$ ).

**Conclusions:** We found little evidence, then, to indicate that age-related changes in SCN function might differentially affect the sleep of young, middle-aged and older rats. Our observations are consistent with the hypothesis that the SCN inhibits NREM sleep, though the effect was quantitatively small. The finding of increased EEG delta power during recovery sleep in the lesioned rats is also consistent with the view that the SCN influences homeostatic processes.

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Research supported by NIH grants 2P01 AG 11412-03 and K07 HL03640.

## 243.E

### EXOGENOUS MELATONIN SHIFTS DIM LIGHT MELATONIN ONSET IN POST-TRAUMATIC DELAYED SLEEP PHASE SYNDROME

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**Introduction:** Circadian rhythm sleep disorders may occur after traumatic brain injury<sup>1</sup>. Here we present a case of a 44-year-old man who developed a prominent delayed sleep phase syndrome (DSPS) consequent on his motor vehicle accident. He suffered what appeared to be only minor injuries, including injuries to a soft tissue of his head, bruises and cuts. He also lost his consciousness for a few minutes and suffered an anterograde amnesia. He did not have any further neurological sequela. However shortly after the accident the patient developed severe sleep onset insomnia (inability to fall asleep before 04:00 h), frequent nightmares, and headaches. The diagnosis of DSPS was established based on several physiological markers of the sleep-wake rhythm: Dim Light Melatonin Onset (DLMO) test<sup>2</sup> using enzyme linked immunosorbent assays (ELISA), wrist actigraphy, sleep log and polysomnographic parameters of sleep architecture.

**Methods:** The patient underwent two overnight sleep studies. On the first night the patient was allowed to go to bed whenever he wanted and to sleep as much as he could. The patient arrived in the sleep clinic at 18:30 h and saliva samples were obtained at hourly intervals from 19:00 to 03:00 h. Ambient light intensity was controlled and did not exceed 15 lx. On the second night, a 24:00 to 08:00 sleep period was imposed.

**Results:** DLMO test revealed significant delay in the endogenous melatonin secretion. DLMO occurred at 23:00 hours. The polysomnographic studies also showed a convincing evidence of delayed sleep phase syndrome. There was normal sleep onset latency (12 minutes), normal sleep duration (7.1 h) and normal sleep efficiency (91.4%) on the night when the patient selected bedtime and rise time. Sleep onset latency was 78 minutes on the second night when conventional bedtime was imposed. Frequent arousals, low sleep efficiency (65.4%) and short sleep duration (5.2 h) were observed on this occasion. Administration of exogenous melatonin 5 mg (Penn Pharmaceutical Ltd) at 18:00 h for 28 days normalised sleep-wake cycle as was evidenced by wrist actigraphy and sleep log. Post-treatment DLMO occurred at 21:00 h.

**Conclusions:** The learning point of this case is that the DLMO assays can be used as a precise tool to assess the phase of the circadian pacemaker in patients suspected of having a chrono-

biologic component to their sleep disorder. The abnormal timing of DLMO can also provide an indication for the optimal timing of treatment (medication administration, exposure to light).

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## 244.E

### CIRCADIAN RHYTHM OF SLEEPINESS AND THE RISK OF HIGHWAY VEHICLE ACCIDENTS

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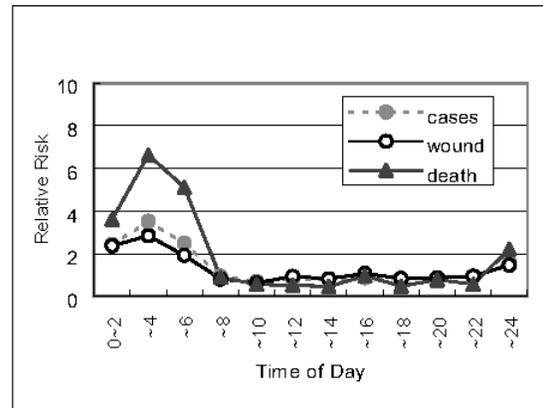
**Introduction:** Due to the multiple factors involved in most of the vehicle accidents, it is extremely difficult to sort out the influence of sleepiness on accidents. In the absence of good data on the 'sleepiness-caused' vehicle accidents in Korea, the present study evaluates the impact of sleepiness indirectly by analyzing the hourly distribution of the Korean highway vehicle accidents adjusted to traffic volume in the light of the circadian rhythm of sleepiness.

**Methods:** The database of vehicle accidents and traffic volume on the Korean highway network during the last two years(1999-2000) was provided by the Korean Road Traffic Safety Authority and the Korea Highway Corporation. The present analysis used both accidents and traffic volume data averaged for weekdays and every 2-hour intervals. To find out how the rate of accidents adjusted to traffic volume is different depending on the time of the day, the relative risks of the 12 intervals were examined by ANOVA. The relative risk (relative probability of accidents corrected for traffic volume) of every 2-hours in the highway vehicle accidents over the 24 hours was calculated as follows: % of accidents during the 2-hour interval out of total accidents for 24 hours divided by % of traffic volume during the 2-hour interval out of total traffic volume for 24 hours.

**Results:** It was found that the relative risks (for all the 3 categories: # of cases, # of the wounded, # of deaths) in the hours of 00-06h and 22-24h were significantly higher than those in the rest of the hours, being the highest during the 02-04h, then 04-06h / 00-02h, and 22-24h, in order (Fig. 1). It is noticeable that in the category of # deaths, the relative risk of 02-04h(the peak) is more than 14 times higher than that of 12-14h(the trough). The pattern reveals the rapid increase in accidents in correspondence with high sleep propensity levels occurring at night, especially in the early morning hours.

Figure 1

Time distribution of relative risk over the 24 hours



**Conclusions:** The hourly distribution of relative risk in the present study closely corresponds with the circadian rhythm of sleep (sleepiness/alertness) (Carskadon & Dement, 1992; Mitler, 1991), thereby confirming the influence of sleepiness on vehicle accidents. Most important, the present findings, based on the total accidents (not on sleep-ascribed accidents but on accidents of all causes), are almost identical to the other findings on the sleep-ascribed vehicle accidents (Garbarino et al., 2001; Horne & Reyne, 2001) and the finding on all the accidents except alcohol-related ones(Akerstedt, Kecklund, Horte, 2001). The present research demonstrates that sleepiness is a very important contributing factor in Korean highway vehicle accidents in the presence of many other contributing factors(e.g., road conditions, weather, vehicle conditions) thought to be randomly or evenly distributed.

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## 245.E

### CAN IMPROVED DAYTIME SLEEP WITH TEMAZEPAM HELP OVERCOME THE CIRCADIAN PERFORMANCE TROUGH DURING A NIGHT SHIFT?

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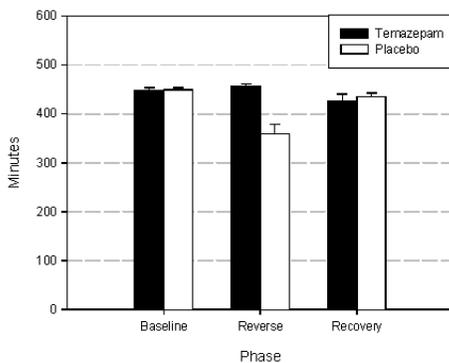
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**Introduction:** It has been well-established that performance during the night is lower than daytime performance. The reasons for this drop in performance are generally two-fold: the circadian drive for sleep and the sleep loss experienced from poor daytime sleep. Some studies have found that an increase in daytime sleep due to administration of a hypnotic does not improve nighttime performance while another study indicated that improved daytime sleep did lead to improved nighttime

performance<sup>2</sup>. The difference in the results of these studies may be due to the hypnotics used (0.5 mg triazolam versus 20 mg temazepam) and the performance measured (assembly line task versus attention task). In order to determine improved performance, the task must show no learning effects and be sensitive to small decreases in sleep length. One task which meets both these criteria is the Psychomotor Vigilance Task (PVT) <sup>3</sup>. To examine performance after daytime sleep with a hypnotic, the present study tested subjects over time with the PVT.

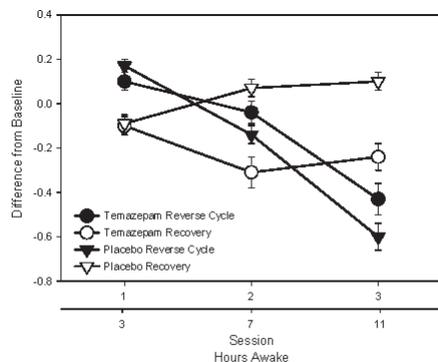
**Methods:** Two groups of eight subjects each were tested over three baseline days, three night shifts, and three recovery days, administering either 30mg temazepam or placebo before daytime sleep. Polysomnographs were recorded during each sleep period. The PVT was administered three times within each shift. Due to a difference between the groups during baseline, the last three baseline sessions were averaged and subtracted from each subsequent session's score to create a difference score. Only the last two days of each shift were used for analysis in order to avoid the confound of complete sleep deprivation which occurred before the first night shift and the first recovery day.

Figure 1



Minutes asleep by drug group and shift.

Figure 2



Reciprocal reaction time from the PVT by drug group, shift, and session.

**Results:** Results from the analysis of variance indicated that daytime sleep for the temazepam group was significantly

longer than for the placebo group ( $F(1,8)=11.82, p=.0089$ ; only 10 subjects' data were used). The temazepam group slept on average 7.6 hours during the two daytime sleep periods, 8 minutes longer than baseline. The placebo group slept on average 6.0 hours during the two daytime sleep periods, 90 minutes less than baseline. Recovery sleep for both groups was near baseline levels. (Figure 1) An interaction among phase of shift, session, and drug group occurred for PVT reaction time ( $F(2,28)=3.34, p=.0501$ ). No difference between the two groups was apparent during the first and second sessions, but the placebo group showed significantly longer reaction times during the third session compared to the first and second sessions, whereas there was no difference in the sessions for the temazepam group (Figure 2).

**Conclusions:** Daytime sleep for the temazepam group was approximately 1.5 hours longer than daytime sleep for the placebo group. Although the circadian trough in performance was apparent at 0300 for the placebo group, this effect was smaller for the temazepam group. This study indicates that extending daytime sleep with a hypnotic can lead to better reaction time. The discrepancy in these results compared to other studies may be the difference in the sensitivity to sleep deprivation of the task used.

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**246.E**

**DECREASED HUMAN CIRCADIAN PACEMAKER INFLUENCE AFTER 100 DAYS IN SPACE: A CASE STUDY**

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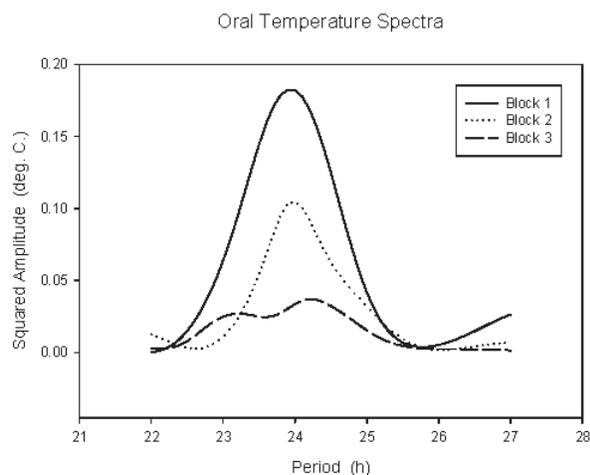
**Introduction:** It is not clear whether the human Endogenous Circadian Pacemaker (ECP) still functions well when removed from the gravity and natural time cues of Earth. We studied an astronaut who lived aboard Space Station Mir for almost five months, testing the hypothesis that the behavior and/or influence of his ECP would change as the mission progressed, and that these changes would affect his sleep.

**Methods:** A fit and healthy 42 y.o. male astronaut (JML) lived aboard Mir from January 15, 1997 to May 22, 1997. Three measurement blocks were recorded, each almost two weeks in duration: Block 1 (Days 37-50), Block 2 (Days 79-91), and Block 3 (Days 110-122). The crew's activities were scheduled

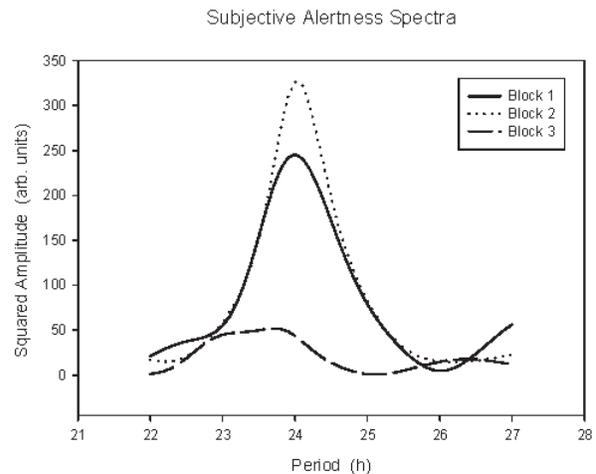
according to Moscow Time, and the subject's habitual bedtimes were fairly standard (bedtime: mean= 23:25, sd=29 mins.; waketime: mean= 08:06, sd =49 mins.). During each measurement block the subject was required to measure his oral temperature and rate his subjective alertness five times per day (approximate times: 09:20, 12:30, 15:30, 18:30, and 21:20). Oral temperatures were measured using a digital thermometer placed under the tongue for a timed 60 seconds. Subjective alertness was assessed using four visual analogue scales, yielding a single "global vigor" score between 0 and 100. A single sinusoid was fitted by least-squares to the entire time series iteratively at period lengths ranging from 22h to 27h in steps of 0.1h. Plotting squared amplitude of sinusoid against period length then gave the equivalent of a power frequency spectrum for the two variables (alertness and temperature). During each "morning" during a measurement block, within 1h of waking, the subject completed the Pittsburgh Sleep Diary, yielding measures of the times of bedtime and waking, the estimated duration of unwanted wakefulness, and the amount and rated quality of the sleep obtained the preceding "night."

**Results:** "Power frequency spectra" for alertness and temperature rhythms are plotted in Figure 1. There was a clear flattening of the spectra in Block 3. Amplitude estimates at 24h were lower in Block 3 for both temperature ( $0.43 \pm 0.21$ ,  $0.32 \pm 0.13$ ,  $0.18 \pm 0.11$  deg. C.) and alertness ( $15.7 \pm 6.1$ ,  $18.1 \pm 5.2$ ,  $6.6 \pm 4.6$  arbitrary units). In both measures, the Block 3 amplitude was outside the 95% confidence interval for the amplitude estimates from both Blocks 1 and 2. These findings were confirmed by an analytic technique which made no assumptions about the shape of the underlying rhythm. Diary measures revealed a reliable decrease in the estimated amount of sleep obtained in Block 3 (430 mins., 487 mins., 408 mins.,  $F(2,31)=5.43$ ,  $p<0.01$ ), resulting mostly from increases in the estimated number of minutes of wakefulness after sleep onset (39 mins., 34 mins., 53 mins.,  $F(2,31)=3.79$ ,  $p<0.05$ ).

**Figure 1**



**Figure 2**



**Conclusions:** After about three months in space there may be a failure of the human ECP to strongly drive a 24h circadian rhythm. This lack of ECP influence could lead to sleep problems in those attempting to live on a rigid 24h work/rest routine during prolonged missions.

**Research supported by NAS9-19407, NAG9-1036, NAG9-1234 (NASA), AG 13396 and AG 15136 (NIA).**

## 247.E

### DELAYED SLEEP PHASE SYNDROME IN ADOLESCENTS: PERSPECTIVES ON PSYCHOSOCIAL OUTCOMES

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**Introduction:** Delayed Sleep Phase Syndrome (DSPS) is a circadian rhythm sleep disorder that results from an aberration in the circadian pacemaker, the suprachiasmatic nuclei. It is characterized by sleep onset and wake times that are intractably later than desired, with an inability to advance the sleep phase to earlier hours. It has been estimated that 2-10% of sleep center patients have a diagnosis of DSPS and the estimated prevalence in adolescents is 7%. Patients with DSPS have been reported to experience psychological, social, and occupational dysfunction. Better longitudinal understanding of these parameters in DSPS patients is needed.

**Methods:** A retrospective computerized search was performed on all Mayo Clinic charts from '94-'00 of persons up to 18 years of age. Demographic characteristics including gender, age of diagnosis with DSPS, concurrent psychiatric diagnoses, and geographic residence were all assessed. All patients received evaluations at the Mayo Clinic Sleep Disorder Center. A standardized questionnaire is being sent to all patients and also a control group to assess parameters of psychologic and social adaptation, degree of DSPS persistence, treatment types used, compliance with treatment, and benefits of treatment.

**Results:** Ninety-two cases of DSPS were identified. Age at

diagnosis ranged from 4 to 18 years, with a mean of 16 years. Current age range is between 7-26 years. Thirty-nine were female (42%) and 53 were male (58%). Local geographic representation was 34.8%, 39.1% regional, and 26.1% national. Seventy patients had psychiatric care at Mayo Clinic (76%) which included 30 with depressive disorders, 18 with behavioral/emotional disturbances, 15 with ADD/ADHD, 12 with learning disorders, 9 with anxiety disorders, 9 with chemical abuse/dependency issues. It is unknown whether psychiatric care was received from institutions other than at Mayo Clinic.

Figure 1

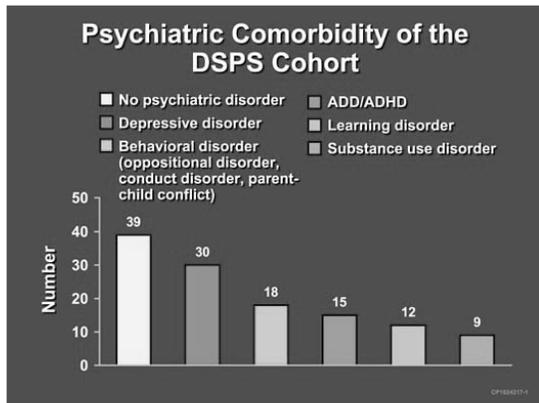
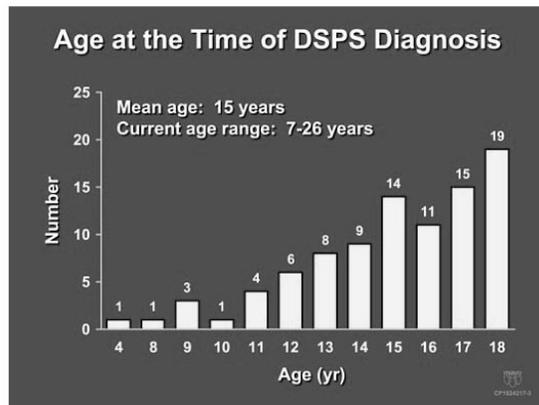


Figure 2



**Conclusions:** DSPS appears to be a relatively common sleep disorder particularly in adolescents. It appears to have an approximate equal gender distribution. Based on the literature and this initial search, persons with DSPS appear to have a significantly increased likelihood of psychiatric complexity/comorbidity. Social adaptation and functioning appear to be negatively effected by the existence of DSPS. There is a paucity of longitudinal psychological and social follow-up in persons diagnosed with DSPS. Future goals will include formal longitudinal follow-up with a social outcome questionnaire. The hypothesis that DSPS is predictive of poorer psychosocial adaptation when compared with persons without DSPS will be examined. This questionnaire will identify diverse parameters of social adaptation. Analysis of the degree

to which the persistence of DSPS symptoms correlates with psychosocial adaptation will be performed. Longitudinal follow-up will allow identification of subjectively reported efficacious treatment modalities. Adherence to various treatment modalities will also be analyzed.

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**248.E**

**RAPID AND PERSISTENT PHASE ADVANCE OF HUMAN SLEEP AND BIOLOGICAL RHYTHMS BY MELATONIN IN A 16-H NIGHT/8-H DAY PROTOCOL**

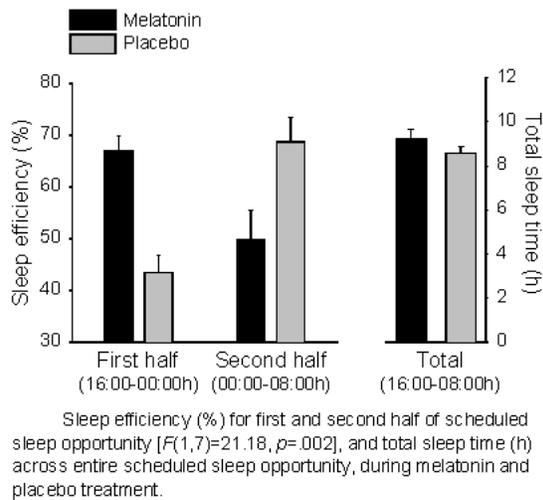
Rajaratnam SM,<sup>1</sup> Dijk DJ,<sup>1</sup> Middleton B,<sup>1</sup> Stone B,<sup>1</sup> Arendt J<sup>2</sup>

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**Introduction:** Prolonged exposure (approx. 4 weeks) to a short day/long night light/dark cycle alters the profile of many circadian and sleep parameters in humans. Timed melatonin administration phase-shifts human circadian rhythms and induces sleep. We examined the effects of melatonin administration on human sleep and circadian rhythms during a 9-day, 16-h night/8-h day protocol.

**Methods:** Eight healthy male subjects (BMI 23.8 ± 3.0; age 24.4 ± 4.4y) attended two 14-day study legs. During each leg either melatonin (1.5mg, surge-sustained release, Penn Pharmaceuticals Ltd) or placebo was orally administered. The study was carried out in a light proof, sound attenuated, temperature- and humidity-controlled facility. Before the study, subjects were instructed to abstain from caffeine for 1 week and maintained a regular sleep-wake cycle (sleep time 23:00-07:00h ± 30 mins) for at least 10 days. After a baseline sleep opportunity (23:00-07:15h, in very dim light <5lux), and a 29-h constant routine (CR, <5lux), an extended sleep protocol (L:D 8:16) was imposed for 9 days (sleep opportunity:16:00-08:00h, <5lux; wake time: 08:00-16:00h, <300lux). For the first 8 days of this protocol, melatonin or placebo was administered in a randomised, double-blind, cross-over design at the start of the scheduled sleep opportunity (16:00h, D3-D10). Subjects were instructed to remain in bed during all scheduled sleep opportunities, and did not have access to recreational material such as books and television. On D11, all subjects took placebo at 16:00h (single-blind). A second 29-h CR (<5lux) was imposed after the extended sleep protocol, followed by a 16-h recovery sleep opportunity. Measurements taken during the study included polysomnography (PSG), core body temperature (CBT), actigraphy/light, plasma melatonin, cortisol and other hormones, subjective mood, alertness and performance.

Figure 1



**Results:** Melatonin administration at 16:00h resulted in elevated plasma melatonin levels during the entire 16-h sleep opportunity. Mean sleep efficiency (PSG) in the first half of the sleep opportunity, calculated across 7 days of melatonin treatment (D4-D10, 16:00-00:00h) was significantly and markedly higher compared to placebo [Fig. 1, effect size ( $\eta_s p s^2$ )=0.842]. In contrast, in the second half of the sleep opportunity, sleep efficiency was significantly lower during melatonin treatment ( $\eta_s p s^2$ =0.560). Total sleep time during the entire 16-h sleep opportunity was not significantly different between the conditions (Fig. 1). After melatonin treatment was stopped (D11), sleep timing remained phase advanced relative to placebo. Exposure to the extended sleep protocol phase advanced plasma melatonin and cortisol rhythms, assessed during CRs in the placebo condition. In the melatonin condition, phase advances in plasma melatonin, cortisol and CBT were substantially larger than in the placebo condition.

**Conclusions:** Artificially elevated plasma melatonin levels throughout a 16-h sleep opportunity phase advances circadian rhythms and leads to a rapid and persistent redistribution of sleep to the beginning of the sleep episode without an increase in sleep duration.

Research supported by Medical Research Council/Ministry of Defence Grant G9810584 and Stockrand Ltd (University of Surrey).

## 249.E

### CHARACTERIZATION OF A NON-24-HOUR SLEEP-WAKE SYNDROME AFTER TRAUMATIC BRAIN INJURY

Caliyurt O,<sup>1</sup> James FO,<sup>1</sup> Boivin DB<sup>1</sup>

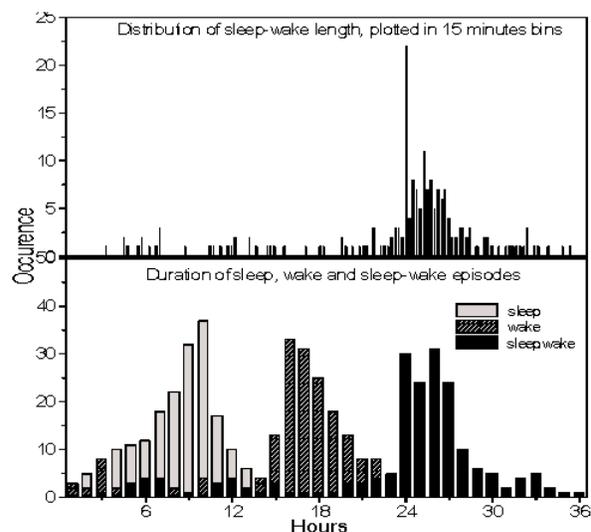
(1) Douglas Hospital Research Center, Department of Psychiatry, McGill University, Montreal, Qc, Canada,

**Introduction:** Sleep disturbances and insomnia occur frequently following traumatic brain injuries. Cases of sleep-wake cycle disturbances, particularly delayed sleep phase syndrome (DSPS), have been observed to occur after head or neck

injuries (1). In the present study, we report the case of a sighted woman who developed an inability to properly adjust to the 24-hour day after a car accident.

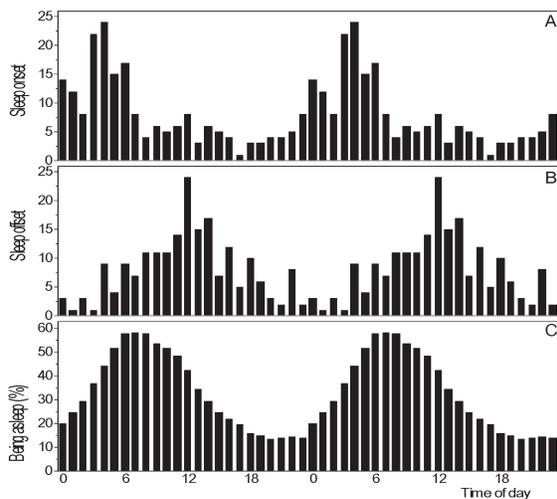
**Methods:** In March 2000, a 38 y.o woman was referred to our clinic by her neurologist because she developed an unusual sleep-wake pattern. The condition appeared several months after a 1991 car accident with resultant head trauma. She tried unsuccessfully to adopt a regular sleep schedule but would suffer from recurrent sleep disturbances that resulted in a worsening of her epileptic attacks. She therefore resigned herself to live on longer than 24-hour «days» and her epilepsy improved. The CT scan, MRI and ophthalmologic exams were normal. At the time of referral, she was taking Valproic Acid 375 mg four times a day for her epilepsy, morphine sulphate and dimenhydrinate as needed for her migraines. She kept a sleep diary that was confirmed by wrist actigraphy (AW-64, Mini Mitter, Oregon, USA). Sleep onset and offset times were derived from the Sleepwatch software. Sleep episodes reported as naps by the patient were excluded from the analysis. If a wake episode between two consecutive sleep episodes was shorter than 30 minutes, the sleep episodes were merged. Descriptive statistics were used to determine the duration of her sleep-wake cycles.

Figure 1



**Results:** The sleep-wake cycle of the patient was found to consist of two main daily components. Sleep-wake cycles longer than 24 hours were observed (mean  $\pm$  SD, 25:05  $\pm$  2:23) and resulted in an hypernycthemeral sleep-wake disorder. The sleep-wake ratio of these days were similar to that of healthy subjects. In addition, 12.5% of sleep-wake episodes showed relative coordination to the 24 hour day (Fig.1). A 24-hour pattern was observable in times of sleep onset and offset and these occurred most frequently around 04:00 and 12:00, respectively. The likelihood of being asleep was lowest in the evening and highest at the end of the night, as observed for patients with DSPS (Fig.2). A number of short sleep episodes followed by short wake episodes were also noticed.

Figure 2



Frequency of temporal distribution of sleep onset (A) and offset (B). Probability of being asleep at a given time of day is shown in C.

**Conclusions:** In this patient, we documented a longer than-24-hour sleep-wake schedule. Her relative coordination to the 24-hour day suggests that environmental synchronizers exert an influence too weak to entrain the patient sleep-wake cycle to the 24-hour day. A daily pattern of sleep onset and offset times consistent with DSPS was also observed. This association is consistent with the prior observation that DSPS might be a predisposing condition for the hypernycthemeral sleep-wake syndrome in humans (2).

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## 250.E

### NONREMS PRESSURE IN DAY-AND NIGHTTIME SLEEP IN WINTER DEPRESSION

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**Introduction:** Seasonal affective disorder (SAD) is characterized by atypical depressive symptoms such as fatigue, daytime hypersomnolence, and difficulties waking up in the morning. It is important to know whether subjective ratings of sleep quality can reflect abnormalities of EEG sleep, and what are the objectively measured mean levels and 24-hr variations of sleep propensity and nonREMS pressure in SAD.

**Methods:** The polysomnographic records were obtained in summer (6 patients with SAD, 6 controls), and in winter before (n=8 and 5) and after a week of 2-hr bright light treat-

ment (LT) in the evening (n=7 and 4). After an adaptation night, EEG-sleep parameters were measured during normally scheduled night sleep (23:00-8:00) and then during multiple sleep latency test in daytime (10:00, 12:00, 14:00, 16:00, 18:00) and nighttime (23:00, 1:00, 3:00, 5:00). Clinical symptoms were rated using the 21-item Hamilton Depression Rating Scale (HDRS) and 29-item SIGH-SAD (HDRS plus 8-item Addendum for the atypical depressive symptoms). To self-assess subjective vigilance after all night sleep and before every 20-min sleep attempt, the subjects used three subscales of the so-called WAM-Test (Well-being, Activity, Mood). Each subscale consists of 10 word pairs with a 7-point response scale printed between each pair of words.

**Results:** The comparison of night sleep EEG in patients and controls provides evidence of an enhanced total sleep time (TST) in SAD in winter ( $p<0.05$ ) and summer ( $p<0.1$ ). The percentage of slow-wave sleep (SWS) tended to be lower in patients than in controls before LT ( $p<0.1$ ). Moreover, in both seasons the declining trend of slow-wave activity (SWA) from the first to the last hour of night sleep was significantly steeper in controls compared to patients. It became steeper after LT in patients with good clinical response (n=4). The percentage of sleep stage 2 decreased in patients and increased in controls by LT ( $p<0.01$ ), while the percentages of SWS increased in patients and decreased in controls ( $p<0.01$ ). Clinical response to LT correlated positively with TST and negatively with SWS in pretreatment conditions. Neither before nor after LT patients differed from controls on mean level and circadian variations of sleep latency. The level of SWA in the first 8 min of non-REMS showed an increasing trend from morning sleep attempts to night sleep attempts. The extent of this buildup in sleep pressure was in the agreement with the quantitative predictions of the somnostat models<sup>1</sup>. The clinical response to light correlated significantly ( $p<0.05$ ) with the difference between daytime and nighttime WAM-scores: in good responders, the difference was low or negative before LT and it significantly increased following LT.

**Conclusions:** Earlier, very rapid buildup of sleep pressure during the first 10 hours of wakefulness was found in SAD compared to controls<sup>2, 3</sup>. Neither these reports of waking EEG nor our recent data on the first 8 min of sleep EEG suggest the pathological changes in time course of sleep propensity in SAD throughout afternoon, evening and nighttime wakefulness. We, however, found that all-night sleep in SAD is characterized by deficits of SWS and atypically slow decline of SWA. Besides, when light succeeds in inducing good clinical response, some of sleep the EEG characteristics improve.

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251.E

**FAILURE TO IDENTIFY PUBERTALLY-MEDIATED MELATONIN SENSITIVITY TO LIGHT IN ADOLESCENTS**

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**Introduction:** We have tested the hypothesis that the phase delay of sleep commonly observed in adolescent development is related to changes in sensitivity of the circadian timing system to light signals. Suppression of melatonin secretion to light was evaluated as a preliminary to assessing phase-shifting effects of light. Specifically, we tested whether more mature adolescents suppress melatonin to lower levels of light during the phase delaying portion of the phase response curve (evening hours) or require greater light levels to suppress melatonin during the phase advancing (late-night/early-morning) portion of the phase response curve(1).

**Methods:** Healthy children with relatively regular sleep patterns, screened for medical and psychological problems, received brief physical examinations and Tanner staging (2). Thirty-two pre/early pubertal participants (Tanner pubic hair stages 1 or 2; ages 9.1 to 13.9 years (11 girls)) and 34 mid/late pubertal participants (Tanner stages 3-5; ages 10.0 to 15.9 (17 girls)) completed the study. Condition assignment (evening (n=40) vs. morning (n=26) light) was based upon participant availability. After >= 10 consecutive nights sleeping at home while wearing eye shades from 2100 to 0700 (confirmed by actigraphy), participants received 1-hr testing at 4 light levels on consecutive nights: ~0.1 lux, 15 lux, 150 lux, and 500 lux, respectively. Saliva was collected at 30-minute intervals, frozen, and melatonin assayed subsequently. Room lights were off (0 lux) for sleep or dimmed (~0.1 lux) while awake from 2100 to 0730 during in-lab nights, with sleep scheduled as shown in Figure 1. Light administration for the evening group occurred from 2300 to midnight and for the morning group from 0300 to 0400. The ~0.1 lux level was included as a control condition.

Figure 1

Sleep and Light Schedules

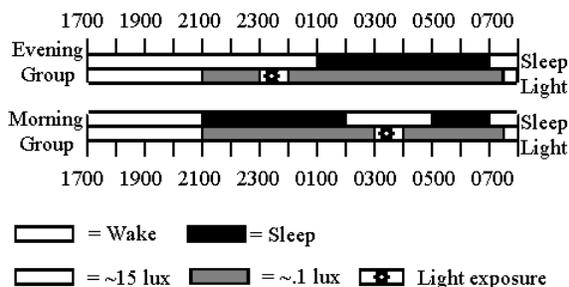


Table 1

Mean Melatonin as a Percentage of Two Pre-Light Samples. Average for Morning (AM) and Evening (PM) Light Exposure				
	.1 lux <sup>a</sup>	15 lux <sup>b</sup>	150 lux <sup>c</sup>	500 lux <sup>d</sup>
<b>AM Pre/Early Pubertal</b>				
30-minutes of light	97 <sup>b,c,d</sup>	82 <sup>a,c,d</sup>	62 <sup>a,b</sup>	53 <sup>a,b</sup>
60 minutes of light	89 <sup>c,d</sup>	76 <sup>c,d</sup>	37 <sup>a,b</sup>	31 <sup>a,b</sup>
<b>AM Mid/Late Pubertal</b>				
30-minutes of light	96 <sup>c,d</sup>	86 <sup>c,d</sup>	62 <sup>a,b</sup>	62 <sup>a,b</sup>
60 minutes of light	89 <sup>c,d</sup>	77 <sup>c,d</sup>	42 <sup>a,b</sup>	36 <sup>a,b</sup>
<b>PM Pre/Early Pubertal</b>				
30-minutes of light	118 <sup>c,d</sup>	113 <sup>c,d</sup>	84 <sup>a,b</sup>	78 <sup>a,b</sup>
60 minutes of light	122 <sup>c,d</sup>	120 <sup>c,d</sup>	67 <sup>a,b,d</sup>	53 <sup>a,b,c</sup>
<b>PM Mid/Late Pubertal</b>				
30-minutes of light	107 <sup>c,d</sup>	103 <sup>c,d</sup>	90 <sup>a,b</sup>	78 <sup>a,b</sup>
60 minutes of light	108 <sup>c,d</sup>	102 <sup>c,d</sup>	77 <sup>a,b</sup>	61 <sup>a,b</sup>

Post-hoc test differences (p≤.006) shown in superscripts referring to light levels for light exposure times within group.

**Results:** Melatonin data were converted to percentages based upon the mean of each subjects' two samples immediately before light exposure. MANOVA within condition showed main effects for light level but no interaction with pubertal group. Planned comparisons within condition and Tanner stage were performed between light levels for samples occurring at 30 and 60 minutes of light exposure and are shown in Table 1. Suppression to 15 lux was found only for pre/early pubertal participants in the Morning light exposure group; otherwise, significant differences were found for 150 and 500 lux versus .1 or 15 lux in the morning and evening and for both pubertal groups.

**Conclusions:** These data indicate that pre/early and mid/late pubertal adolescents do not show differential sensitivity for melatonin suppression at the levels of light tested in this experiment. Although unlikely it remains possible that sensitivity to light's phase shifting effects differs pubertally. We plan to examine this issue in subsequent studies along with whether developmental changes in other processes, such as sleep/wake homeostasis and/or phase angle of entrainment of sleep to the circadian system may mediate pubertal phase delay.

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Research supported by MH52415 and MH01358.

252.E

**RELATIONSHIP BETWEEN INFANTS' QUIET SLEEP RESPIRATION RATES AND BLOOD OXYGENATION: IMPLICATIONS FOR COGNITIVE DEVELOPMENT**

Montgomery-Downs HE,<sup>1</sup> Thoman EB<sup>1</sup>

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**Introduction:** In a previous study (1) we found a significant,

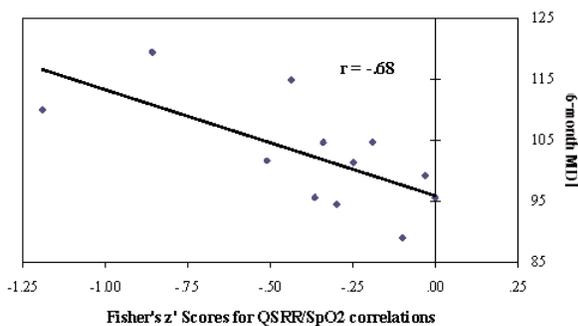
negative relationship between infants' Quiet Sleep respiration rates (QSRR) on postnatal day 2 and 6 months with their mental scores at 6 months and 1 year. Because the purpose of involuntary respiration during Quiet Sleep (QS) is the maintenance of blood gas homeostasis, the two goals of the present study of infants over the first 6 postnatal months were: 1) to measure changes over age in, and relationships between, infants' QSRR and their blood oxygenation (SpO<sub>2</sub>); and 2) to measure the relationship between infants' SpO<sub>2</sub> during QS at successive ages and their mental development assessed at 6 months.

**Methods:** Sleep and SpO<sub>2</sub> were longitudinally recorded in 12 healthy infants at 2 days, 2, 6, and 12 weeks, and 6 months. The all-night sleep recordings were made non-intrusively using the Motility Monitoring System (2). From these recordings, average QSRR was calculated from 1-minute counts during the first, middle, and last 5-minute periods of each QS bout  $\geq 15$  minutes, SpO<sub>2</sub> during QS was simultaneously recorded, averaged over 2-second periods, then averaged over the periods that were synchronous with the respiration counts. At 6 months the Bayley Scales of Mental and Motor Development was administered in the subjects' homes. For each infant, QSRR and SpO<sub>2</sub> were correlated at each age, and these r-values were converted to Fisher z' scores in order to analyze the correlation between these relationships and the infants' mental scores.

**Results:** QSRR decreased linearly after the Day 2 recording; SpO<sub>2</sub> levels showed a linear increase after Week 2 with higher values from 6 Weeks to 6 Months than on Day 2 and Week 2. As expected, QSRR and SpO<sub>2</sub> were negatively correlated within individuals at each age. At Week 12, the correlation (using Fisher's z' scores) between QSRR and SpO<sub>2</sub> was significantly correlated with 6-month MDI ( $r = -.68, p < .05$ ). Thus, the more highly related (negatively) QSRR and SpO<sub>2</sub> are, the higher the infants' mental development scores.

**Figure 1**

**Relationship of Week 12 within-person QSRR/SpO<sub>2</sub> correlations (Fisher's z' scores) to 6-Month Mental Scores**



**Conclusions:** The results are consistent with and extend our previous study (1), and they suggest a developmental advantage on the part of infants with lower respiration rates in association with higher oxygenation levels during QS. While early sleep characteristics have been linked to mental development (3), our results emphasize that respiration in association with oxygenation during sleep, plays a significant role in the com-

plex neural systems involved in cognitive development.

**References:**

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**253.G**

**CHASING THE SLEEP-ADHD LINK: WHAT DOES "NORMAL" MEAN?**

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**Introduction:** Despite a wealth of clinical observations and the obvious connection between daytime sleepiness and attention problems, there has been very little systematic objective study of sleep and ADHD until recently (Chervin et al., 1997; Picchiatti et al., 1998; Harnish et al., 2001). Inconsistency in the diagnostic criteria used to define ADHD samples makes it difficult to compare and synthesize findings across studies. Further, there is lack of consensus on what constitutes "normal" sleep in children and how to measure it. The following outlines our struggle to address these difficulties in a pilot study.

**Methods:** Six boys, aged 8-10, were selected for study. Three were diagnosed with ADHD by the co-director of a hyperactive children's clinic, based on a detailed history with parents, analysis of information from the Conners Parent and Teacher Behavior Rating Scales, consultation with the classroom teacher, performance on a continuous performance task, and a one-hour diagnostic interview with the child. The control children were volunteers who received the same screening as the ADHD children to rule out obvious ADHD symptomatology. The following assessments were conducted: 1. A brief sleep history and physical examination 2. The Pediatric Sleep Questionnaire, filled out by parents 3. A standard overnight polysomnogram (PSG) with simultaneous leg movement monitor (PAM-RL) and actigraph (Micro-Mini Motionlogger) recordings. 4. A standard Clinical Multiple Sleep Latency Test (MSLT) the day after the PSG. 5. The Psychomotor Vigilance Task (PVT) 6. Four consecutive in-home nights of sleep monitoring with the PAM-RL leg movement monitor and the Micro-Mini Motionlogger 7. A sleep log, filled out by the parents, for the four in-home assessment days

**Results:** 1. One of the boys with ADHD exhibited PLM's during more than a third of his sleep time, and had 16 PLM arousals. He also averaged 15 PLMs per night at home. He had seven errors on the PVT (the only child who did). 2. Two of the control boys had RDI's of > 5 events/hr. 3. MSLT scores for all

children were greater than 12 minutes. 4. Actigraphic scoring of sleep correlated well with PSG scoring. 5. Actigraphic readings at home averaged 94.5 minutes more total sleep than the lab PSG readings and 14.1% greater sleep efficiency.

**Conclusions:** Despite efforts to get distinct samples of ADHD and non-ADHD children, these subjects did not markedly differ on a vigilance task, and control subjects had more sleep problems than ADHD children. In-lab sleep was poorer than at home. These preliminary results suggest that it may be extremely difficult to select appropriate controls and procedures to test the link between sleep disorders and ADHD.

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The University of Kentucky Research Committee  
The University of Kentucky Psychiatry Department  
IM Systems, Inc.**

## 254.G

### MELATONIN PRODUCTION IN HEALTHY INFANTS: NORMAL VALUES AND SEASONAL VARIATIONS

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**Introduction:** In mammals, including humans, the nocturnal production of melatonin by the pineal gland reflects the photoperiod and plays a key role in seasonal acclimation. There is only little information on whether the development of melatonin production in infants is seasonally regulated. The evaluation of melatonin production in infants as a clinical and diagnostic marker of child development is, however, limited by the lack of a definition of the normal range of melatonin for a given age group. The urinary metabolite of melatonin, 6-sulphatoxymelatonin (6SMT), has been proven to be a very reliable index of melatonin production in humans including infants. The purpose of the present study was to establish the normal range of nocturnal 6SMT excretion in full term infants at 8 and 16 weeks of age using a large sample of healthy infants. In addition, we sought to reassess whether the production of melatonin in infants depends on season. This was achieved using a recently developed method for extraction of the urinary components from disposable diapers and for determination of 6SMT content.

**Methods:** 6SMT was assessed in urine samples extracted from disposable diapers removed from full-term, 8-week (n=317) and 16-week old (n=93) infants over the nocturnal period (19:00-08:00h). In addition, 6SMT was assessed in 8-week old (n=35) healthy infants over the entire 24-hr period. 6SMT was determined by an ELISA assay.

**Results:** 6SMT excretion at 8 weeks of age exhibited diurnal variations with (mean±SD) 61±18% of the daily production excreted during the nocturnal period regardless of season. The nocturnal 6SMT values in the entire cohort (at 8 as well as 16 weeks of age) were found to significantly depart from normal distribution (Kolmogorov-Smirnov test). A normal distribution was obtained using a natural base logarithmic (Ln) transformation of the data. The normal range (2.5-97.5 percentile of the Ln 6SMT excretion per night) was thus defined as 4.66-8.64 (106-5646 ng/night) for 8-weeks old and 5.19-9.67 (180-15820 ng/night) for 16-weeks old infants. A significant effect of the month of birth on 6SMT production at the age of 8 weeks was found (ANOVA, p<0.002) with maximal levels produced by infants born in June (summer solstice) and minimal excretion in infants born in December (winter solstice). Short photoperiod born infants excreted in average about 3 fold less 6SMT compared to long photoperiod born infants (t-test, p=0.01). The seasonal variations were no longer present at 16 weeks of age. No effect of breast-feeding at the time of sampling on seasonality of 6SMT was found.

**Conclusions:** Normal ranges for the nocturnal urinary excretion of 6SMT in full term infants at 8 and 16 weeks of age are defined. This enables the evaluation of nocturnal 6SMT excretion as a prognostic and diagnostic factor for child development. The strong effect of season on the normal excretion of nocturnal 6SMT in 8 but not 16 weeks of age suggests prenatal influence of the photoperiod on the ontogeny of melatonin.

## 255.G

### SLEEP HABITS OF INTERNATIONALLY ADOPTED CHILDREN

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**Introduction:** Recent research suggests that 25% of children who are adopted as babies are found to have at least one behavioral or mental health concern later in life. One area that has never been evaluated, however, is the sleep habits and sleep problems of adopted children. It was hypothesized that internationally adopted children would experience significantly more sleep disturbances immediately after adoption in comparison to a matched control group of biological children.

**Methods:** Parents of 17 internationally adopted children and 15 nonadopted children between 3 and 30 months (M = 11 months) participated in this study. All families were recruited from online list services, local daycares, and referrals from other families. Parents of the children completed a demographic and parental sleep questionnaire and the Sleep Habits Questionnaire (Acebo et al., 1994) that assesses sleep patterns (e.g., usual bedtime, total sleep time) as well as specific behaviors associated with sleep (e.g., night wakings). From this questionnaire, five subscales are derived: bedtime prob-

lems, sleep problems, night waking, morning problems, and daytime sleepiness. In addition, parents completed the Sleep Associations Scale that assesses co-sleeping and sleeping conditions. Adoptive families completed the questionnaires two weeks post-adoption.

**Results:** To assess differences in sleep patterns while controlling for the multiple comparisons, a one-way multivariate analysis of variance (MANOVA) was calculated with type of family (adopted vs. nonadopted) as the independent variable for each of the six sleep pattern items of the SHQ (bedtime, latency to sleep onset, total minutes of night wakings, total sleep time, total nap time, and morning wake time) and five sleep problem subscales. Overall, only one difference was found, with adopted children ( $M = 16.69$ ) experiencing a significantly longer duration of night wakings than nonadopted children ( $M = 6.80$ ),  $p < .05$ . No differences were found for the other five sleep pattern variables and the six sleep problem subscales,  $p > .05$ . Additionally, no differences in the parents' sleep were found.

**Conclusions:** The findings indicate that there is little effect of family status, adopted versus nonadopted, on young children's sleep patterns. Of 13 variables, differences were only found on one variable, duration of night wakings. It was surprising that the infants in this study who were two weeks post-adoption displayed similar sleep patterns and virtually no sleep problems when compared to nonadopted children. However, it would be beneficial for future research to investigate the sleep of internationally adopted children as they get older since previous research suggests that adopted children typically do not display difficulties in adjustment until they reach post-infancy or early childhood. Overall, this study is the first to examine sleep patterns and behaviors of internationally adopted infants with results indicating few, if any, sleep problems immediately post-adoption.

**256.G**  
**COSLEEPING IN THE UNITED STATES: PARENTS' PRACTICES AND OPINIONS FROM 1992-2001**

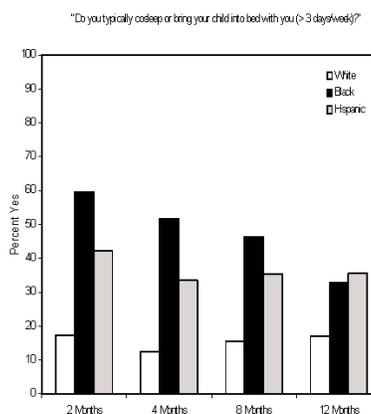
Borkowski MM,<sup>1</sup> Johnson CM,<sup>1</sup> Famoye F,<sup>1</sup> Hether NW<sup>1</sup>  
 (1) Central Michigan University, (2) Gerber Products Company,

**Introduction:** Cosleeping is a controversial issue because of perceived benefits such as promoting breastfeeding, reduction of SIDS, and fostering attachment as well as potential risks including overlayment, entrapment, and suffocation.(1,2,3) Differences in cosleeping rates of families from different ethnic backgrounds have been shown and some children who cosleep are more likely to have sleep problems.(2) This study investigated cosleeping practices and how they relate to sleeping problems in 3 cohorts within the United States.

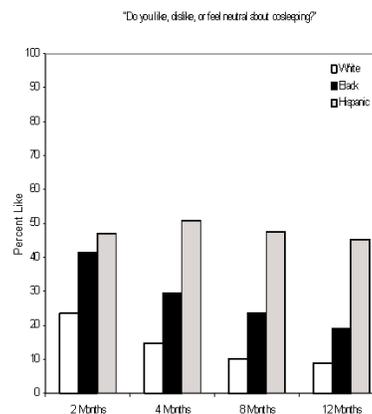
**Methods:** Three prospective longitudinal telephone surveys were conducted over 9 years. Respondents from 1992-1994 were mostly White parents ( $n=201$ ) from rural Michigan, 1994-1996 participants were primarily Black mothers ( $n=206$ ) from cities in the Midwest, and a national sample of Hispanic mothers ( $n=237$ ) was obtained from 2000-2001. Parents were called when their infants were 2-, 4-, 8-, and 12-months-old and asked if they typically coslept and their opinions of

cosleeping. Data on problems of settling and awakening were also collected. Repeated measure categorical data analysis was used to test for changes over time and to examine the differences between the three cohorts. Chi-square tests of independence were run to compare the three groups on their practices and opinions of cosleeping. Chi-square tests also were used to examine the relationships between cosleeping and the problems of awakening and settling.

**Figure 1**



**Figure 2**



**Results:** Cosleeping did not change over time within any of the three cohorts. White parents, however, coslept less ( $p < .0001$ ) and liked cosleeping less ( $p < .0001$ ) than Black or Hispanic mothers. In each cohort, cosleepers were not more likely to have settling problems. However, within the White cohort, cosleepers were more likely to have awakening problems ( $p < .05$ ).

**Conclusions:** Cosleeping practices and opinions differ significantly between White, Black, and Hispanic parents. While there was no apparent relationship between cosleeping and settling problems for Black, White, or Hispanic infants, White cosleeping infants had more night wakings that were viewed problematic by their parents.

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#### Research supported by Gerber Products Company

### 257.G

#### A CROSS-SECTIONAL SURVEY TO ASSESS THE PREVALENCE OF DISTURBED SLEEP AMONG CHILDREN WITH CYSTIC FIBROSIS

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**Introduction:** Owens and Chervin have established normative data for the prevalence of disturbed sleep among healthy pediatric populations.<sup>1,2</sup> Although cystic fibrosis (CF) children may be at increased risk of sleep disturbance due to 1) nocturnal hypoxemia 2) chronic cough 3) recurrent pain 4) sinusitis/polyposis (SP) related to CF, this has not previously been described in the medical literature. The objectives of this study were to 1) investigate the prevalence of disturbed sleep among CF children and 2) evaluate the relations between disturbed sleep and pulmonary function and SP.

**Methods:** The Children's Sleep Habit Questionnaire (CSHQ) validated by Owens et. al and the Pediatric Sleep Questionnaire (PSQ) validated by Chervin et. al were given to 107 subjects aged 4-18 years with a confirmed diagnosis of CF at the Cystic Fibrosis Center at Texas Children's Hospital. Parents completed the questionnaires for subjects less than 13 years of age whereas older subjects completed the questionnaires themselves. The control group was taken from the normative data described by Owens. Statistical analysis was done using SPSS 10.0. Means subscale scores were compared between CF and control groups using the student t-test. ANOVA was used for post hoc analysis evaluating the effects of pulmonary function and SP on subscale items.

**Results:** 95% of the CF group identified at least one sleep related problem compared to 14.9% of the control group. In the subscale items, subjects with CF demonstrated increased bedtime resistance ( $p=0.05$ ), delayed sleep onset ( $p=0.009$ ) and increased daytime sleepiness ( $p=0.03$ ) compared to controls. The CSHQ questionnaire did not reveal significant differences between CF and control groups for sleep disordered breathing; however data from the PSQ was strongly suggestive of significant differences. For 18.6% of CF subjects positive responses on the PSQ suggested the occurrence of sleep disordered breathing. Post hoc analysis of CHSQ subscale items did not identify SP as a contributing factor for sleep disturbances between CF subjects with or without SP. Post hoc analysis did suggest that significant differences exist between subjects with mild ( $FEV1 > 80\%$  predicted), moderate ( $FEV1$

60-80% predicted) and severe disease ( $FEV1 < 60\%$  predicted) for some subscale items related to increased daytime sleepiness ( $p=.012-.028$ ).

**Conclusions:** Children with CF have an increased incidence of disturbed sleep when compared to healthy children. This potentially has a negative impact on overall health, but may not be adequately assessed by CF caregivers. The CHSQ and PSQ are useful screening tools to identify children with disturbed sleep. Formal polysomnography testing maybe indicated for the confirmation of sleep disordered breathing in children with positive screen.

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### 258.G

#### ACTIGRAPHY MEASURES OF SLEEP IN CHILDREN WITH CANCER

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**Introduction:** Disturbed sleep in children with acute lymphoblastic leukemia (ALL), and of the families who care for them, has had little research. Between 53%<sup>1</sup> and 74%<sup>2</sup> children with cancer have reported sleep disturbances. Sleep deprivation was a common theme in a qualitative analysis of 31 parents.<sup>3</sup> The purpose of this report is to describe sleep disturbances in schoolage children during their chemotherapy. Data were from a pilot study that collected 72 hours of actigraph data on target child, primary caregiver, and sleep partner at home.

**Methods:** Nine families participated in the pilot study. A family was defined as the target child (patient), caregiver (usually mother), and sleep partner of caregiver. Children were recruited who were either newly diagnosed or in first remission undergoing chemotherapy for ALL. Study instruments were activity-sleep diaries for the target child, caregiver and adult sleep partner, as well as a medical record review. Objective sleep activity data for each family member was obtained using a wrist motion sensor on the non-wrist. Data for this analysis are from the 9 children's first 3 nights at home after receiving intravenous vincristine at a scheduled out-patient appointment. Data collection occurred on weekdays and weekends during summer months. Measures included: total sleep time (minutes from sleep start time to end of scored sleep), sleep after sleep onset (% of total sleep time), number of awakenings, and mean duration of wake episodes in minutes.

**Results:** Average age of the children in the sample was 11 years (7 to 16). There was no significant difference between night 1, 2 and 3. Average for 3 nights at home after chemotherapy for total sleep time was 482 minutes (SEM = 21.3; range

= 367 to 572), wake time averaged 64 minutes (SEM = 16.1; range = 2 to 131), wake after sleep onset was 11.5% (SEM = 2.9; range = 0 to 24)], number of awakenings averaged 19.8 (SEM = 4.1; range = 1 to 37), mean duration of wake episodes was 3.1 minutes (SEM = 0.6; range = 1 to 6).

**Conclusions:** These pilot data suggest that children during chemotherapy for ALL range between 6 and 10 hours of sleep with frequent awakenings. Because children are scheduled for chemotherapy Monday through Friday, the effect of chemotherapy on sleep activity includes weekends. Larger studies are needed to examine weekday versus weekend effects on both the child and the family members. Understanding the type and severity of sleep disturbance will contribute to the development of comprehensive interventions that can benefit both children with cancer and their families.

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Research supported by Lee, K. (2001). *Nursing Research Training in Symptom Management*. NIH/NINR, No. T32 NR07088

**259.G**

**SLEEP HABITS OF STUDENTS IN ELEMENTARY SCHOOLS, JUNIOR AND SENIOR HIGH SCHOOLS IN JAPAN.**

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**Introduction:** It is widely accepted that children in Japan spend shorter time in sleep than they need. The sleep habits of students have also been altered due to the habit of sitting up until late at night. However, epidemiological data on sleep habits among Japanese students are rather scarce (1,2). The objective of this paper is to study sleep habits and related problems among children in elementary schools, students in junior and senior high schools in Akita Prefecture.

**Methods:** A self-rated sleep habit questionnaire (SHQ) was given to 658 schoolchildren in 25 elementary schools (age10), 803 students in 24 junior high schools (age13), and 705 students in 18 senior high schools (age16) randomly selected in Akita Prefecture. The survey was carried out at the time of regular medical checkup in their schools. The SHQ was a short version of the questionnaires designed by Hori et al. (3). Those who replied with effective answer to SHQ were: 578 (87.8%) schoolchildren in elementary schools, 495 (61.6%) students in

junior high schools, and 577 (81.8%) students in senior high schools.

**Results:** The schoolchildren in elementary schools spend about 9h for sleep, and there was no remarkable difference of their sleeping habit between weekdays and holidays. Students in junior and senior high school spend 7h38m and 6h58m in sleep on weekday respectively (Table1). The difference of sleep time between weekday and weekend were over 80m in them. Those who replied that they slept too short on weekdays were: 124 (21.5%) among schoolchildren, 200 (40.4%) among students of junior high schools, and 303 (52.5%) among students of senior high schools. When those who slept shorter than 6h a day were defined as “short sleepers”, and those who slept for 9h or longer are defined as “long sleepers”, the short sleepers were 3 (0.5%), 34 (6.9%) and 106 (18.4%) respectively, and the “long sleepers” were 330 (57.1%), 48 (19.7%) and 30 (5.2%) respectively. Among “short sleepers”, those who replied that they had sufficient time for sleep, i.e. those who may be regarded as “true short time sleepers”, were 2 (0.3%), 8 (1.6%) and 14 (2.4%) respectively. Among “long sleeper”, 45 (7.8%) in primary school, 8 (1.6%) in junior high and 8 (1.6%) in senior high school answered that their sleep were short or too short. Those who replied that they had taken afternoon naps at home twice or more per week were 31 (5.4%), 53 (10.7%), and 114 (19.8%) respectively. Those who nodded off during classes twice or more per week were 45 (7.8%), 93 (18.8%), and 251 (43.5%) respectively.

**Table 1**

Sleep time of weekdays and weekends, and discrepancy of sleep time

	Elementary	Junior High	Senior High
	Schools	Schools	Schools
sleep time			
weekdays	8:54	7:38	6:58
weekends	9:11	8:39	8:25
discrepancy	16 m	61 m	87 m
subjective sleep quantity			
too short	21.5 %	40.4 %	52.5 %
short	42.6 %	41 %	35.2 %
enough / too long	35.8 %	18.6 %	12 %
nodding off during			
classes twice or more	7.8 %	18.8 %	43.5 %

**Conclusions:** The results of the present study reveal that schoolchildren in elementary schools in Akita Prefecture seem to have spent sufficient time for sleep. However, the students of junior and senior high schools were apparently short of sleep, and they seem to compensate the shortage of sleep by extending sleep on weekends. Those who slept 6 hours or less on weekdays showed rapid increase among the students of junior and senior high schools. Since “true short time sleepers” are not many, most of “short sleepers” are thought to be insufficient sleepers. Consequently, about the half of students of

senior high schools answered that they nodded off during classes twice or more per week. These results are quite concordant with previous reports (2,3). Further study should be needed to elucidate the relationship between sleep habits and other life styles such as sports habit, attending crammer school.

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**Research supported by This research supported by a grant from the Japanese Ministry of Health and Welfare, and Special Coordination Funds for Promoting Science and Technology from the Science and Technology Agency.**

**260.G**

**ACADEMIC ACHIEVEMENT AND ATTENTION IN CHILDREN SCHEDULED FOR ADENOTONSILLECTOMY IN COMPARISON TO CONTROLS**

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**Introduction:** Sleep-disordered breathing (SDB) is among the most common indications for adenotonsillectomy (AT), but children who undergo the procedure for other reasons often have enlarged tonsils and may also be at risk for SDB.1 Consequences of childhood SDB may include inattention, hyperactivity, and related behaviors, as well as poor school performance.2-3 However, the specific deficits in cognition and achievement that may be present in children who undergo AT have not been well defined.

**Methods:** We recruited 51 children (27 girls) aged 5 to 12 years (M=7.78, SD=1.90): 43 patients had been scheduled for adenotonsillectomy (AT) and 8 had been seen at a general surgery clinic (scheduled for hernia repair). In an ongoing research protocol, estimates of verbal and nonverbal intelligence were made using the Wechsler Abbreviated Scales of Intelligence (WASI). Academic achievement was measured using the specific subtests of the Wechsler Individual Achievement Test (WIAT). Attention and concentration were objectively measured using the Integrated Visual and Auditory (IVA) Continuous Performance Test, and subjective ratings were obtained using the Conners' Parent Rating Scale, Revised: Long Version.

**Results:** Group means for included variables are presented in Table 1 below. Independent samples t-tests showed that the AT and control groups did not differ with respect to age or grade. Furthermore, inspection of estimates of Verbal and Performance IQ scores revealed no significant differences between the groups. However, the AT group performed more poorly on a number of academic achievement tests, including Mathe-

matics Reasoning, Spelling, and Numerical Operations (Table 2). A similar trend was shown for Basic Reading performance. No difference between the groups was noted for a measure of Reading Comprehension. Children in the AT group performed more poorly than the control group on the Auditory Attention Quotient of the IVA, whereas both groups performed similarly on the Visual Attention Quotient. Parent ratings of oppositional behaviors and cognitive problems/inattention were significantly greater for the AT group as compared to the control group. No significant differences were noted between the groups for ratings of hyperactivity.

**Table 1**

Mean values (standard deviations) for key variables

	AT group	Control group
Age	7.77 (1.88)	7.88 (2.17)
Grade	2.40 (1.77)	3.13 (2.17)
Verbal IQ	108.33 (16.24)	114.13 (20.24)
Performance IQ	104.33 (13.64)	113.88 (20.59)
Basic Reading	103.14 (15.13)	114.75 (17.84)
Mathematics Reasoning	104.56 (12.59)	118.63 (12.27)
Spelling	101.09 (13.70)	113.63 (16.49)
Reading Comprehension	104.45 (16.37)	112.71 (23.75)
Numerical Operations	99.81 (16.52)	114.13 (20.24)
Auditory Attention	77.16 (22.54)	94.13 (20.95)
Visual Attention	83.19 (19.78)	86.25 (29.44)
Oppositional	47.02 (16.22)	46.88 (4.73)
Cognitive Problems/Inattention	56.65 (16.16)	48.00 (5.26)
Hyperactivity	53.53 (12.99)	47.50 (7.01)

**Table 2**

Independent samples test results

	t	p = (2-tailed)
Basic Reading	-1.94	.06
Mathematics Reasoning	-2.91	.01
Spelling	-2.30	.03
Reading Comprehension	-1.14	.26
Numerical Operations	-2.30	.03
Auditory Attention	-1.97	.05
Visual Attention	-0.37	.71
Oppositional	2.30	.03
Cognitive Problems/Inattention	2.80	.01
Hyperactivity	1.90	.07

**Conclusions:** Children who are scheduled to undergo AT, as a group, demonstrate poorer academic skills and greater auditory attention difficulties than children scheduled for other surgery. Consistent with these results, behavioral ratings by parents demonstrate significant problems with cognition, inattention, and oppositional behaviors among the AT group. The results of this study underscore specific academic and behavioral vulnerabilities in children who undergo AT.

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**261.G**

**PARENTAL ASSESSMENT OF SLEEP DIFFICULTIES IN CHILDREN WITH ADHD REFERRED TO A PEDIATRIC SLEEP MEDICINE CENTER.**

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**Introduction:** Based on parental reports, children with ADHD are believed to be at higher risk for sleep-disordered breathing (SDB), periodic leg movement disorder of sleep, sleep initiation and maintenance difficulties, and excessive daytime sleepiness (1-2). To gain more insights into sleep in ADHD, we conducted a systematic assessment of the most frequent complaints of parents of children with ADHD referred to a pediatric sleep medicine center.

**Methods:** The charts of 86 consecutive children with ADHD were reviewed. There were 67 male; 75 Caucasian; and their age range was 3-18 years, with a median age of 8.3 years. The parents' primary sleep-related complaint leading to the child referral, and their responses to a structured clinic-based sleep questionnaire, the Pediatric Symptom Checklist, and the Clinical Attention Problems Scale were extracted.

**Results:** The majority of these 86 children were on medications, namely psychostimulants (65%), sleep-promoting agents (trazodone, clonidine, melatonin; 36%), and other psychotropic agents (valproic acid, sertraline; 22%). In 28% of the children, co-morbid psychiatric conditions such as mood and/or anxiety disorders were present. The most frequent sleep-related complaints were snoring and SDB (60%), restless sleep with or without multiple awakenings (44%), and delayed sleep onset (43%). Based on the questionnaire, 49% of children were reported to have long sleep latencies (>30 minutes at bedtime), and the mean estimate for sleep latency was 61.7 minutes. Furthermore, 79% of parents reported that their children awoke in a negative mood, and 74% thought that their child's sleep problems were moderate to severe. The most frequently reported sleep problems included restless sleep (91%), snoring (78%), somnolence (67%), nightmares (60%), and nocturnal enuresis (48%). The Pediatric Symptom Checklist mean score for the sample was 36.3 (normal<28). Similarly, the mean Child Attention Problems Scale scores for the inattentive and overactive subscales were 10.8 and 8.2,

respectively (normal<3).

**Conclusions:** Children with ADHD present 3 major types of sleep disturbances. Delayed sleep onset could be related to the severity of hyperactivity, or alternatively to limit-setting difficulties. Snoring was 7-fold more frequent than in a general pediatric population, such that SDB may be playing a role in the daytime and nighttime manifestations reported. In addition, the frequency of restless sleep may underlie an intrinsic component of ADHD manifesting during sleep. Thus, systematic exploration of actigraphic and polysomnographic patterns will be needed in children with ADHD and sleep problems, in order to obtain objective sleep correlates that can ultimately guide the clinical management of sleep disturbances in these patients.

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**Research supported by NIH Grant HL-65270 and Department of Education Grant H324E011001**

**262.G**

**EVENING NAPS AND DELAYED NIGHTTIME SLEEP SCHEDULE TYPICALLY FOUND IN JAPANESE ADOLESCENTS CAUSES THEIR DAYTIME MALFUNCTIONING**

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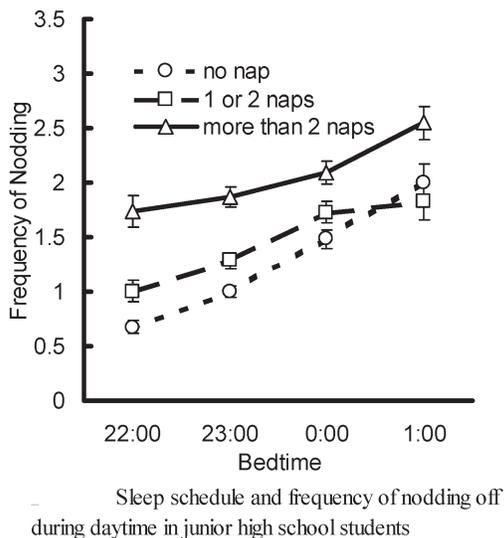
**Introduction:** Fukuda and Ishihara (2001) administered a questionnaire concerning sleep related lifestyle to junior high and high school students and revealed that nighttime sleep length was shortest and several physical and mental conditions were worst at high school age. About a half of junior high and high school students take routine afternoon or evening naps to keep themselves awake to study at night at home and to compensate for their chronic sleep insufficiency (Fukuda and Ishihara, 2002). At the same time late naps are known to disturb nighttime sleep. This study aimed at investigating relationship between the schedule of evening naps and delayed nighttime sleep and daytime functioning in the Japanese junior high and high school students.

**Methods:** Questionnaire concerning sleep related lifestyle, and physical and mental health was administered through the teachers to the students of junior-high schools (12-15 years) and high schools (15-18 years) in Fukushima (North East) and Okayama (West) prefectures of Japan. About 10,000 students (5,461 junior high school students, 4,880 high school students) participated into the survey as a volunteer subject. Students were classified into groups according to their bedtime and frequency of evening naps. The classification was made in junior high and high school students separately. MANOVA was con-

ducted to investigate the effects of bedtime and frequency of naps on several daytime physical and mental symptoms (e.g., frequency of nodding off, anxiety, depression, fatigue, irritability, moody on rise).

**Results:** The statistical test revealed that significant main effects of evening naps and bedtime were found in the most daytime symptoms in the both junior high and high school students. Fig.1 shows the relationship of frequency of naps and bedtime with frequency of nodding off during daytime in the junior high school students. The more frequently the students take evening naps and the later they go to bed, the more frequently they nod off during daytime.

Figure 1



**Conclusions:** Students who take frequent naps and/or go to bed later are found to suffer from undesirable daytime symptoms, including daytime sleepiness, suggested by the presence of frequent nodding. As there is a little individual difference in morning rise time among the students compared with their bedtime, the late bedtime means short nighttime sleep consequently. It is quite understandable that the students who go to bed later showed daytime sleepiness and other undesirable symptoms, however, the fact that the students who take additional naps, i.e., longer total sleep time during a day, complained stronger daytime sleepiness and other symptoms seems more difficult to understand. This finding may suggest that a custom of taking late naps, which the students intend to compensate their insufficiency of nighttime sleep caused their daytime malfunctioning. Custom of taking long naps might be considered in terms of polyphasic or interrupted sleep and wakefulness regimen.

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**Research supported by a Special Coordination Fund for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan.**

**263.G**

**LATE BEDTIMES MAY BE THE NORM FOR EVEN VERY YOUNG, MINORITY CHILDREN IN URBAN AMERICA**

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**Introduction:** Although the Delay in Adolescent Bedtimes is well known from large surveys (1-2), it has generally been assumed that toddlers through pre-teen children go to bed much earlier than their teenage counterparts. We questioned this assumption in current American society and hypothesized that the Delay in Adolescent Bedtimes is an acute, exaggeration of a Bedtime Delay Pattern that begins very early in childhood and is then reinforced over time by current societal norms.

**Methods:** A retrospective analysis of clinical and polysomnographic data on 202 children and adolescents (18-months to 18 years) evaluated at our Sleep Center for complaints of snoring and daytime somnolence was performed. Parent/child/teen reported, Bedtime (BT) and Total Sleep Duration (TSD) data were available on 157 children and adolescents. We focused on weeknight, Bedtime and TSD because weekend sleep patterns are usually different (3). We chose a regression analysis approach to BT and TSD by Age, Sex, and Race. We then subdivided the database into 3 Age groups of 1-5 years, 6-12 years old, and 13-18 years old.

Table 1

Sex	Number	Percentage
Males	89	56.7%
Females	68	43.3%
Race	Number	Percentage
African American	89	56.7%
Hispanic	54	34.4%
Caucasian	14	8.9%

**Results:** Group demographics are presented in Table 1. There were 89 males and 68 females with 9% Caucasians and a predominance of minorities (91%). About 64% of the sample was considered below the poverty line due to qualification for Public Aid Assistance. A regression of reported Sleep Duration with Age was significant ( $r=0.4998$ ,  $F(1,153)=50.95$ ,  $p=.0000$ ,  $Adj\ R\text{-squared}=0.2449$ ). About 25% of the variance in decreasing, TSD was accounted for by increasing age. There was a weaker gender difference with girls averaging slightly less TSD (9 hours, 37 minutes) compared to boys (9 hours, 59 minutes) across the entire age range by a one-tailed, t-test (

p=.0455). Regression of reported Bedtime failed to demonstrate significance by Age, Gender, or Race. Results for Gender distribution of BT and TSD across the 3, Age-groups are presented in Table 2. There were no gender differences in either BT or TSD by Age groups. However, the Adolescents had a Later Bedtime ( $F(2,155)=8.31, p=.0004$ ) and shorter TSD ( $F(2,154)=17.22, p=.0000$ ) than both of the younger age groups. While there were no significant differences in BT or TSD between the 1-5 year and 6-12 year age groups, the Late (9:38pm), average Bedtime of the 1-5 year olds was striking (See Table 2).

Table 2.

	Ages 1-5	Ages 6-12	Ages 13-18
<b>Number (M,F)</b>	61 (40,21)	75 (37,38)	21 (12,9)
<b>Mean Group BT</b>	9:38pm	9:20pm	10:10pm
<b>BT – Females</b>	9:31pm	9:19pm	10:26pm
<b>BT – Males</b>	9:41pm	9:22pm	9:59pm
<b>Mean Group TST</b>	10hrs25mins	9hrs50mins	8hrs4mins
<b>TST -Females</b>	10hrs4 mins	9hrs49mins	7hrs40mins
<b>TST - Males</b>	10hrs38mins	9hrs51mins	8hrs23mins

**Conclusions:** The Late Bedtime of Adolescence may be an acute exaggeration of a delayed bedtime that is set early in childhood development and reinforced by current societal practice. An acute, additional delay specific to the adolescent years also appears to be present.

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**264.G**

**SLEEP ORGANIZATION IN PREMATURE 33/34-WEEK POSTMENSTRUAL AGE INFANTS TREATED WITH MAINTENANCE-DOSE CAFFEINE.**

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**Introduction:** Behavioral sleep-wake states, an index of normal brain development and functioning (ref. in 1), may be altered by caffeine, which is currently used to prevent or decrease apneas in premature babies (2).

**Methods:** To assess the potential effect on sleep organization

of caffeine in standard maintenance dosages, we performed 10-hour polysomnographic recordings (3) in 15 neurologically normal and clinically stabilized, appropriate-for-gestational-age 33/34-week postmenstrual age (w PMA) neonates, of whom ten had been treated for longer than 3 days with once-a-day oral caffeine citrate, 5 mg/kg, given around 2 p.m. We analyzed (a) the usual sleep-wake parameters, including wakefulness (W), active sleep (AS), quiet sleep (QS), and indeterminate (IS) sleep expressed as the number of episodes, duration, and percentage of total sleep time (TST); (b) the duration and order of parameter modifications during transitions (trans) between the main AS and QS states and; (c) the characteristics of morning data (before caffeine) compared to evening data (after caffeine). Statistical analyses were performed using a multivariate linear model, taking into account independent effects of morning versus afternoon, caffeine versus no caffeine, AS versus QS, and transition from AS to QS versus from QS to AS, with the subject factor as a cluster. Because data distribution was non-normal, all analyses were tested also by the nonparametric Wilcoxon rank-sum test. A chi-square test was designed to analyze the order of parameter changes during between-state transitions.

**Results:** We found no significant differences between the controls and the infants on maintenance caffeine. The main data are shown on the following table:

Table 1

Criteria	Caffeine	No Caffeine	P value
W: number	14.9 ± 8.9	20.4 ± 11.3	0.3
AS: number	26.7 ± 6.8	33.6 ± 9.8	0.2
QS: number	9.7 ± 3	9 ± 3.5	0.9
IS: number	30.7 ± 6.9	28.2 ± 8	0.6
W: % of record.	6.1 ± 4.3	7.6 ± 4.3	0.5
AS: % of TST	64.3 ± 9.7	63 ± 15.2	0.8
QS: % of TST	14.8 ± 3.4	14.9 ± 5.4	1
IS: % of TST	20.9 ± 8.2	22.1 ± 10.5	0.8
State trans(n)	81.6 ± 22.9	91.2 ± 15.1	0.4
AS-QS trans(min)	6.4 ± 3.1	6.1 ± 3.7	0.7
QS-AS trans(min)	1.7 ± 1.8	1.5 ± 1.8	0.7

**Conclusions:** We conclude that caffeine in a standard maintenance dosage does not modify sleep organization in neurologically normal and clinically stable 33/34 w PMA infants.

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**265.H**

**IMPACT OF MOOD, FUNCTION, AND BEHAVIORAL DISTURBANCE ON THE SLEEP OF ALZHEIMER'S DISEASE PATIENTS AND CAREGIVERS**

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**Introduction:** Most of the research on sleep disturbances in persons with Alzheimer's disease (AD) has examined the changes in sleep architecture and circadian rhythms associated with the disease. Little is known about the psychosocial factors that may alter an individual's risk for developing or not developing sleep problems, or that may influence their persistence and severity.

**Methods:** Subjects were 24 AD patients (mean age = 78.2 years; mean dementia duration = 5.5 years; 65% male) recruited as part of an ongoing study of sleep disturbance in dementia (the NITE-AD study). Subjects had at least one sleep problem on the Neuropsychiatric Inventory (NPI) Nighttime Behavior scale occurring three or more times per week. One week of sleep-wake activity was inferred for patients and their family caregivers (mean = 66.8 years; 96% female) using an Actillum Sleep Watch. Nocturnal in-bed sleep periods were determined from daily sleep logs kept by caregivers during the same period. Patient behavioral disturbance (Time-Based Behavioral Disturbance Questionnaire, TBDQ; Revised Memory and Behavior Problem Checklist, RMBPC; Agitated Behavior in Dementia, ABID), cognitive and functional status (Mini-Mental State Examination, MMSE; Lawton-Brody Physical Self-Maintenance [ADL] and Instrumental Activities [IADL] scales), and mood (Cornell Depression Scale) were rated by caregivers and trained interviewers. Patient self-ratings of mood (Geriatric Depression Scale, GDS) and caregiver self-ratings of sleep (Pittsburgh Sleep Quality Index, PSQI) were also completed.

**Table 1**

**Baseline actigraphic sleep characteristics (mean values)**

Variable	Patient	Caregiver
Bedtime	9:34 pm	10:37 pm
Rising time	7:22 am	7:15 am
Time in bed	9.4 hours	8.2 hours
# awakenings	10.2	5.4
Total sleep time	7.5 hours	7.4 hours
Sleep efficiency	.81	.91
% sleep med use	26%	22%
PSQI	--	8.6

**Results:** Table 1 shows mean baseline sleep characteristics for patients and caregivers. Caregivers reported an average of 3.3 patient sleep problems on the NPI occurring 3 or more times per week (range 1 - 5 problems), including waking the caregiver at night (85%), excessive daytime sleepiness (67%), and wandering/inappropriate acts (63%). Patient and caregiver bedtime ( $r = .66$ ), rising time ( $r = .62$ ), and acrophase time ( $r = .83$ ) were all significantly correlated ( $p \leq .01$ ). Decreased patient sleep was associated with self-reported depression (Table 2). Decreased caregiver sleep was associated with greater patient cognitive and functional impairment, and overall levels of behavioral disturbance. Similar although less robust patterns were observed between patient sleep, cognitive/functional status, and agitation. Caregiver circadian quotient of sleep (24-hr amplitude over mesor) was inversely related to total ABID ( $r = -.42$ ;  $p \leq .05$ ) scores, further suggesting the relationship between patient behavior problems and circadian organization of sleep in caregivers. No associations with patient or caregiver demographic characteristics were observed.

**Table 2**

**Correlations of patient data with total patient and caregiver sleep time (Pearson's Product Moment Correlation, r; \* $p < .05$ , \*\* $p < .01$ )**

Variable	Patient	Caregiver
MMSE	0.34	<b>0.56**</b>
ADL	0.01	-0.17
IADL	-0.21	<b>-0.44*</b>
GDS	<b>-0.66*</b>	0.01
Cornell	-0.04	-0.03
RMBPC, depression	-0.17	-0.14
RMBPC, disruption	0.16	<b>-0.58**</b>
TBDQ, total disruption	0.16	<b>-0.48*</b>
ABID	0.33	<b>-0.54**</b>

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RMBPC, depression	-0.17	-0.14
RMBPC, disruption	0.16	<b>-0.58**</b>
TBDQ, total disruption	0.16	<b>-0.48*</b>
ABID	0.33	<b>-0.54**</b>

**Conclusions:** The study provides preliminary evidence of the relationship between depression and sleep disturbance in community-dwelling AD patients, and the influence of patient cognitive, functional, and behavioral disturbance on the sleep of family caregivers. Limitations of the study are the imprecision of monitoring sleep/wake from wrist activity and the relatively small number of participating patient/caregiver dyads to date. Future research should further explore the extent to which mood, cognitive/functional status, and behavioral disturbances interact with disease progression to impact the sleep of AD patients and their family caregivers.

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**266.H**

**SLEEP AND MEMORY IN OLDER ADULTS**

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**Introduction:** Sleep disturbances and memory impairment are common complaints in older adults and previous studies have suggested a connection between the two. Poor sleep also leads to problems with daytime functioning, and the relationship between memory and daytime functioning warrants further investigation. The aim of this study was to ascertain if poor sleep and impaired daytime functioning (excessive daytime sleepiness (EDS), fatigue, decreased alertness) can affect

memory in older adults.

**Methods:** Our independent variables consisting of sleep quality (Pittsburgh Sleep Quality Index), EDS (Epworth Sleepiness Scale), fatigue (Fatigue Severity Scale) and alertness (The Toronto Hospital Alertness Test) were subjectively assessed using the aforementioned questionnaires. These variables were correlated with memory which was assessed using the following tests: Hopkins Verbal Learning Test, Letter – Number Sequencing Test, Digit Symbol – Coding Test and Incidental Learning, and the Animal Naming Test. Subjects were recruited from community retirement homes.

**Results:** Fifty healthy subjects (average age: 77; range: 60-97) were included in this study. No significant differences were found between the independent variables and the different components of memory measured. The results indicated that poor sleep quality, EDS and alertness did not significantly correlate with each other. However, fatigue was positively correlated to poor sleep quality [ $p < 0.001$ ], positively correlated to EDS [ $p < 0.002$ ] and negatively correlated to alertness [ $p < 0.001$ ].

**Conclusions:** Poor sleep quality, EDS, fatigue and impaired alertness did not significantly correlate with the different components of memory measured. These findings suggest that these variables do not contribute to memory impairment in healthy older adults. Our study further demonstrated that our measures of sleep quality, sleepiness and alertness were separate and independent constructs while fatigue was not and was strongly correlated to sleep quality, sleepiness and alertness. Other factors such as medication use, medical history and alcohol/drug abuse may contribute to memory impairment in older adults, but these were not investigated in this study.

## 267.H

### AGE-RELATED GENE EXPRESSION PROFILES IN MURINE HIPPOCAMPUS

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**Introduction:** A frequent correlate of human aging is a decline in neurological functions such as sleep, learning and memory. Functional declines in these parameters have also been observed in aged rodents. The hippocampus is clearly involved in both learning and memory and exhibits theta activity during REM sleep. In a companion abstract, we describe age-related changes in the levels of both hypocretin/orexin receptor 1 and 2 mRNAs in the hippocampus of male C57BL/6 mice. To obtain a more global view of the changes in gene expression in the aged hippocampus, we examined this brain region in young (3 mo), middle-aged (12 and 18 mo) and old (24 mo) male C57BL/6 mice using Affymetrix Murine U74A GeneChips.

**Methods:** Mice (n=3 per age group) were sacrificed between 1100-1400h and hippocampi removed and quick-frozen. Total RNA was isolated and the 3 samples pooled for each age group. Double-stranded cDNA was synthesized from 20 µg total RNA per pool. Biotinylated cRNA was synthesized using these double-stranded cDNAs as templates and was then chemically fragmented before hybridization. The four cRNA

samples were hybridized to Murine U74A GeneChips (Affymetrix, Santa Clara, CA). The tissue sampling, RNA extraction and hybridization was repeated on another set of mice (n=3 per age group) so that a total of eight GeneChips were used in this aging study. Data were analyzed using the Affymetrix Microarray Suite 4.0 and GeneSpring version 4.1 (Silicon Genetics, Redwood City, CA).

**Results:** 4514/12488 elements represented on the GeneChip (36.1%) were categorized as “present” in all four age groups in the two replicate experiments, indicating that only a third of genes are constitutively expressed in the hippocampus across all ages. Of these, the expression of 74 known genes and 54 ESTs changed in direct proportion with age. These 128 elements were subjected to hierarchical cluster analyses including GeneTree, Experimental Tree, and Self-Organizing Maps (SOM). Using a 2x2 SOM, 95 elements showed increased expression and 33 elements showed decreased expression with age. Among those genes indicated to systematically increase with age are the precursor mRNA for beta2-microglobulin, tissue plasminogen activator (tPA), the immediate early gene Jun-D and the mRNA for the prion protein. Genes whose expression decreases with age include the potassium channel Kv4.2, the G protein beta 1 subunit and beta-actin.

**Conclusions:** These results indicate that a small percentage of genes either increase or decrease in expression in the hippocampus in direct proportion to age. Whether such changes in mRNA levels are reflected in protein levels, as well as the functional consequence of such changes, remain to be elucidated. However, tPA mRNA has previously been found to increase in the cerebral cortex after sleep deprivation and prion knockout mice are known to have an altered sleep/wake distribution.

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## 268.H

### AGE AND SLEEP LATENCY: A META-ANALYSIS

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**Introduction:** The purposes of this meta-analysis were: (a) Precise estimation of the correlation between age and sleep latency (SL); and, (b) exploration of factors affecting the magnitude of this correlation. It is generally accepted that sleep characteristics change over the lifespan and are normal in the sense of typical; however, questions remain regarding the extent to which reported sleep changes are due to aging itself versus other factors. In an earlier meta-analysis we were unable to account for differences in reported correlations between age and SL (1). This meta-analysis refines and extends the earlier study by exploring the influence of many uncontrolled health, substance use, and sleep schedule variables.

**Methods:** Studies were included in this meta-analysis if they: (a) were reported in English, (b) measured SL by polysomnography in a sleep laboratory setting, and (c) provided statistical information required to estimate rho. Search, retrieval, and

coding methods have been reported previously (1). Three scores were computed for each study reflecting the extent to which: (a) unhealthy subjects were eliminated, (b) psychoactive substance use was eliminated, and (c) sleep schedule variables (circadian, homeostatic, and first-night) were controlled. Standard methods for averaging and analyzing correlations were used including Fisher's r-to-Z transformations, weighting effect sizes by sample size, homogeneity testing, and use of weighted regression analysis to examine possible moderators (2).

**Results:** Reported correlations between age and SL (N=24) ranged between -.60 and .81. After winsorizing two outliers the correlations ranged between -.03 and .48. The subsequent test for homogeneity was not rejected ( $Q = 20.13, p = .63$ ). The weighted mean  $r$  was .176 (95% CI = .113-.238). Neither failure to eliminate unhealthy subjects nor lack of control of sleep schedule factors moderated reported correlations. There was a trend toward psychoactive substance use moderating correlations ( $z = -1.86, p = .06$ ). Examination of each psychoactive substance showed that failure to control for alcohol use accounted for a significant amount of variance in reported correlations (QBET = 4.23,  $p = .04$ ). The average correlation between age and SL for samples from studies where alcohol use was controlled ( $n = 10$ ) was .112, while  $r = .243$  for samples from studies failing to report control for alcohol use ( $n = 14$ ). Further examination of studies showed the mean SL for younger subjects was significantly shorter in uncontrolled ( $M = 12.5$  min.) than controlled studies ( $M = 19.1$  min.),  $t(22) = 2.84, p = .01$ , but not significantly different for older subjects. No significant gender differences were found, but few all-female samples were available for analysis.

**Conclusions:** A small but significant positive correlation appears to exist between age and SL. Given the Q-test was not significant, it is possible that variance in correlations is due to normal variation from study to study; however, failure to control for alcohol use during studies may inflate the observed correlation between age and SL by shortening younger subjects' SL.

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## 269.H

### ARGININE IMPROVES SLEEP IN ELDERLY MEN

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**Introduction:** Somatostatin is the major endogenous antagonist of growth hormone (GH)-releasing hormone (GHRH) in the release of GH. GHRH and somatostatin exert also antagonistic effects on sleep. Pulsatile iv GHRH promoted slow wave sleep and GH and inhibited cortisol in young men. Sleep was impaired after somatostatin in elderly subjects (1). In old

rats somatostatin activity is not much affected whereas GHRH activity decreases (2). Hence the influence of somatostatin functionally dominates. This may explain the reduced efficacy of exogenous GHRH to promote sleep in the elderly (1) and the parallel decrease of SWS and GH during ageing as well. Arginine is known to antagonize somatostatin and to facilitate the effects of GHRH on GH during aging. The aim of our study was to investigate the capacity of arginine to counteract the age-dependent decline of the influence of endogenous and exogenous GHRH on sleep in elderly men.

**Methods:** In a double blind randomized protocol 8 healthy elderly men (age mean  $\pm$  SD 69.7  $\pm$  7.3 years) participated in 3 sessions, which were divided by one week. Prior to study diseases were excluded by extensive examinations including sleep-EEG screening for sleep apnea syndrome and RLS. Each session consisted of one night of adaptation and one examination night. During the latter sleep EEG (2300-0700) and the secretion of ACTH, cortisol and GH (2200-0700) were investigated simultaneously. In order to do this blood specimens were collected every 20 min via long catheter between 2200 and 0700. During the examination nights subjects received either placebo (A) or infusion of 29.5 g L-arginine-hydrochloride (2205-2335) in combination with hourly iv administration of placebo (B) or 4 x 50  $\mu$ g GHRH (C). Group differences were analyzed by tests with contrasts in MANOVA.

**Results:** Intermittent wake time (min) decreased significantly in group C (mean  $\pm$  S.E.M. 102.06  $\pm$  16.64) vs. group A (118.56  $\pm$  19.58;  $p < 0.05$ ). Stage 4 time (min) increased ( $p < 0.05$ ) in groups B (4.25  $\pm$  3.71) and C (2.75  $\pm$  2.13) vs. group A (0.88  $\pm$  0.54). GH secretion was elevated significantly ( $p < 0.05$ ) in group C (mean area under the curve [ng/ml x 20 min] 30.07  $\pm$  8.28) vs. group A (8.65  $\pm$  2.11). Other sleep-EEG and endocrine variables including ACTH and cortisol secretion did not differ between groups.

**Conclusions:** Our data show an increase of stage 4 sleep after arginine infusion near to sleep onset in elderly men. Combined administration of arginine and GHRH prompted increases of stage 4 sleep and GH and a decrease of wakefulness. The sleep-promoting effect in this protocol was superior to administration of GHRH only in elderly men and women in our previous study (1). We suggest that somatostatin antagonism by arginine facilitates the promotion of sleep by endogenous and exogenous GHRH in the elderly.

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270.I

**THE BODY POSTURE OF SLEEP-DEPRIVED SUBJECTS AFFECTS PERFORMANCE ON THE PSYCHOMOTOR VIGILANCE TASK**

Caldwell JA,<sup>1</sup> Prazinko BF,<sup>1</sup> Caldwell JL<sup>1</sup>

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**Introduction:** Relatively little research has examined the impact of body posture on arousal. However, researchers have established a link between sleep quality, sleepiness, and body posture. Nicholson and Stone<sup>1</sup> found that volunteers slept more poorly when reclining than when lying down. Cole<sup>2</sup> found that tilting volunteers from a reclined to an upright position increased the time to sleep onset and produced more high-frequency EEG. Caldwell, Prazinko, and Hall<sup>3</sup> found that sitting versus standing improved alertness as indicated by a reduction in slow-wave EEG activity. In the present study, the effects of posture on psychomotor vigilance were examined.

**Methods:** Sixteen subjects between the ages of 22 and 45 were tested during 27 hours of continuous wakefulness following a 2-day rotation from day to night shift. Each volunteer completed a 10-minute Psychomotor Vigilance Task (PVT) after 3, 7, 11, 19, 23, and 27 hours awake. During half of the sessions, volunteers remained seated, and during the other half, they stood (the sit/stand order was counterbalanced). These data are a subset of a larger set of data collected during this study.

**Results:** A within-subjects analysis of variance revealed session main effects on overall reaction time (RT), the slowest RT, the fastest RT, and the percentage of performance lapses ( $p < .05$ ). These were due to a linear slowing of performance from the first to the last session. Posture main effects on the fastest RT and the percentage of lapses ( $p < .05$ ) resulted from better performance under the standing versus the sitting condition. Session-by-posture interactions were observed on the overall RT, the slowest RT and the percentage of lapses as well ( $p < .05$ ). Analysis of simple effects on reciprocal (but not raw) RT data revealed better performance under standing than sitting at the last three sessions. The percentage of lapses was smaller under standing than sitting at the last two sessions.

Figure 1

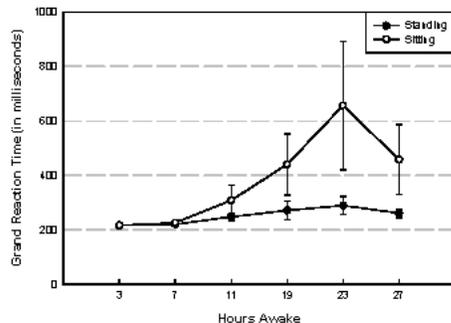
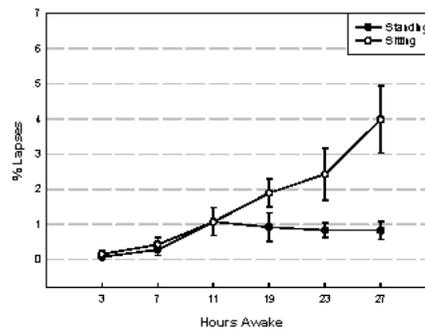


Figure 2



**Conclusions:** These results suggest that the improved physiological arousal previously associated with upright posture contributes to improved performance as well. This is especially true when subjects are sleepy.

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271.I

**SLEEP DEPRIVATION ABOLISHES MAINTENANCE OF LONG-TERM POTENTIATION IN CA1**

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**Introduction:** The lack of post-training sleep is detrimental to performance on a variety of procedural and declarative memory related tasks. In addition, neuronal activity is augmented during REM sleep following task acquisition in the hippocampus (a known memory area) and several other cortical areas. These findings have led to the conclusion that sleep is crucial for the acquisition and consolidation of memory. Long-term potentiation (LTP) is an increase in synaptic efficacy as the result of repeated stimulation. This electrophysiological phenomenon is the putative basis of memory at the cellular level. LTP has a transient "induction phase" sustained by kinase activity, followed by a more permanent "maintenance phase" upheld by gene expression and protein synthesis.

**Methods:** Male Sprague-Dawley rats (150-250 g) were divided into three groups: Control (C), Pedestal Control (PC), and Sleep Deprived (SD). Prior to sacrificing, SD rats were sleep deprived for 2 consecutive days for 12 h during the light cycle. Deprivation was accomplished by the flowerpot method using stacked pots with a base diameter of 4.5cm surrounded by water (5cm deep). The PC rats were treated identical to the SD rats except their flowerpot base diameter was large enough for them to rest comfortably (7cm). The C rats spent those two

days in their home cage. On the morning of the third day, each rat was anesthetized and decapitated. Following extraction of the hippocampus, slices from the middle third portion (400  $\mu$ m thick) were transferred to a gassed (95% O<sub>2</sub>/5% CO<sub>2</sub>) incubation chamber containing aCSF. After at least 1 h (at 24 °C) single slices were secured in a perfusion-recording chamber and were superfused with gassed aCSF (30-31°C) at 1-1.5 ml/min. Glass micropipettes filled with 0.15 M NaCl (2 - 3 M-Ohms) were used to record from the CA1 stratum radiatum layer. A concentric bipolar stimulating electrode was positioned adjacent to the recording electrode and provided orthodromic activation of the Schaffer collaterals. LTP induction consisted of 10 theta burst stimulations containing four pulses at 100 Hz each, separated by 200 ms. High frequency stimulation was repeated three times with an inter-train interval of 10 s. Extracellular signals were amplified (gain 1000 $\times$ ) and filtered (1 kHz). Three successive peak slope measurements of the initial phase of the fEPSP response were averaged and recorded for 30-min post-tetanus.

**Results:** The PD group showed a slight decrement in fEPSPs compared to the C group. The SD group showed normal induction to 70% above baseline, followed by a marked decline to 50% below baseline.

**Conclusions:** This suggests an interference with the biochemical pathways that sustain the maintenance phase of LTP. Possible mechanisms underlying this sleep-deprivation-induced impairment of LTP will be discussed.

## 272.I

### DOES SLEEP DEPRIVATION AFFECT EFFORT?

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**Introduction:** Sleep loss increases fatigue and seems to deplete internal resources. Holding (1983) suggests that for tests of fatigue and effort to be maximally sensitive, they must include options to shift to low-effort work preferences. This study sought to understand how sleep loss of one night affects effort and motivation by examining choice behaviors when participants are free to increase or decrease task demands.

**Methods:** Twenty-two male and thirty-six female undergraduates were randomly assigned to either a no sleep deprivation (NSD) condition or to one night of sleep deprivation (SD). The participants in the NSD group slept in their homes and the participants in the SD group were kept awake in the Department of Psychology for one night. All participants were assessed at 9:00 AM. Four tasks assessed effort. The math task presented a series of 40 consecutive addition problems. The verbal task presented a series of 30 consecutive trivia questions. The math and verbal questions were organized into five levels of difficulty. Prior to each math or verbal problem, each participant selected the level of difficulty of the next problem. In a non-academic task choice each participant chose one task, from a list of five tasks, to perform for the next 20 minutes. The five tasks had been normed for perceived difficulty. A subjective effort question asked participants to rate the effort they had applied to the entire assessment. The assessment also included

the Stanford Sleepiness Scale, the Profile of Mood States, a simple reaction time task, and a sleep diary.

**Results:** Analyses of variance indicate that both groups reported equivalent effort expenditures. However, the SD group was significantly more likely to choose simpler math problems throughout the entire assessment [ $F(1,56) = 5.062, p < .05$ ] beginning with the first trial. There were no differences between groups in the percentage of correct responses. The SD participants were also significantly more likely to select the least difficult non-academic tasks [ $F(1,56) = 5.486, p < .05$ ]. Difficulty of task chosen was negatively correlated with reaction time ( $r = -.277, p < .05$ ) and sleepiness ( $r = -.429, p < .01$ ). There was no difference between groups on the verbal effort assessment task.

**Conclusions:** Sleep loss results in low effort work preferences. Participants, however, do not perceive a reduction in effort. The maintenance of correct responses in sleep deprived participants occurs at the expense of task difficulty. These results support the compensatory regulation model (Hockey, Wastell and Sauer, 1998; & Kahneman, 1971) which suggests that under the stress of sleep deprivation, active reductions in task difficulty are necessary to maintain effective responding. Methods of assessing sleep deprivation must include tasks sensitive to low and high effort strategies.

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## 273.I

### NAPPING AND SLOW-RELEASE CAFFEINE AS COUNTERMEASURES TO DRIVER SLEEPINESS: A DRIVING SIMULATOR STUDY

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**Introduction:** Two countermeasures to driver sleepiness induced by partial sleep deprivation - a 30-minute nap and 300 mg slow-release (SR) caffeine - were evaluated experimentally by using a driving simulator. Until today, driving simulator studies comparing the value of naps and caffeine as countermeasures were only done using immediate-release caffeine (Horne & Reyner, 1996).

**Methods:** Twelve subjects, with a mean age of 21.9 years, underwent four experimental conditions, a 30-minute nap opportunity or no nap opportunity with 300 mg SR caffeine or placebo, according to a Latin square design and with a one-week washout. The nights before the testing days subjects were allowed 4.5 hours time in bed at the laboratory. Driving performance was measured twice by a 45-minute driving task on a simulator (De Valck & Cluydts). Subjective

sleepiness/alertness and mood were assessed four times, by means of the SSS and POMS. A MANOVA procedure was used for the statistical analysis of this 2(NAP)x2(SUBSTANCE)x2(TIME) design.

**Results:** The level of lane drifting was lower following SR caffeine intake as compared with placebo and this effect was more expressed in the afternoon sessions [F(1,11)=7.60;p<0.05]. The administration of SR caffeine also significantly reduced subjective sleepiness [Rao's R(3,9)=4.23;p<0.05]. A nap only led to a decrease in lane drifting in the morning sessions. The speed deviation and accident liability parameters yielded no significant differences between any experimental conditions.

**Table 1**

Means for lane drifting (cm), speed deviation (km/h) and accident involvement (%)

Condition	Lane Drifting	Speed Deviation	Accident frequency
No nap	31.80	3.02	6
Nap	31.14	3.00	8
Placebo	32.88	2.94	6
Caffeine	30.06	3.08	8
9:00 am	31.74	3.42	12
1:00 pm	31.20	2.60	2

**Conclusions:** A 30-minute nap opportunity and 300 mg of SR caffeine both turned out to be successful in counteracting driver sleepiness. The remedial effect of SR caffeine was more expressed and lasted longer as compared to that of the nap. This suggests that it represents a valuable countermeasure that - in some circumstances - is preferred to a nap. However, these findings need to be replicated in real traffic situations and some potential risks related to SR caffeine have to be investigated.

**References:**

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**274.I**

**THE NIGHT FLOAT ROTATION TO DECREASE RESIDENT SLEEP DEPRIVATION: GOOD SOLUTION OR A NEW PROBLEM?**

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**Introduction:** Serious incidents in patient care have been

attributed to work overload and night call duty for physicians in training (1). To correct these problems residency programs developed the night float rotation characterized by night call duties without daytime work. Shift work, however, is associated with sleep disturbances, mood alterations and diminished alertness (2). We evaluated the impact of night float on residents' sleep, attention and mood.

**Methods:** Night float at our hospital consists of work from midnight to 8-9AM for 2 consecutive weeks with 3 interspersed days off. Study participants were 38 residents, 13 male, 25 female, ages 28.7 + 1.7 years. The study included 1 night float phase and 1 or 2 control phases of 2 consecutive weeks of daytime work. In all phases residents completed a sleep diary daily and performed tests of attention (Conners' continuous performance test) and mood (Profile of Mood Symptoms) 3 times a week. All 38 residents completed one night float phase; 10 completed one and 28 completed two control daytime phases.

**Results:** The duration of the main sleep period for daytime and night float was 7.2 ± 1.7h and 6.3 ± 2.5h, respectively, p < 0.0001. During daytime 48% of the main sleep periods had only 0 or 1 awakening and 52% had 2 or more awakenings. In contrast, during night float only 38% of the main sleep periods had 0 or 1 awakening, while 62 % had 2 or more awakenings. Measures of attention were not significantly different between daytime and night float and they were, respectively: omission errors 1.42 ± 4.52 and 4.04 ± 15.85; commission errors 9.57 ± 7.29 and 10.22 ± 8.03; mean hit reaction time in milliseconds 337.09 ± 62.2 and 340 ± 64.9; and hit reaction time block change -0.00271 ± 0.02809 and 0.00169 ± 0.02. Likewise, mood measures of tension-anxiety, depression-dejection, anger-hostility and confusion-bewilderment were not significantly different between the two phases. In contrast, the scores for vigor-activity and fatigue-inertia were significantly different between the two phases and they were, respectively, for daytime and night float: vigor-activity 14.71 ± 7.11 and 10.43 ± 6.93, p = 0.019, and fatigue-inertia 5.17 ± 4.75 and 8.94 ± 6.04, p < 0.0001. There was no significant effect of the order (sequence) of the two study weeks per phase on any of the sleep, attention or mood variables.

**Conclusions:** This study shows that the night float rotation, which is characterized by a sudden reversal of sleep/wake activities during residency training, is accompanied by significant alterations in sleep with decreased sleep duration and more frequent awakenings, increased fatigue and decreased vigor. Despite these problems, residents were able to maintain adequate alertness in a testing situation. Alertness tests, however, may not fully represent actual work performance, which may be compromised by sleep deprivation and shift change. Further studies are needed to examine the full impact of the night float rotation on resident performance and patient safety.

**References:**

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275.I

CAFFEINE CHALLENGE AFTER TOTAL SLEEP DEPRIVATION TO PRIMARY INSOMNIAC PATIENTS AND NORMAL VOLUNTEERS.

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**Introduction:** Insomnia is a common clinical condition with a prevalence of 30-36 % among adults. Adenosine is a modulator that has a pervasive and generally inhibitory effect on neural activity. Receptor antagonist such as caffeine could make relief from that inhibition. Since primary insomniacs reported avoidance to caffeine beverage, a sensitivity of this substance that could be related to low adenosine receptors in some insomniac patients was explored.

**Methods:** Primary insomniacs patients (PIP) (DSM-IV) and Normal Volunteers (NV) were studied. After the protocol was explained an informed consent was obtained. All subjects were caffeine and nicotine free for at least one year previous to the study. They undergo the following sleep procedures: (a) Baseline polysomnographic 8 hrs recordings; Multiple Sleep Latency Test (MSLT) starting at 10:00, 12:00, 14:00 and 16:00 hrs. The following night all subject were Total Sleep Deprived (TSD). (c) MSLT after sleep deprivation were performed but half an hour before the first nap, 200 mg of caffeine or placebo were administered in a double-blind design. One week apart TSD and MSLT were repeated, with the administration of placebo or caffeine capsule at the same time than before.

**Results:** There were three subjects per group. PIP, were all female (Age=37.3±19.0) while NV were two female and one male (Age=30.3±4.9). Baseline Efficiency Index were: PIP = 79.6 % vs. NV = 90.23. Table 1 shows no differences in MSLT at baseline and in recovery after TSD+ placebo, but significant differences were found when PIP received caffeine after TSD (last two rows), with an increase of the sleep latencies in all the naps compared to NV (Two-Ways ANOVA for repeated measures. Group effect: F=17.8, p<0.006).

Table 1

MSLT IN BOTH GROUPS				
Baseline	10:00	12:00	14:00	16:00
NV	6.0±1.3	10.1±3.0	12.5±7.5	6.0±2.6
PIP	6.3±6.6	7.0±7.8	7.0±11.3	3.6±2.9
TSD+Placebo				
NV	3.5±2.3	5.0±3.7	5.0±3.4	4.0±0.8
PIP	3.1±2.3	1.6±0.28	2.0±0.8	1.6±1.2
TSD+Caffeine				
NV	1.6±1.04	3.8±3.2	3.8±0.7	3.0±2.29
PIP	15.6±7.5	15.8±7.2	16.0±6.9	15.0±7.5

**Conclusions:** The same dose of caffeine that in NV did not stop the shortage of sleep latencies after TSD, produced the opposite effect in PIP group. That may account for a low number of adenosine receptors that can be saturated with the dose of caffeine that was used for both groups. Of course other non-adenosine mechanisms related of caffeine may be important for this effect, that also may be different in PIP than NV.

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276.I

“ASLEEP AT THE WHEEL”

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**Introduction:** Alexandria, VA Oct 28-29 2001—” Sleep Fatigue and Medical Training; Optimizing Learning and the Patient Care Environment Conference” One objective of this conference was to “ evaluate the effectiveness of countermeasures and other strategies designed to overcome the effects of fatigue “ in physician training. The distinguished panel agreed that fatigue while driving a motor vehicle merits research, public safety being a major concern. Washington, D.C. Sept. 26 2001— With results of a new national survey reporting that one half of all American adults- particularly young males-admit to driving drowsy in the past year, and one in five actually fell asleep behind the wheel, the National Sleep Foundation (NSF) today called for a national consensus to implement solutions. NSF Executive Director Richard L. Gelula said, “We are facing enormous public consequences. We have more vehicles and more drivers driving more miles each year, and a huge number are literally asleep at the wheel. This cannot be ignored as an unfortunate consequence of hectic, modern day living.” “ Safety experts express concern that despite successful efforts to get most Americans to buckle up, major reductions in drunk driving, and significant safety advances to vehicles themselves, that we continue to have so many deaths and injuries on our roads. The missing part of the puzzle is too many drowsy drivers,” Gelula said.

**Methods:** 200 long haul truckers, representing a geographic cross section of American truckers were polled. The truckers aged 20-70 years, 90% male, 10% female were polled Nov 1, 2001-Nov 5, 2001 inclusive at 5 truck stops in the Northeast. The truckers were asked the following: How do you keep awake behind the wheel when your tired? Caffeine was so predominant that the question was changed to: What do you do when the effects of stimulants, loud music, cold air, tobacco etc. no longer helped you stay awake?

**Results:** Gender was not a factor. 155 professional drivers responded that they “ put their head on the wheel” or “ slept over the doghouse “This means drivers would park their trucks and put their head on the steering wheel and go to sleep in that position. Drivers state that sleeping in this uncomfortable position, many times for as little as 15 minutes, markedly increased their alertness, allowing them to continue driving. 11

drivers used isometric exercise, utilizing the steering wheel and floor, to stimulate arms and legs. 18 drivers would park and walk around the truck several times. 8 would jog for a period of time. 8 would get out of the truck and stretch.

**Conclusions:** An unusually high percentile of professional drivers agree: 1) Eyes closed, head down resting for as little as 15 minutes can add 30 minutes of alertness. 2) Parking your vehicle in a safe area limits distraction and improves rest efficiency. The commuting public would benefit from this practice. Informed that 15 minutes of rest can effectively get them home safely when they feel fatigue behind the wheel.

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**277.I**

**EFFECTIVENESS OF NADH IN ALLEVIATING EFFECTS OF ACUTE SLEEP DEPRIVATION IN HEALTHY MIDDLE-AGED ADULTS**

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**Introduction:** Sleep deprivation is a common problem affecting most people at one time or another. It impacts otherwise healthy individuals who cross time zones, work shifts, or have infant children; and patients with sleep disorders, certain psychiatric disorders, and medical conditions. Sleep deprivation can lead to declines in cognitive performance, impacting the quality of waking time and can lead to vehicle collisions and occupational consequences. Few substances have been shown in rigorously designed studies to improve daytime alertness following sleep deprivation. Manufacturers of a number of nutritional supplements claim that their products improve alertness, concentration, or cognitive performance. However, most of these claims are not supported by well-designed clinical studies that measure sleepiness and performance. We tested the ability of sublingual NADH to improve alertness, mood, and performance on a range of cognitive tasks in middle-aged men and women who had undergone one night of total sleep deprivation. NADH was tested since it has been reported to increase energy in patients suffering from chronic fatigue syndrome (1) and to improve some aspects of cognitive performance in people suffering from jet lag (2).

**Methods:** This was a double blind, placebo-controlled, randomized crossover study involving twenty-five non-smoking men and women ages 40-59. Subjects were screened for medical, psychiatric, and sleep disorders and maintained a regular sleep schedule. Subjects completed a baseline cognitive assessment using a computerized battery. Before baseline testing, subjects consumed open-label sublingual placebo and had electrodes placed to simulate experimental conditions. They returned to the laboratory for one night of enforced wakefulness under the supervision of a technologist followed by con-

sumption of sublingual NADH (20 mg) or placebo determined by random assignment. Cognitive testing, mood assessment using the POMS, assessment of subjective sleepiness (Stanford Sleepiness Scale and Epworth Sleepiness Scale) and objective sleepiness (Multiple Sleep Latency Test with three naps) were then performed. The 45-60 minute cognitive battery (CogScreen-Aeromedical Edition; CogScreen-AE) assessed attention, immediate- and short-term memory, visual-perceptual functioning, sequencing functions, logical problem solving, calculation skills, reaction time, simultaneous information processing abilities, and executive functions. After the first laboratory testing session, subjects returned to the laboratory for testing using the other substance.

**Results:** Three composite measures of cognitive performance were derived by summing speed, accuracy, and throughput (correct answers/min) scores on all subtests of the cognitive battery with data available from enough subjects. Throughput, a combination of speed and accuracy, was significantly better following consumption of NADH than after placebo. Overall measures of accuracy and speed were not different between conditions. Subjective and objective measures of sleepiness and mood did not differ between conditions. Although several subjects reported typical effects of total sleep deprivation, no adverse effects were reported after consumption of NADH or placebo.

**Conclusions:** This study is among the first to rigorously evaluate a non-prescription substance aside from stimulants in alleviating the effects of sleep deprivation. NADH is one of the first non-stimulant non-herbal substances to show increased aspects of cognitive performance, despite expected subjective reports of increased fatigue following sleep deprivation. NADH may have an important role to play in mitigating the effects of unavoidable sleep deprivation.

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**278.I**

**SLEEPINESS AND FATIGUE IN UNIVERSITY STUDENTS**

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**Introduction:** Carskadon<sup>1</sup> pointed out that although these terms are often confused, sleepiness and fatigue are different and should be considered as separate concepts. In contrast, Lee and her colleagues<sup>2</sup> included items in their fatigue scale which assessed sleepiness. Our purpose in this study was to provide data which provide empirical elaboration of the relationships between sleepiness and fatigue.

**Methods:** We tested a large group of undergraduates and identified 309 students who scored low in fatigue, i.e., the bottom 20% on the FIS-10, and 353 students who scored high in fatigue, i.e., the top 20% on the FIS-10. For these Low and High Fatigue Groups, we asked “How long do you sleep on an average night?”; “Are you generally satisfied with your sleep each night?”; and “How much sleep would you like to get each night?” Then, the responses of the two fatigue groups to each of these sleep-related items were compared.

**Results:** The Low Fatigue Group averaged more sleep per night ( $M = 7.00 \pm 1.09$  hrs.) than the High Fatigue Group ( $M = 6.82 \pm 1.09$  hrs.) but the difference between these means was not either statistically significant ( $t = 1.79$ ) or meaningful (est.  $O^2 = .0034$ ). Thus, in testing the difference between these extreme fatigue groups, we observed that their normal habitual sleep durations were about the same. These data clearly support Carskadon’s view that sleepiness and fatigue should be considered as separate variables. However, we also observed substantial differences between these Low and High Fatigue Groups in their responses to the sleep satisfaction question. The majority of the Low Fatigue Group ( $n = 186$  or 60.2%) reported that they were *satisfied* with their sleep while the majority of the High Fatigue Group ( $n = 239$  or 67.7%) reported that they were *dissatisfied* with their sleep. The difference between these response distributions is statistically significant ( $\chi^2_{(1)} = 51.75$ ) and meaningful ( $\phi^2 = .08$ ). Finally, in response to the need for sleep question, the Low Fatigue Group claimed to need less additional sleep ( $M = 1.50 \pm 1.05$  hrs.) than the High Fatigue Group ( $M = 1.96 \pm 1.18$  hrs.). The difference between these means is statistically significant ( $t = 5.17$ ,  $p < .001$ ) but the meaningfulness of this difference is marginal (est.  $O^2 = .04$ ).

**Conclusions:** Overall, these data suggest that the quantity of sleep obtained by these extreme fatigue groups is roughly the same, but that they perceived the quality of their sleep differently. This difference in the perception of sleep quality may be due to the fact that we typically attribute reduced performance to treatments for sleepiness or exhaustion rather than to fatigue. Since the treatments for sleepiness and fatigue are different, it seems prudent for sleep disorders therapists to routinely distinguish between these states.

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## 279.I

### SEX DIFFERENCES IN WORKING MEMORY FOLLOWING PARADOXICAL SLEEP DEPRIVATION

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**Introduction:** Substantial evidence exists in support of the

relationship between paradoxical sleep (PS) and learning (Smith 1996). Research has shown that PS increases exceed baseline levels during specific intervals following the acquisition of a task. Selective paradoxical sleep deprivation (PSD) administered during these paradoxical sleep windows (PSWs) results in memory impairments affecting task performance. Although the majority of animal research studies investigating the effects of PSD on memory have been conducted with male rats, a surprising number of studies (10%) used females. Because the timing of the PSW is sensitive to variations in the species and strain of the subject, the type of task and the intensity of training (1), it is important to question whether the effects of PSD may vary as a function of the sex of the subject as well.

**Methods:** Male ( $n=35$ ) and female ( $n=33$ ) Sprague-Dawley rats were trained on the eight-arm radial maze for ten days. Food rewards were placed in the same four arms and never in the alternate four arms. Following each training session, rats received either 0, 4 or 12 hours of PSD using the “platform” method. The control group was returned to their home cage immediately following training. Three different groups received four hours of PSD either immediately (GR1-4), 4 hours (GR5-8) or 8 hours (GR9-12) after training. The remaining group received PSD for 12 hours beginning 12 hours after training (GR13-24). Re-entries into baited arms after the reward had been taken were scored as working memory errors (WMEs).

**Results:** 1) The analysis of WMEs revealed a significant group effect ( $p < .005$ ). Post-hoc tests indicated that GR9-12 and GR13-24 groups made significantly more WMEs than the control group ( $p < .05$ ). 2) Females committed significantly more WMEs than males ( $p < .001$ ). 3) The performance over trials improved significantly in all groups (learning occurred) ( $p < .005$ ). 4) The group by sex interaction was also significant ( $p < .05$ ). Further analyses indicated that the females in GR13-24 made significantly more WMEs than all other groups ( $p < .05$ ), with the exception of GR9-12 females. This group also performed worse than all groups, except the females from GR5-8 and GR13-24 ( $p < .05$ ). There were no differences in WMEs between any of the male groups.

**Conclusions:** In the male rats, the lack of effect of PSD on working memory is consistent with previous research (2). Overall, the females performed worse than the males, regardless of PSD condition. Most notable is the critical impairment of working memory in GR13-24 and GR9-12 females. These results indicate the presence of a working memory PSW in females.

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## 280.I

### SEX DIFFERENCES IN REFERENCE MEMORY FOLLOWING PARADOXICAL SLEEP DEPRIVATION

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**Introduction:** The connection between paradoxical sleep (PS) and memory is supported by several decades of research (1). There are, however, no published data examining sex differences on the relationship between paradoxical sleep deprivation (PSD) and memory. Recent findings suggest that sex differences exist in the quantity and timing of PS (2). Differences in cognitive abilities, especially those related to spatial memory have also been reported. However, numerous contradictory findings suggest that sex differences in learning can be influenced by a number of factors (3). The purpose of the present study was to observe the effects of PSD on reference memory performance in males and females.

**Methods:** Male (n=35) and female (n=33) Sprague-Dawley rats were trained on the eight-arm radial maze for ten days. Food rewards were placed in the same four arms and never in any of the alternate four arms. Following each training session, rats received either 0, 4 or 12 hours of PSD by means of the "platform" method. The control group rats were returned to their home cage immediately following training. Three different groups received four hours of PSD either immediately (GR1-4), 4 hours (GR5-8) or 8 hours (GR9-12) after training. The remaining group received PSD for 12 hours beginning 12 hours after training (GR13-24). The number of entries into unbaited arms, entries into baited arms without taking the food bait and failure to enter baited arms were recorded as reference memory errors (RMEs).

**Results:** 1) The analysis of RMEs revealed significant group differences ( $p < .005$ ). Post hoc tests confirmed in both males and females that the control group made less errors than GR5-8, GR9-12 and GR-13-24 ( $p < .05$ ). 2) The females committed significantly more RMEs than the males ( $p < .001$ ). 3) There were no initial pre - PSD differences between the various female groups or between the various male groups. 4) The female rats were inferior on these scores prior to PSD ( $p < .001$ ). 5) There was a significant reduction in errors across trials ( $p < .001$ ).

**Conclusions:** Overall, the females performed worse on reference memory than the males, regardless of PSD condition. An impairment for reference memory was evident in males and females from GR5-8 and GR9-12 indicating that there were two common PS Windows (PSW) vulnerable to PS deprivation. However, the GR13-24 female group performed very badly compared to the coinciding male group at this time period, indicating the possibility of yet another additional PSW for the females. Further, more detailed PSD groups must be run to establish the exact position of the PSWs in the 13-24 post training time period.

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## 281.J

### SPLIT-NIGHT POLYSOMNOGRAPHY IN CHILDREN WITH SLEEP-DISORDERED BREATHING

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**Introduction:** Split-night polysomnography (PSG) with continuous positive airway pressure (CPAP) titration has been routinely performed in adults since the 1990s to help reduce the cost of diagnosis and management of obstructive sleep apnea (OSA). The split-night protocol is adequate in determining the effective CPAP pressure, particularly when the apnea-hypopnea index (AHI) is  $>20$  <sup>1</sup>. Its usefulness in children with sleep disordered breathing, however, has not been established. The objective of this retrospective study is to evaluate the effectiveness of split-night PSG with CPAP titration in children with sleep-disordered breathing.

**Methods:** The medical records and PSG results on all children (up to age 18 years) who were seen from July 1999 to October 2001 at our accredited sleep center for suspected sleep-disordered breathing were analyzed.

**Results:** Forty-four patients had split-night PSG's with CPAP titration ordered between July 1999 and October 2001 at our sleep center for suspicion of sleep disordered breathing. Of the 44 patients, 23 did not require CPAP titration because of a normal AHI  $\leq 2$  (n=19) or low AHI of 3-5 (n=4) during the diagnostic segment of the study. CPAP titration was attempted in the remaining 21 patients with AHI  $> 5$ , but was unsuccessful in 4 due to CPAP intolerance. Split-night PSG was successfully carried out in 17 patients (10 males, 11 overweight) who had a mean age of 13 years (range 9-17 years, SD 2) and a mean Epworth sleepiness scale score of 9 (range 0-18, SD 5). Primary symptoms in these 17 subjects were snoring (5), hypersomnolence (4), disturbed sleep (3), fatigue (2), apnea (1), headache (1), and insomnia (1), respectively. Significant co-morbidities were noted in 12 patients: neuropsychiatric (9), respiratory/ENT (4), cardiovascular (2), endocrine (2), orthopedic (2), and gastrointestinal (1). Six had undergone tonsillectomy and adenoidectomy prior to PSG. The mean value of the PSG results (n=17) are shown on the table. REM sleep occurred in 16 of 17 (94%) patients during both the diagnostic and therapeutic segments of the study. A positive diagnosis of OSA was established in 16 of 17 (94%) during the diagnostic segment of the study. The overall CPAP titration failure rate was 4/17 (24%), mainly due to CPAP intolerance. Twelve (71%) reported that they slept more soundly on CPAP. Nasal mask was preferred over nasal pillows (15 to 1), while 1 required a full-face mask for leakage. Seven were prescribed CPAP with a mean level of  $8 \pm 1.5$  cmH<sub>2</sub>O, 5 were referred for tonsillectomy/adenoidectomy, and 5 were managed conservatively (weight loss/positional therapy/antihistamine).

**Table 1**

Parameter	Diagnostic Segment	CPAP Trial Segment	p
TST, min	204.2±54.2	170.7±69	0.23
Sleep efficiency, %	82.2±16.2	80.3±18.8	0.71
Stage 1, %	5.0±3.1	7.9±11	0.24
Stage 2, %	49.4±11.2	55.8±15.6	0.15
Stages 3 & 4, %	34.8±11.3	15.0±13.3	0.001*
Stage REM, %	10.8±5.7	21.3±13.6	0.01*
REM supine, min	10.0±9.7	24.3±24.5	0.04*
AHI	27±35	3±2	0.01*
Lowest O2sat %	85±8	90±3	0.01*
Mean O2sat %	95±2	96±2	ns
Arousal index	18.4±16.6	9.9±9.4	0.10

\*significant p value <0.05

**Conclusions:** Split-night polysomnography is feasible and moderately successful in the diagnosis and management of sleep-disordered breathing in childhood.

**References:**

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**282.J**

**IS CONTINUOUS POSITIVE AIRWAY PRESSURE THERAPY INNOCUOUS?**

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**Introduction:** Use of nasal continuous positive airway pressure (CPAP) has been a major advance in the treatment of obstructive sleep apnea (OSA). Multiple factors influence patients' acceptance of nasal CPAP. These include mechanical characteristics of the device such as weight, dimensions and portability. Noise level, tolerance by the bed partner, and social embarrassment are also important factors. Side effects related to mask and air pressure also influence patients' acceptance. There is paucity of literature regarding long-term consequences of CPAP use. The purpose of this study was to better characterize the long-term patient-based side effects of CPAP use.

**Methods:** Patients were surveyed at VAMC Sleep center Out-patient Clinic. Survey data included: 1) Demographics (age, height, sex, and race), 2) diagnosis and type of treatment (CPAP/BIPAP, type of mask, type of machine, use of chin strap, machine settings, oxygen/humidifier use, Epworth Sleep Scale, CPAP compliance, Length of CPAP use, time to diagnosis of OSA), and 3) CPAP complications (runny nose, stiffed/blocked/congested, complaints from partner about CPAP noise, change in voice, pain on swallowing, jaw pain, toothache, sense of suffocation, excessive salivation, difficulty chewing). Data was analyzed using SPSS 10 for windows (SPSS, Inc., Chicago, Illinois).

**Results:** 112 patients completed the surveys over a 3 month period of time. Mean age 50 years (range 26 to 80), 77% males, Mean length of treatment was 21 months (range 1 to 180 months) and mean CPAP settings were 7.35 (range 3 to

20). Epworth 10 (range 0 to 23), 75% of patients were on CPAP. 57% knew their prescribed pressures, 37% reported that at one point, they were given written information on CPAP. 10% patients wanted machines with less noise, about 15% wanted improved masks, and 40% would miss CPAP if the machine was taken away. Bivariate analysis of data showed that, those using CPAP the longest reported fewer symptoms (such as runny nose, nasal congestion, sore throat etc).

**Table 1**

Category	Complaints		Recently (last 4 weeks)	
	Ever (Since CPAP Started)		Frequency	%
Runny nose	41	36.6	48	42.9
Stuffed nose	55	49.1	34	30.4
Dry nose/throat	54	48.2	36	32.1
Soreness of nose	27	24.1	18	16.1
Headaches	34	30.4	19	17
Eye irritation	30	26.8	15	13.4
Waking repeatedly at night	45	40.2	30	26.8
Air leakage from nasal mask	37	33	17	15.2
Rash on face	37	33	22	19.6
Sense of suffocation	30	26.8	15	13.4

**Conclusions:** A significant number of patients being currently treated with CPAP for OSA, complain of symptoms (stuffed nose, dry nose and throat, headaches, gum aches and swelling). It is interesting to note that about a quarter of patients using CPAP complained of a sense of suffocation. Longitudinal studies are needed to determine if longer use results in fewer symptoms or continued symptoms resulted in disuse.

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**283.J**

**DOES OVERNIGHT PSG OR LEVEL 3 TESTING CONTRIBUTE TO ASSESSMENT OF UNCOMPLICATED OSA?**

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**Introduction:** Patients with obstructive sleep apnea (OSA) who have similar sleep study results (apnea-hypopnea index (AHI) cumulative oxygen desaturation, or arousal index), nevertheless show wide variations in severity of symptoms.

Selection of patients for treatment therefore depends on both clinical and laboratory assessment. The apnea-hypopnea index does not accurately predict improvements in patients' quality of life or compliance with therapy. We measured the ability of experienced sleep physicians to predict whether patients would improve with CPAP treatment, with and without the aid of overnight sleep testing.

**Methods:** A random sample of patients referred for suspicion of OSA excluding those with complications or major comorbidity was assessed clinically, including history, a sleep questionnaire and Sleep Apnea Quality of Life Index (SAQLI), Epworth Sleepiness Score and physical exam, after which the physician estimated the probability of successful treatment as < 25% (category I), 25-50% (category II), 50-75% (category III) or > 75% (category IV). An overnight sleep test was then done. Half the patients had standard polysomnograms, half had home studies with SnoreSat, a level 3 monitor whose operating characteristics compared to PSG are well known to the physicians. With this additional data, the physician made a second estimate of probability of success. All patients were treated 4 weeks with automatically adjusting CPAP. Improvement was defined as an increase  $\geq 1.0$  in SAQLI, a criterion established as a clinically important difference by patients. 230 patients have been studied.

**Results:** For the whole group, compliance defined as mean use > 4 hrs/night was 65%, mean change in SAQLI was 0.84 and 45% of the patients improved by  $\geq 1.0$ . The table shows the proportion of patients in each category who improved on CPAP. Although 60% of patients had their category changed after review of the overnight sleep test, the numbers for the categories show no significant differences, and no trend toward improved accuracy. For comparison, the proportion of patients who improved according to the quartile in which fell their initial SAQLI, Epworth Score and AHI are shown. The correct prediction rate, taken as (number in category I and II who did not improve, plus number in category III and IV who did improve)/total patients, was .64 on clinical assessment, .64 post test, and using the median values as cutoffs, .65 for SAQLI alone, .62 for Epworth Score alone, .67 using AHI alone.

Table 1

Proportion of patients who actually improved				
By Categories	I	II	III	IV
Categories decided clinically	.15	.34	.51	.63
Categories decided post-test	.24	.38	.38	.68
By Quartiles of:				
SAQLI	.14	.39	.48	.65
Epworth	.24	.32	.54	.52
AHI	.30	.21	.52	.63

**Conclusions:** It is not clear that overnight testing improves the ability of experienced sleep physicians to predict which patients will benefit from treatment for uncomplicated OSA. There may be an important role for therapeutic trials after initial clinical assessment in these patients.

## 284.J

### CLINICAL SIGNIFICANCE OF SLEEP-RELATED RESPIRATORY DISORDERS SYNDROME (SRDS) WITHOUT RESPIRATORY EPISODE DURING REM SLEEP

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**Introduction:** The respiratory episodes (RE, apnea and/or hypopnea) in obstructive sleep apnea-hypopnea syndrome (OSAHS) usually occur during sleep stages 1 and 2, are rare during stages 3 and 4, and are more prevalent and can occur solely during rapid eye movement sleep[1]. Several occasions of OSAHS with RE bypassing REM sleep and occurring solely during non-REM sleep were encountered in our lab: no reference reporting this phenomenon was found in the literature. A preliminary investigation was performed and potential clinical significance is discussed.

**Methods:** Fourteen cases without RE during REM sleep were randomly selected as study subjects (Group A), another 14 cases with similar respiratory disorder indices (RDI) during REM sleep and non-REM sleep were chosen as controls (Group B) from 503 adults who have been diagnosed with SRDS but lack apparent cardiac and/or pulmonary diseases. All subjects underwent overnight polysomnography (PSG) and were asked to complete a questionnaire. There was no statistical difference between ages of group A and group B ( $49.71 \pm 13.46$ ,  $46.14 \pm 14.22$  years respectively). BMI (kg/m<sup>2</sup>) of group A ( $24.99 \pm 3.05$ ) was less than that of group B ( $27.96 \pm 3.45$ );  $p=0.023$  (Table 1). Sleep stage scoring and classification of respiratory episodes were performed in accordance with Rechtschaffen & Kales [2]. In addition, hypopnea was further classified as central or obstructive. Irregular oral/nasal airflow was classified as central RE, while others were considered obstructive RE. Symptoms and PSG parameters between groups were statistically tested.

**Results:** 1. Snoring presented in both groups, but habitual loud snoring in group A was significantly reduced compared with group B ( $p<0.01$ ). Insomnia predominated in group A while sleepiness predominated in group B; more patients with depression, anxiety and/or cerebrovascular diseases were found in group A ( $p<0.01$ ). Other symptoms, such as dizziness, daytime tiredness, fatigue, difficulties with concentration and memory, sluggish responsiveness, palpitation, shortness of breath, and hypertension presented equally among both groups ( $p>0.05$ ; Table 1). 2. Sleep structure was abnormal in both groups, with decreased stages NREM 3 and 4, and REM sleep ( $p>0.05$ ). However, the incidence of increased NREM 1 was higher in group A, and an increased NREM 2 stage was higher in group B ( $p=0.01$ ). Additionally, numbers of awakening (>5min), sleep efficiency (SE) <80%, and prolonged REM sleep latency were found more often in group A ( $p<0.05$ ), but episodes of REM sleep were significantly less than group B ( $p=0.01$ ). 3. Group A demonstrated lower degrees of sleep oxygen de-saturation and less total RDI, but higher central RDI ( $p=0.000$ ). Further, the number of patients without mixed RE in group A was significantly greater than group B ( $p<0.05$ ; Table 2).

Table 1

	Group A	Group B	P
Snoring	12 (85.7%)	14 (100%)	>0.05
Loud snore	5 (35.7%)	12 (85.7%)	<0.01
Insomnia	7 (50%)	1 (7.1%)	<0.02
Sleepiness	5 (35.7%)	11 (78.6%)	<0.05
Depressive mood	5 (35.7%)	0 (0.0%)	<0.02
Anxiety	7 (50%)	1 (7.1%)	<0.02
Cerebrovas. Disease	6 (42.9%)	1 (7.1%)	<0.05

Table 2

	Group A	Group B	P
Freq. of Awakening (>5min)	4.50±2.95	2.50 ± 2.47	0.063
% S1	33.31±18.79	16.44±9.96	0.006
% S2	49.42±13.07	63.10±12.51	0.009
% S3-4	5.38±6.02	4.19±5.58	0.592
% REM Sleep	11.89±6.02	16.28±7.36	0.096
Resp. episodes/hr	18.14±12.55	63.40±18.55	0.001
Episodes REM	2.29±0.91	3.36±1.22	0.014
% Central RE	26.18±25.44	6.47±7.61	0.010
Total ODI	17.41±16.94	47.11±25.90	0.001
Lowest %SaO <sub>2</sub>	77.71±6.51	62.29±9.02	0.000
Awake %SaO <sub>2</sub>	95.11±1.35	95.43±1.00	0.479

**Conclusions:** The sleep quality of SRDS with no RE during REM sleep was poor. PSG indicated that non-REM sleep was shallow and difficult to maintain. The disturbance of REM sleep patterns was even more prominent, indicating that certain functional disorders of brainstem reticular structures may exist[3]. Although group A demonstrated a reduced severity of RE with less O<sub>2</sub> saturation, there was a significantly enhanced probability of finding central RE and cerebrovascular disease in this group. Thus, when patients who demonstrate SRDS but lack RE during REM sleep are clinically encountered, examination for potential cerebrovascular lesions is indicated.

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**285.J**

**OBSTRUCTIVE SLEEP APNEA (OSA) IN PEDIATRIC ATTENTION DEFICIT DISORDER (ADD) PATIENTS REPORTING SYMPTOMS OF SNORING AND DAY-TIME SLEEPINESS**

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**Introduction:** Pediatric patients diagnosed with OSA can have symptoms of ADD and display high scores on diagnostic tests for ADD (1). Chervin et. al. (2000) have designed and validated a questionnaire for assessing snoring, sleepiness and associated behavioral problems in pediatric OSA patients. In this study, a questionnaire based on their results was utilized to select patients for polysomnography in order to assess the incidence of OSA in pediatric patients presenting with ADD, snoring and daytime sleepiness.

**Methods:** A questionnaire including eight questions on snoring and breathing (snoring more than ½ the time, always snoring, snoring loudly, heavy breathing and struggling nocturnal breathing, dry mouth in AM, mouth breathing during the day, and observed apnea), four questions on daytime sleepiness (waking un-refreshed, sleepiness, difficulty waking, and reports of sleepiness in class) and four constitutional questions (enuresis, morning headaches, overweight, and stopping growth) was administered to thirty-four pediatric (age 4-15) patients being evaluated by a pediatric psychiatrist at a community mental health center with either the diagnosis of ADD, or in the younger patients, referral for symptoms and evaluation for presumptive ADD. Patients responding positively to the questionnaire were referred to a sleep medicine physician for evaluation and polysomnography. Patients with a previous history of ear nose and throat surgery (T & A) and chromosome abnormalities known to be associated with upper airway obstruction (Downs Syndrome) were not included in this study.

Table 1

Comparison of Means by RDI Group (questionnaire responses, polysomnogram and physical exam data)

RDI	RDI Less than 2. #8 – Mean 1.4	RDI Between 2 & 5 #12 – Mean 3.2	RDI Greater than 5 #14 – Mean 10.2
BMI	15	21	21
Phy. Exam: Enlarged Tonsils	3/8 – 37%	6/12 – 50%	9/14 – 64%
Lowest SaO <sub>2</sub>	85.6	83.9	84.9
Arousal Index	16.3	15.7	12.5
PLMI	10.4	19.1	14.4
(+) Snore Questions Range (0-8)	3.2	2.0	3.0
(+) Sleepiness Questions Range (0-8)	2.4	2.9	2.4
(+) Systemic Questions Range (0-4)	1.1	1.2	1.0

**Results:** 41.1 percent of these patients (14/34) were found to have an RDI > 5.0. Study patients are divided into three groupings for statistical comparison based on Respiratory Disturbance Index (RDI): (RDI < 2.0 – minimal OSA), (RDI > 2.0 and < 5.0 – borderline OSA), and (RDI > 5.0 – diagnostic OSA)[Table 1]. No specific, categorical (snoring, sleepiness or constitutional), or total number of positive responses to the questionnaire varied significantly between groups. No significant variation between groupings was found for age, gender, tonsillar hypertrophy, body mass index (BMI), lowest SaO<sub>2</sub>, sleep latency, or arousal index. Tonsillar hypertrophy and/or elevated BMI occurred with higher frequency in the RDI > 5.0 grouping. Periodic limb movement index (PLMI) was elevated (> 10) in 70% of these patients, however, PLMI did not vary significantly between groupings.

**Conclusions:** In this study, a high percentage (> 40%) of pediatric patients presenting with symptoms of ADD, and reporting daytime sleepiness and snoring on questionnaire were found to have OSA (polysomnographically defined RDI > 5.0).

**References:**

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**286.J**

**THE ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND VENTRICULAR PREMATURE COMPLEXES IN THE WISCONSIN SLEEP COHORT STUDY**

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**Introduction:** Previous studies have shown an association between sleep-disordered breathing (SDB) and cardiac arrhythmias in patients with symptomatic SDB. To date, there has been no study investigating the association of occult SDB with resting electrocardiographically (ECG) indicated ventricular ectopy in the general population. We investigated the association between polysomnographically (PSG) determined SDB and ECG indicated ventricular premature complexes (VPCs) in a population-based sample of middle-aged men and women enrolled in the Wisconsin Sleep Cohort Study.

**Methods:** We performed a cross-sectional analysis on 352 overnight in-laboratory PSG studies to compare the occurrence of VPCs observed in a subgroup of participants with occult SDB to an age- and sex-matched subgroup of participants with no SDB. Participants taking prescription or over-the-counter medications considered to be potentially arrhythmogenic or antiarrhythmic were excluded from the analysis. SDB status was defined by the apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour of sleep, as a summary measure. Occult SDB was defined as an AHI >= 5.

Occurrences of VPCs were recorded from a continuous, overnight ECG rhythm tracing by trained readers blinded to the participant's SDB status. The relationship between AHI categories (AHI < 5, n=195; AHI 5-30, n=139; AHI >= 30, n=18) and 5 or more VPCs per night during sleep was investigated using multiple logistic regression analysis, controlling for age, sex, total sleep time, BMI, history of heart disease, and alcohol and smoking status.

**Results:** The mean age of study participants was 48 years; 72% were men, 28% women. The overall prevalence of 5 or more VPCs per night was 15%. The proportion of participants with 5 or more VPCs in each AHI category (AHI < 5, 5-30, >= 30) was 13%, 14%, and 44%, respectively. As shown in Table 1, the adjusted odds ratio of 5 or more VPCs for AHI >= 30 vs. AHI < 5 was 6.9 (95% CI: 2.04, 23.50). The adjusted odds ratio of 5 or more VPCs for AHI 5-30 vs. AHI < 5 was 1.1 (95% CI: 0.5, 2.2). Age and history of heart disease were also significantly associated with VPCs.

**Table 1**

**Association between VPC Prevalence and AHI Categories**

AHI	VPCs ≥ 5 (%)	Adjusted O.R.	95% C.I.
<5	13	Reference category	---
5-30	14	1.1	0.50-2.20
≥30	44	6.9	2.04-23.50

**Conclusions:** We found a significant association between SDB and VPCs in a subgroup analysis of participants from the Wisconsin Sleep Cohort Study. This association was limited to the moderately severe SDB category of AHI >= 30. These findings suggest that moderately severe SDB may be a risk factor for cardiac electrical instability, which can lead to more serious cardiac arrhythmias.

**287.J**

**AN UPPER AIRWAY CEPHALOMETRIC COMPARISON BETWEEN UPRIGHT AND SUPINE BODY POSITIONS IN OBSTRUCTIVE SLEEP APNEA PATIENTS**

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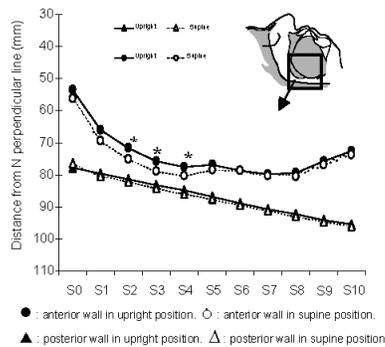
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**Introduction:** A supine-related reduction in upper airway (UA) size is known to increase UA resistance and may lead to a worsening of Obstructive Sleep Apnea (OSA)(1). It is known that OSA may worsen, or occurs only when the patient adopts a supine posture (2). Since the UA acts like a tube structure, UA resistance appears to increase at the narrowest segment. Identification of the most constricted site in the UA of supine OSA patients would be useful to determine possible treatment options and to evaluate the effects of a specific therapy (3). The purpose of this study was to locate the area of the UA which underwent the greatest constriction after a change in body position from upright to supine.

**Methods:** Fifteen OSA patients with an Apnea Hypopnea Index greater than 10/hour participated in the study. A set of upright and supine cephalograms were traced and digitized for each patient by the same investigator. Two tailed paired t tests were used to compare differences between the upright and supine position for each variable. Bonferroni's inequality corrections for significance levels were applied. A statistically significant difference between means was defined as a value of  $p < 0.05$ .

**Results:** The most constricted site in the upright position was in the velopharynx (figure 1). When the body position changed from upright to supine, a significant reduction in the antero-posterior dimension was observed only in the velopharynx ( $p < 0.05$ ). Saggital cross-sectional areas of the velopharynx and the oropharynx decreased significantly ( $p < 0.05$ ), but the soft palate increased ( $p < 0.05$ ). In addition, the vertical airway length significantly decreased ( $p < 0.05$ ) (table 1).

**Figure 1**



**Table 1**

**Comparison of Upright and Supine Area Variables**

Area (mm <sup>2</sup> )	Upright	Supine	Difference	SD	p
Tongue	3855.73	3829.27	-26.46	273.16	NS
Soft Pal	441.77	491.65	49.88	44.02	0.0006**
Nasopx	256.76	243.78	-12.98	22.86	0.0451*
Velopx	395.56	302.59	-92.97	87.73	0.001**
Oropx	280.48	236.22	-44.26	63.8	0.0177*
Hypopx	280.00	335.91	55.91	152.87	NS

\*:  $p < 0.05$     \*\*:  $p < 0.01$     NS: not significant

**Conclusions:** We conclude that the velopharynx is not only the most narrowed site in both the upright and supine body positions but also the most changeable site in response to an alteration in body position. Backward displacement of the soft palate in conjunction with a change of in shape may contribute to UA occlusion in OSA patients.

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**288.J**

**DAYTIME SLEEPINESS IN THE APNEIC PATIENT AS A FUNCTION OF DIFFERENT MSLT SLEEP ONSET CRITERIA.**

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**Introduction:** Previously we suggested that arousals due to repetitive disturbances (apneas, hypopneas, or PLMS) during MSLT recording could affect sleep latencies (Mahajan et al, 2001; Neeb et.al; 2001). We speculated that arousals during the transition to sleep but prior to meeting the sleep onset criteria (16 s) could result in longer sleep latencies and an under-estimation of sleepiness. The latter may be why some patients with high RDI scores fall within the normal alertness range on the MSLT. Others have made a similar argument. Presumably the more frequent these repetitive disturbances, or the greater the opportunity for their occurrence, the longer the delay in meeting the standard sleep onset criterion (16 s 30 s epoch). The present research further evaluates the above hypothesis using four sleep onset durations combined with three RDI levels. According to the hypothesis the greater the probability of an arousal during wake/sleep transition, the longer the delay in meeting the sleep onset criterion. Therefore, longer duration criteria for sleep onset and higher patient RDIs should result in more frequent arousals and thus longer sleep latencies.

**Methods:** Archival records of 90 patients diagnosed with obstructive sleep apnea were selected (three groups of 30 patients each) based on their RDI: Low (5-20); Medium (21-40); Severe (41-60). Each patient's MSLT record was scored using four different sleep criteria for defining sleep onset (5 s, 10 s, 15 s and the standard 16 s). In the first three conditions, sleep onset was determined at the first occurrence of 5, 10 or 15 s of uninterrupted sleep. In the 16 s condition sleep was accumulative across a 30 s epoch.

**Table 1**

	Sleep Onset Duration				Mean
	5 s	10 s	15 s	16 s	
RDI (5-20)	5.93	7.07	8.95	9.94	7.97
RDI (21-40)	5.75	7.12	9.62	9.88	8.09
RDI (41-60)	5.86	7.22	9.21	10.15	8.11
Mean	5.86	7.14	9.26	9.99	

Mean MSLT latencies (min) with different sleep onset durations and RDIs

**Results:** Table 1 contains mean sleep latencies for the three RDI levels and four sleep onset durations. The data reveal that the duration criterion used for defining sleep onset has a marked effect on MSLT latency. The shorter the duration of

sleep for defining sleep onset, the shorter the sleep latency. Statistical analysis (ANOVA and individual comparisons) of column means revealed that all duration comparisons were significant ( $p < .01$ ). Surprisingly, RDI had little effect on sleep latency (row means). There was no interaction ( $p > .05$ ) and latency scores for the three RDI levels were not significant. Correlations of RDI with sleep latency were generally low and non-significant.

**Table 2**

	Sleep Onset Duration				
	5 s	10 s	15 s	16 s	
RDI (5-20)	17	12	6	4	39
RDI (21-40)	14	9	6	3	32
RDI (41-60)	13	8	4	4	29
Total	44	29	16	11	

Number of sleep onset latencies (min) 5 min or less.

**Conclusions:** These data suggest the duration criteria used to define sleep onset can be a major factor in determining sleepiness. The shorter the duration criteria, the more frequent the diagnosis of pathological sleepiness. The most parsimonious explanation relates to the intermittent intrusions of brief sleep episodes during the wake/sleep transition. It remains to be determined, however, the specific cases or conditions in which it would be beneficial to use a shorter criterion.

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**289.J**

**KIPPEL-TRENAUNAY SYNDROME AS AN UNUSUAL CAUSE OF OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Klippel-Trenaunay Syndrome (KTS) is a congenital dysplastic angiopathy with no known cause. KTS is characterized by a triad of port-wine stains, varicose veins, and bony or soft tissue hypertrophy of one or more extremities. Seizures have been described in association with this disorder, but no reports exist (to the author's knowledge) which describe an association with sleep disordered breathing. This case study presents a novel and unusual cause for obstructive sleep apnea.

**Methods:** Two polysomnograms were performed upon the subject: The first to evaluate the patient's sleep and the second, a CPAP titration study, to maximize treatment of the patient's observed sleep apnea. An otolaryngology consult was

obtained and a fiber-optic laryngoscopy of the nasal, oral and pharyngeal cavities was performed. A MRI and MRA examination of the head and neck was performed. Long-term video EEG monitoring was performed to clarify the etiology of the patient's symptoms and localize the origin of them.

**Results:** A 30-year-old woman presented with hemi-hypertrophy and subcutaneous hemangiomas involving primarily the right side of her body. She had a past history of epilepsy as well as spells of unresponsiveness which were presumed to be secondary to epilepsy and a long history of daytime sleepiness. She also described that if she laid flat, her neck would "swell" and she would "stop breathing". The polysomnogram showed severe obstructive sleep apnea, with a respiratory disturbance index of 94.4 per hour. The events occurred both in REM and non-REM sleep when the head of the bed was not elevated and in any position. The patient had a minimum oxygen saturation of 77 percent during the apneic episodes, CPAP titration showed that a final setting of 8 cm of water was tolerated well, and caused a resolution of the previously documented obstructive respiratory events. It was also found that the patient needed to have the head of her bed elevated. Otolaryngologic and MRI examinations disclosed that the patient had varicosities within the upper airway which were contributing to the obstruction of the patient's airway. Long term video EEG monitoring disclosed bilateral, independent epileptiform activity and complex partial seizures with multifocal onset not associated with patient's apneic episodes. The patient's obstructive sleep apnea has been improved with the use of CPAP with clinical improvement in symptoms of daytime sleepiness. The patient underwent surgical intervention to reduce the size of the varicosities, both externally and within the airway. Seizure control was improved with medication changes.

**Conclusions:** This case study presents a rare and unusual cause of obstructive sleep apnea. The information gained from this case study provides a model for collaborative evaluations of complex patients with sleep complaints not only this rare syndrome. Further polysomnographic studies of this patient may be beneficial to show the improvement after the patient has had additional treatment to reduce the size of these blood vessels.

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**290.J**

**PERSONALITY TRAITS OF COMPLIANT CPAP USERS**

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**Introduction:** Personality is a critical factor in the manifestation and expression of many disease states. Personality significantly impacts on patient compliance and acceptance of treat-

ment. Although behavioral attitudes represent heritable temperaments based upon neurobiological substrates, theoretically they might be influenced by environmental factors and chronic illnesses. To date, there are very few studies considering personality factors in the diagnosis and treatment of sleep disorders in general. To the best of our knowledge there are no studies specifically focused on behavioral attitudes and compliance in sleep apnea. The purpose of the present study was to evaluate personality traits in a sample of compliant CPAP users as judged by two personality scales – The Temperament and Character Inventory (TCI)<sup>1</sup> and Behavioural Attitudes and Search Evaluation test (BASE)<sup>2,3</sup>.

**Methods:** Twenty two patients (12 males and 9 females, aged  $56.4 \pm 13.4$ ) of the Sleep and Alertness Clinic who have been successfully using CPAP therapy for 1.5-2 years nightly for at least 7 hours per night participated in the study. All patients received TCI and BASE tests in an interview setting. Personality traits such as novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence have been assessed in the analysis. The semiprojective test BASE was used to assess different behavioral attitudes including search activity pattern, stereotyped, panic and passive behaviors. Analysis of variance using a general linear model procedure was employed to detect statistically significant differences in personalities' traits. Further analysis included Tukey post hoc paired comparisons and non-parametric Mann-Whitney's U-test.

**Results:** There were no significant gender differences with respect to CPAP compliance. All CPAP users had high search activity scores as judged by the BASE questionnaire. However female patients scored significantly lower on search activity than that of the male patients ( $p=.01$ ). Both males and females scored lowest in those patterns classified as passive and chaotic behaviors. There were no significant differences on male and female scores for stereotyped behavior. On the TCI, CPAP patients demonstrated a combination of high harm avoidance scores and average scores for novelty seeking behaviors. Females scored significantly higher on harm avoidance scale than male CPAP users ( $p=.02$ ). It is noteworthy that there were no gender differences on novelty seeking patterns of behaviors. Males scored significantly higher than females on self-directedness scales ( $p=.01$ ) There were no any significant differences on other personalities' traits as measured by the TCI.

**Conclusions:** In this study we have shown that a group of patients with high CPAP compliance had strong search activity attitudes as judged by the BASE questionnaire. The discrepancy between prominent search activity patterns and average scores on novelty seeking behaviors as measured by the TCI implies that these two similar personality traits' instruments measure different behavioral domains.

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## 290.J

### PERSONALITY TRAITS OF COMPLIANT CPAP USERS

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**Methods:** Twenty two patients (12 males and 9 females, aged  $56.4 \pm 13.4$ ) of the Sleep and Alertness Clinic who have been successfully using CPAP therapy for 1.5-2 years nightly for at least 7 hours per night participated in the study. All patients received TCI and BASE tests in an interview setting. Personality traits such as novelty seeking, harm avoidance, reward dependence, persistence, self-directedness, cooperativeness and self-transcendence have been assessed in the analysis. The semiprojective test BASE was used to assess different behavioral attitudes including search activity pattern, stereotyped, panic and passive behaviors. Analysis of variance using a general linear model procedure was employed to detect statistically significant differences in personalities' traits. Further analysis included Tukey post hoc paired comparisons and non-parametric Mann-Whitney's U-test.

**Results:** There were no significant gender differences with respect to CPAP compliance. All CPAP users had high search activity scores as judged by the BASE questionnaire. However female patients scored significantly lower on search activity than that of the male patients ( $p=.01$ ). Both males and females scored lowest in those patterns classified as passive and chaotic behaviors. There were no significant differences on male and female scores for stereotyped behavior. On the TCI, CPAP patients demonstrated a combination of high harm avoidance scores and average scores for novelty seeking behaviors. Females scored significantly higher on harm avoidance scale than male CPAP users ( $p=.02$ ). It is noteworthy that there were no gender differences on novelty seeking patterns of behaviors. Males scored significantly higher than females on self-directedness scales ( $p=.01$ ) There were no any significant differences on other personalities' traits as measured by the TCI.

**Conclusions:** In this study we have shown that a group of patients with high CPAP compliance had strong search activity attitudes as judged by the BASE questionnaire. The discrepancy between prominent search activity patterns and average scores on novelty seeking behaviors as measured by the TCI implies that these two similar personality traits' instruments measure different behavioral domains.

**References:**

- (1) Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The Temperament and Character Inventory (TCI): a guide to its development and use. St. Louise, MO: Washington university Center for Psychobiology of Personality, 1994.
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- (3) Hossain NK, Kayumov L, Rotenberg V, Shapiro CM. Behavioural attitudes and sleep patterns in depression and sleep apnea. *Sleep Research Online* 1999; 2: 308.

**291.J**

**SUCCESSFUL TREATMENT OF OBSTRUCTIVE SLEEP APNEA THROUGH CORRECTION OF DENTAL OCCLUSAL ABNORMALITIES**

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**Introduction:** Investigators have demonstrated physiologic and anatomical abnormalities in the upper airway of patients with obstructive sleep apnea (OSA) including increased daytime genioglossus muscle activity, an alteration in shape of the airway, and cephalometric changes with low placement of the hyoid bone. The ability of the upper airway to change physiologically and anatomically secondary to longstanding malocclusion was eloquently developed by Nove in a series of articles in 1946, and by Enlow in his classic text on facial growth.<sup>2</sup> Nove observed that "When the jaws are incorrectly opposed, this indispensable pivot or fulcrum for normality is out of true and all of the structural units concerned with mastication, deglutition and respiration are compelled to function by means of adaptation." Recent experience with several patients with OSA, presenting with malocclusion, have led us to postulate that the changes described are secondary to abnormal adaptation by the upper airway to compensate for a chronically disturbed bite resulting in persistence of an infantile (deviate) swallowing pattern; and that correction of the occlusal abnormalities using daytime and nighttime splints may reduce the severity of the apnea.

**Methods:** Three patients with obstructive sleep apnea were evaluated for dental occlusal abnormalities using a technique consisting of an extensive dental examination, craniometric measurement and dynamic recordings with a ball-bearing bite recorder. These techniques are described in detail elsewhere.<sup>3</sup> Appliances to improve mandibular positioning were made. This required several visits with alteration in the appliance as adaptive changes occurred in the musculature. A nighttime appliance, also designed to maintain normal dental relationships was constructed. One of the patients had tried mandibu-

lar advancement devices and surgical intervention with little success. All tried and were unable or unwilling to use nasal CPAP or BiPAP. Polysomnography was performed before and after dental therapy.

**Results:** The cases in this report were found to have abnormal medial, anterior, posterior or vertical alignment. Each patient was corrected in a specific way designed to address the problem. The three patients all had dramatic drops in RDI, arousal indices and ESS scores on their PSM's performed after treatment (See Table.1). No reduction in BMI occurred. The results were comparable to or better than CPAP and BiPAP, in the two patients who had tried positive-pressure therapy. They experienced improved swallowing, posture, and daytime breathing and found the splints quite comfortable.

**Table 1.**

Patient	Age	BMI	Therapy	RDI	Arous-I	ESS
RO	53	31.2	None	56	60	8
			Occlusal	6	7	2
JM	27	25.9	None	31	33	17
			Tons. UPPP	31	31	18
			CPAP	15	40	12
			BiPAP	10	33	17
			Occlusal	13	15	5
JB	51	24.3	None	38	80	11
			CPAP	43	78	18
			Occlusal	10	47	12

**Conclusions:** The benefit observed in these three patients with OSA, treated with correction of occlusal abnormalities, supports an alternative dental approach to this disorder. Correction of the abnormal opposition of the maxilla and mandible should, with time, reverse these abnormal adaptations. While occlusal therapy requires that an appliance be worn during the day to maintain appropriate craniofacial relationships and muscle balance, these devices, adjusted over time, provide normal and more comfortable dental relationships and appear to be well accepted in our patients.

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**292.J**

**CHANGES IN BECK DEPRESSION INVENTORY (BDI) SYMPTOMS AFTER CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT FOR OBSTRUCTIVE SLEEP APNEA (OSA)**

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**Introduction:** Many studies have documented elevated

depression levels in OSA patients that improve subsequent to CPAP treatment. However, few researchers have considered type (i.e., affective/cognitive vs. somatic/vegetative) of depressive symptom change in these patients. The overlap in somatic symptoms between OSA and depression has led Lee and colleagues (1) to postulate that depression in OSA patients predominantly reflects OSA symptoms. The present study explored differences in affective versus somatic symptoms of depression in OSA patients after CPAP treatment.

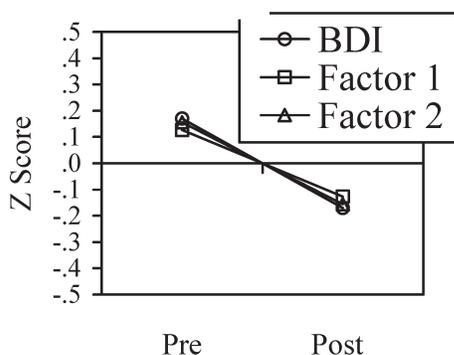
**Methods:** Thirty-nine outpatients (90% male; M age=57.8 years) undergoing routine diagnostic polysomnography (PSG) for OSA at a sleep disorders center completed the BDI prior to PSG and 3 months following initiation of CPAP. Participants had no co-existing sleep disorders, no psychiatric history, and were not taking psychotropic medications. The BDI was selected for this study because previous factor analyses (2) have yielded two main factors that correspond with the distinction between affective and somatic symptoms.

**Table 1**

	Non-Depressed	Mild	Moderate	Severe
Pre-CPAP	64.1%	25.6%	7.7%	2.6%
Post-CPAP	69.2%	25.6%	5.1%	0.0%

Note. Non-Depressed = BDI score <10;  
Mild = 10-18; Moderate = 19-29; Severe = >29.

**Figure 1**



**Results:** The difference in BDI scores from baseline (M = 9.59, SD = 7.63) to follow-up (M = 7.26, SD = 5.85) was significant ( $t[38] = 2.92, p < .01$ ). Table 1 presents the distribution of BDI scores before and after CPAP. Although most patients were non-depressed, there were fewer moderately and severely depressed patients after CPAP (Chi-square [6, N = 39] = 34.93,  $p < .001$ ). Factor scores for affective symptoms

(Factor 1) and somatic symptoms (Factor 2) were computed. Symptom change was analyzed using a repeated measures MANOVA, with total BDI and factor scores entered as dependent variables. There was a significant effect for time (Wilks  $\lambda$  [3, 36] = .80,  $F [3, 36] = 2.98, p < .05$ ). Univariate F tests were significant for all three dependent variables: total BDI ( $F [1, 38] = 8.52, p < .01$ ), Factor 1 ( $F [1, 38] = 5.39, p < .05$ ), and Factor 2 ( $F [1, 38] = 4.70, p < .05$ ). To compare change in symptoms, z-scores were calculated using the overall mean and standard deviation (Figure 1). These results suggest that although scores improve after treatment, affective symptoms improve to the same extent as somatic symptoms.

**Conclusions:** OSA patients treated with CPAP showed improvements in BDI scores, although pre-treatment mean scores were in the non-clinical range. Analysis of symptom change suggests that patients are not only endorsing somatic symptoms of depression but are expressing affective symptoms as well. The present study provides suggestive evidence that depressive symptoms in OSA patients are not entirely attributable to somatic symptoms shared by OSA and depression.

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**293.J**

**AN EVALUATION OF A NEW BILEVEL MODE FOR THE TREATMENT OF OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME (OSAHS)**

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**Introduction:** Bilevel positive airway pressure is a treatment modality where expiratory and inspiratory pressures are set independently to prevent apnea, hypopnea and snoring. BiFlex™ is a bilevel mode that alters the end-inspiratory and initial expiratory pressure characteristics. BiFlex reduces inspiratory pressure (IPAP) towards end-inspiration smoothing the transition from the inspiratory to the expiratory phase. With the BiFlex mode a lower expiratory pressure (EPAP) is delivered during the beginning of the expiratory phase (1). The BiFlex feature is expected to improve patient comfort and compliance with positive pressure therapy without negatively influencing sleep quality. This study was undertaken to determine if BiFlex alters conventional bilevel pressure requirements.

**Methods:** Ten patients (8 male, 2 female, mean age 58.3 ± (SD) 12.7 years, BMI 33.6 ± 9 (SD)) who were previously diagnosed with OSAHS and who were already receiving CPAP therapy were recruited. Full night polysomnography was performed on two, non-consecutive nights. Patients were blinded as to which mode they were receiving (bilevel or bilevel with BiFlex). On the first night, patients received con-

ventional bilevel therapy to determine pressure requirements. On the second night, patients received bilevel therapy with BiFlex. BiFlex gains were set at a level the patient found to be most comfortable while awake, prior to the second PSG. Therapy pressure requirements, RDI, apnea index, hypopnea index, and mean saturation were compared from the PSG recordings on both nights. Paired data (bilevel versus bilevel with BiFlex) were analyzed with Student's t-Test assuming unequal variance.

**Results:** Comparing the results of bilevel therapy to bilevel therapy with BiFlex, there were no significant differences in the frequency and severity of sleep related breathing events (Table 1). The inspiratory and expiratory pressure required to treat the patients did not differ significantly. (Table 2).

Table 1

**Results: Sleep Parameters**

Variable	Bilevel Therapy Mean (±S D)	Bilevel with BiFlex Mean (±S D)	p-Value
RDI	1.37 (1.63)	1.07 (1.20)	0.64
Apnea Index	0.5 (1.2)	1.2 (1.1)	0.21
Hypopnea Index	5.3 (7.1)	4.8 (7.7)	0.88
Mean Saturation	95.3 (0.24)	95.2 (0.27)	0.89
Sleep Latency	5.3 (4.46)	6.56 (8.61)	0.71
Sleep Efficiency	81.24 (14.83)	75.6 (11.14)	0.43
% TST Stage 2	52.54 (12.70)	51.24 (14.38)	0.85
% TST Stage 3/4	17.02 (13.95)	15.35 (8.23)	0.77
% TST REM	17.41 (6.11)	19.33 (9.13)	0.63

Table 2

**Results: Therapy Comparison**

Variable	Bilevel Therapy Mean(±S D)	Bilevel with BiFlex Mean(±S D)	p-Value
Inspiratory Positive Airway Pressure	12.1 (3.8)	12.2 (7.7)	0.95
Expiratory Positive Airway Pressure	6.6 (3.4)	6.7 (3.4)	0.94
Patient Preference	3	6	

**Conclusions:** In a group of patients who by age and BMI, are typical of patients with OSAHS, this evaluation detected no difference in therapy requirements between standard bilevel and bilevel therapy with BiFlex. There were no significant differences in sleep quality. Twice as many patients preferred bilevel with BiFlex compared to standard bilevel therapy. BiFlex may offer advantages in comfort over conventional positive pressure therapy without altering therapy pressure requirements.

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**294.J****EFFICACY OF ORAL CPAP IN THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA.**

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**Introduction:** Continuous positive airway pressure (CPAP) is considered the 'gold standard' treatment for obstructive sleep apnea (OSA). This positive pressure is traditionally applied via a nasal mask or full-face mask, which some patients find intolerable due to nasal discomfort, mask or mouth leaks and cumbersome headgear. These adverse effects can lower patient compliance, and in some cases, cause patients to cease treatment altogether. This randomised, crossover study assessed the efficacy of an innovative oral device, which allows positive pressure to be delivered via the mouth, compared with traditional nasal CPAP.

**Methods:** Twenty-two CPAP-naive OSA sufferers (18 Male, 4 Female) were randomised to receive CPAP treatment via a nasal mask (Aclaim™, Sullivan Standard, Mirage® or Ultra Mirage™) (13 patients, mean age 42.0 ± 10.2 years, mean BMI 41.6 ± 7.5 kg/m<sup>2</sup>) or the Oracle™ oral interface (9 patients, mean age 48.6 ± 11.4 years, mean BMI 43.3 ± 7.1 kg/m<sup>2</sup>). Patients were diagnosed in a sleep laboratory using a standard polysomnography (PSG). When OSA was evident (AHI > 20/hr slept) after a 2-hour minimum diagnostic period, CPAP therapy was initiated with the first treatment arm. CPAP pressure was titrated to eliminate all evidence of upper airway obstruction. The diagnostic and treatment studies, at the final titrated pressure, were analysed in a blinded fashion. The study end-points were patient compliance with CPAP and subjective and objective data on CPAP efficacy with each interface. Calculations for significant differences with rejection of the null hypothesis at a p < 0.05 were carried out using two-tailed student t-tests. This trial is currently in progress and therefore only data from the first treatment arm is presented here.

**Results:** Two patients in each treatment group withdrew because they could not tolerate CPAP. One additional patient in the oral group was excluded because compliance data was unobtainable. Disease severity was similar between the two groups (Table 1). There was no significant difference in the monitored compliance between the two interfaces with a mean compliance of 3.8 ± 2.3 hrs/night and 3.2 ± 1.5hrs/night for nasal and oral, respectively (p = 0.60). Mean (SD) Epworth Sleepiness Scores at baseline were 16.5 (± 3.2) and 18.5 (± 2.1) for nasal and oral, respectively (p = 0.24). After four weeks of CPAP treatment on the randomised interface this decreased to 6.4 (± 3.2) and 8.0 (± 6.1), respectively (p = 0.53). There was no significant difference in PSG data between the two treatment groups (Table 1 & 2).

**Table 1**

Mean (SD) baseline PSG parameters			
	NASAL (n = 11)	ORAL (n = 6)	p value
AI (per hr of sleep)	75.0 (36.1)	72.8 (30.1)	0.90
AHI (per hr of sleep)	88.3 (37.0)	92.9 (39.3)	0.81
Sleep efficiency (%)	81.7 (7.0)	82.3 (11.6)	0.90
Minimum SaO <sub>2</sub>	68.6 (14.1)	69.3 (5.2)	0.91
REM (% TST)	11.1 (9.0)	8.8 (8.2)	0.61

**Table 2**

Mean (SD) PSG parameters on CPAP			
	NASAL (n = 11)	ORAL (n = 6)	p value
AI (per hr of sleep)	8.9 (5.8)	15.7 (13.0)	0.15
AHI (per hr of sleep)	14.4 (19.9)	19.4 (18.8)	0.62
Sleep efficiency (%)	94.5 (5.4)	92.8 (5.2)	0.53
Minimum SaO <sub>2</sub>	86.8 (7.7)	82.8 (10.9)	0.91
REM (% TST)	23.5 (13.3)	26.0 (5.3)	0.67

AI = Arousal Index  
 AHI = Apnea/Hypopnea Index  
 TST = Total sleep time

**Conclusions:** Sleep parameters and CPAP compliance revealed no significant differences between the nasal and oral interfaces. CPAP delivery through the mouth is as effective as delivery through the nose. In addition, oral and nasal CPAP were equally accepted by patients.

Research supported by Fisher & Paykel Healthcare

**295.J**

**TWO-POINT PALATAL DISCRIMINATION RESPONSE IS NORMAL IN UPPER AIRWAY RESISTANCE SYNDROME AND REDUCED IN OBSTRUCTIVE SLEEP APNEA SYNDROME**

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**Introduction:** Patients with Upper Airway Resistance Syndrome (UARS) show increased respiratory effort, arousals related to increased effort and hypopneas. By contrast patients with Obstructive Sleep Apnea Syndrome experience obstructive apneas and hypopneas associated with oxygen desaturation. UARS patients show increased 7 to 9 cps electroencephalographic (EEG) power spectrum of the central leads compared to normals. The EEG power spectrum of patients with OSAS shows a delayed arousal response. Friberg et al(1). have shown abnormalities including evidence of neurogenic lesions in histological analyses of palatopharyngeal muscle biopsies obtained from OSAS patients. These findings corroborate earlier work by Edstrom et al(2). We hypothesize that there also may be differences in sensory input in UARS compared to OSAS. We theorize sensory differences associated with neurogenic lesions may play a role in the delayed response to arousal found with abnormal breathing events in OSAS. Our investigation analyzed the response to a two-point

discrimination test applied to the palatal mucosa

**Methods:** Fifteen each of normal subjects, OSAS patients and UARS patients between 35 and 50 years of age were age, sex and body mass index (BMI) matched. Subjects were recruited from the community and patients from the Stanford Sleep Disorders clinic. All participants underwent full nocturnal polysomnogram (PSG) with esophageal manometry following interview and physical examination. OSAS patients were included who had an apnea-hypopnea index (AHI) >15 events/hour, UARS patients an AHI <5 and normal controls were included only if they had an AHI < 1 without evidence of increased respiratory effort as described for UARS. A preliminary evaluation was performed using a modified 25gauge needle on a tuberculin syringe. The patient was first given a tactile stimulus with the needle in contact with the mucosa at 0.5 mm. If no sensation noted, at two minute intervals pressure was applied at 1 mm then 2 mm if needed. After preliminary measurements, a compass type device was then used to evaluate two-point discrimination. Two-point detection was measured twice in the three selected palatal locations in a random way. The best result of 6 measurement trials is presented in Table 1.

**Table 1**

OSAS two-point discrimination compared to UARS

S	AGE	BMI	AHI	2 pt	A	BMI	AHI	2 pt	ERA
F	39.6	24.1	21	3.5	39.1	23.9	2.0	1.5	17
F	41.1	23.9	28	3.0	39.6	23.7	1.3	1.0	22
M	40.6	25.1	35	3.5	43.0	24.8	3.0	1.5	29
M	42.3	25.7	39	4.0	40.2	25.1	3.1	2.0	31
M	37.0	25.3	29	3.5	37.0	24.2	1.6	1.5	23
M	48.7	24.8	33	3.0	47.1	24.4	3.3	2.0	24
M	42.2	25.6	37	4.0	43.8	24.8	2.3	2.0	31
M	39.3	24.8	32	3.5	41.4	24.6	1.8	2.5	26
M	41.9	25.2	38	4.5	40.6	24.7	2.1	1.5	34
M	38.9	24.7	32	4.0	40.1	25.0	1.6	1.5	26
M	38.1	25.8	31	3.5	37.1	24.7	2.9	1.5	28
M	46.6	25.9	32	4.0	47.1	25.0	3.1	1.5	27
M	44.2	25.6	36	4.5	44.9	24.9	2.4	1.0	31
M	41.7	25.5	39	5.0	42.1	25.0	2.2	2.0	34
M	41.9	24.9	40	4.5	40.2	24.4	1.9	2.0	36
OSAS					UARS				

**Table 2**

OSAS two-point discrimination compared to Normal Controls

S	A	BMI	AHI	2 pt	A	BMI	AHI	2 pt
F	39.6	24.1	21	3.5	38	23.6	0.0	1.5
F	41.1	23.9	28	3.0	40	23.4	0.0	1.5
M	40.6	25.1	35	3.5	42	24.4	0.2	1.5
M	42.3	25.7	39	4.0	41	25.2	0.7	1.5
M	37.0	25.3	29	3.5	36	24.5	0.1	2.0
M	48.7	24.8	33	3.0	48	24.1	0.2	1.5
M	42.2	25.6	37	4.0	43	24.9	0.1	1.5
M	39.3	24.8	32	3.5	40	24.3	0.0	1.5
M	41.9	25.2	38	4.5	41	24.6	0.4	2.0
M	38.9	24.7	32	4.0	39	24.3	0.1	2.0
M	38.1	25.8	31	3.5	37	25.2	0.2	1.5
M	46.6	25.9	32	4.0	47	25.2	0.4	1.5
M	44.2	25.6	36	4.5	44.2	24.5	0.8	1.5
M	41.7	25.5	39	5.0	42	24.7	0.3	1.5
M	41.9	24.9	40	4.5	40.6	24.1	0.6	2.0
OSAS					Normal Controls			

**Results:** Results5 OSAS patients needed the 1 mm marker to recognize pressure at one point and 4 with OSAS needed pressure to the 2 mm mark to note sensation. One OSAS patient was an outlier with a two-point discrimination distinction at 15 mm. Review of clinical history implicated coexistent GERD, this subject was excluded from the analysis of results. Two point distinction evaluation revealed a significant difference between the OSAS patients and the other two groups. The mean ( $\pm$ SD) values were 3.86 (0.58), 1.66 (1.0) and 1.63 (0.29) for OSAS, UARS and Controls respectively (Mean rank = 38.0, 15.9, 15.1).  $p = .0001$ .

**Conclusions:** The normal two-point discrimination responses seen with UARS indicate that these patients are more capable of transmitting sensory inputs than those with OSAS. This may be one element in explaining the arousal response previously documented in UARS compared to OSAS. These conclusions are consistent with the recent work of Kimoff<sup>3</sup> et al. who concluded a selective impairment in the detection of mechanical stimuli in OSAS patients could be partially reversed with CPAP.

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**296.J**

**A NEW AIRFLOW SENSOR FOR THE DETECTION OF FLOW LIMITATION IN SLEEP-DISORDERED BREATHING**

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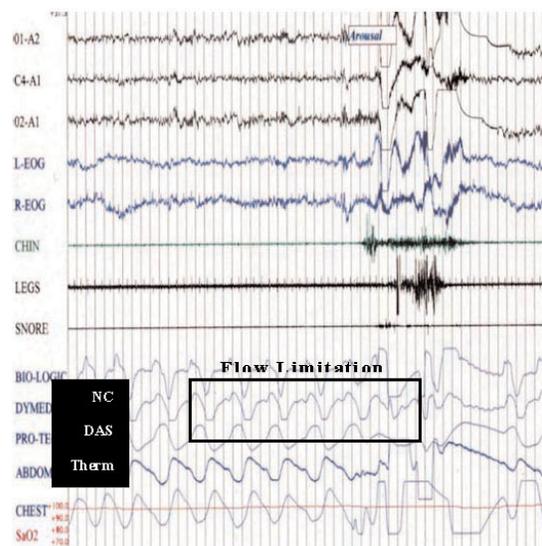
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**Introduction:** The diagnosis of Sleep-Disordered Breathing has become more dependent on the capacity of airflow monitors to detect subtle breathing disturbance termed flow limitation or respiratory effort related arousal (RERA). Still, the most widely used device to assess SDB is the thermistor/ thermocouple, but it does not detect subtle respiratory events. Only esophageal manometry (EM) and nasal cannula pressure transducer (NC) have been validated for this purpose. Yet, each of these devices has drawbacks. EM, although deemed the gold standard (1), is invasive and may be poorly tolerated by patients. In comparison to EM invasiveness, NC appears more promising, but anecdotally, NC has shown decreased accuracy during cases of mouth breathing, nasal congestion, and nasal prong obstruction or displacement/dislodgment. These difficulties in respiratory monitoring indicate the continued need to develop sensors that are non-invasive and accurate in detecting subtle breathing disturbance. The new Dymedix airflow sensor (DAS) (Dymedix, Minneapolis, MN)

is one such device. The DAS utilizes Polyvinylidene Fluoride (PVDF) film that is a specially processed flexible plastic film that responds rapidly to both pressure and temperature changes. As a first step prior to formal validation of the DAS, we compared the DAS to both NC and thermocouple in a patient suspected of upper airway resistance syndrome (UARS).

**Methods:** One 32-year-old non-obese female with snoring and sleepiness, suspicious for UARS underwent polysomnography with simultaneous respiratory monitoring with DAS, NC, and standard thermocouple at the Eastern New Mexico Sleep Disorder Center in Roswell, NM. The recording included a 16 channel montage: LOC-A2; ROC-A1; C3-A2; C4-A1; O1-A2; O2-A1; chin EMG; EKG; L-R leg EMG; Snore; NC (Biologic Systems, Mudelein, IL); DAS; thermocouple (Protech, Woodinville, WA); chest effort; abdominal effort; pulse oximetry. Respiratory monitoring for each device was assessed for the presence of flow limitation events. Flow limitation events were defined as two or more consecutive breaths with a flattened or non-sinusoidal appearance without airflow decrements meeting 50% reduction criteria for hypopnea.

**Figure 1**



**Results:** Figure 1 is a 60-second PSG window displaying the simultaneous NC, DAS, and thermocouple signals. At the beginning of the tracing, all sensors show their particular sinusoidal shape. Then, both the NC and the DC show a flow limitation event with a non-sinusoidal flow signal terminating in an arousal. The thermocouple signal shows no decrease in amplitude and remains sinusoidal during the event. Many flow limitation events seen in this patient were similar to the event in Figure 1 and confirmed a UARS diagnosis.

**Conclusions:** This preliminary case study shows that the DAS may be an alternative device used to measure subtle breathing disturbance. Anecdotally, during mouth breathing in this patient, the DAS sustained its average baseline while the NC signal was dampened and difficult to interpret. In order to formally validate the DAS, future studies will assess intersignal

agreement between the DAS and both nasal cannula pressure transducer and esophageal manometry on an event-by-event basis in a larger sample of SDB patients. In the interim, the DAS appears useful for diagnosing SDB, including UARS, and may be appropriate for patients with mouth breathing, nasal congestion, or intolerance to esophageal manometry.

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**297.J**

**PILOT STUDY FOR SAFETY AND EFFICACY OF CORUS-1010 NASAL/THROAT SPRAY IN THE TREATMENT OF SNORING AND OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** CORUS-1010 (Tyloxapol Nasal Solution) is a mucolytic and surface active agent developed for aerosol use. In this pilot study we investigated the effect of nasally applied CORUS-1010 on snoring and sleep apnea.

**Methods:** In an open study design 10 consecutive habitual snorers or patients with mild to moderate OSA were included (8 males, 50.2 ± 10.6 years old, RDI: 23.8 ± 18.8/h). After the baseline polysomnographic recording, in a second night drug effect was investigated. The intervention consisted of 5 sprays in each nostril and the throat 15-30 minutes prior to lights off. After a treatment period of 4 weeks, both the adverse effects caused by CORUS-1010 and the snoring intensity (the latter by the bed partner) were evaluated based on a questionnaire.

**Results:** The main findings concerning respiratory events and sleep quality are given in the table. At the end of the 4-week observation period the patients did not report adverse effects. Simultaneously, 7/10 spouses reported a mild to moderate reduction of snoring.

**Table 1**

	Baseline	P (t-test)	CORUS-1010
AHI [1/h]	23.8 ± 18.8	0.13	16.4 ± 9.3
Desaturation Index [1/h]	16.6 ± 12.8	0.23	13.3 ± 11.3
SaO <sub>2</sub> mean [%]	93.4 ± 2.3	0.16	93.0 ± 2.6
Snoring-Index [1/h]	401.1 ± 193.0	0.99	400.8 ± 266.7
NREM 1/2 [%]	75.8 ± 9.6	0.06	67.7 ± 10.3
NREM 3/4 [%]	13.3 ± 7.3	0.18	17.0 ± 8.5
REM [%]	11.0 ± 7.8	0.11	15.8 ± 5.2
Arousal Index [1/h]	34.2 ± 11.5	0.09	27.0 ± 8.2

**Conclusions:** Although the trial was underpowered in sample

size, we found some non-significant trends to improvement of both sleep disordered breathing and sleep quality. Further adequately powered, placebo controlled trials in snoring and sleep apnea are ongoing.

**Research supported by This work was supported by Corus Pharma Inc.**

**298.J**

**AN EVALUATION OF DME VENDOR PERFORMANCE IN THE EDUCATION OF NEW CPAP USERS**

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**Introduction:** Durable Medical equipment (DME) vendors are assumed to play an important role in the health care network, and in terms of sleep disorders, an important role in CPAP compliance. The DME company is the last entity to see the patient before treatment begins; therefore, it is their performance that may directly affect CPAP compliance. Our objective was to determine whether the DME vendor provided the education and service that is required to obtain a satisfactory outcome.

**Methods:** A retrospective analysis was performed by contacting patients who have undergone sleep testing and have recently been prescribed CPAP. A phone interview was conducted asking the patients several questions about the DME service with regard to speed of delivery, equipment setup and education. The vendor score was based on the number of affirmative answers to 13 questions. The questionnaire results were broken down into two parts; one part analyzing components of the machine setup, and the other analyzing components of patient education.

**Results:** Two hundred and six patients were called with complete data available in 104 cases. The interviews were conducted ranging from 60 to 90 days after CPAP delivery. Eight vendors were identified. Sixteen patients (36%) were unable to name their vendor. Seventy-five percent (75%) of the patients contacted were using the CPAP device. Seventy-eight percent (78%) of those patients were using the machine > 5 hours per night with an average usage of 6.7 hrs. per night. The equipment was utilized an average of 6 nights per week. The overall scores for machine setup were higher than that of the patient education component (86% v. 73%). Based on the 13 questions asked, the vendors scored within a range of 86% to 96% on all questions except knowledge of how to travel with the device (67%), knowledge of CPAP pressure (69%), proper mask fit (54%), and knowledge of how to manage nasal dryness (59%). Mask fit pertained to whether or not the DME vendor provided only one mask (negative response) or the vendor actually measured the patient's face before providing a mask (affirmative response).

**Conclusions:** Two major factors that contribute to CPAP compliance are proper mask fit and the ability to manage or prevent nasal dryness. We believe that further efforts must be made to properly inform patients regarding the appropriate fit and use of this equipment and that failure to do so may be a contributing factor to poor compliance with therapy.

## 299.J

### THE THREAT OF MANDATORY REPORTING TO A DRIVER'S LICENSE AGENCY DISCOURAGES SLEEPY DRIVERS FROM BEING EVALUATED FOR SLEEP APNEA

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**Introduction:** Drivers with obstructive sleep apnea have a 2-4 fold higher rate of automobile crashes than controls. This increased risk has prompted some governments to mandate that physicians report the names of their patients with sleep apnea to a driver's license agency. However, mandatory reporting may provoke fear of losing their driving privilege and discourage drivers from being evaluated for sleep apnea. To evaluate the effect of mandatory reporting we interviewed subjects undergoing evaluation for sleep apnea.

**Methods:** We interviewed a consecutive group of 30 outpatients having an initial evaluation for sleep apnea. These subjects were referred for evaluation of snoring and excessive sleepiness or fatigue. We asked each subject if mandatory of their name to the state driver's license agency would cause them to avoid evaluation of their sleepiness.

**Results:** There were 18 males and 12 females with a mean age of 50 years + 13 (SD). Twenty-one of the 30 subjects (70%) said they would avoid medical evaluation of their sleepiness because of fear of losing the ability to drive. There was a trend of a higher percentage of males avoiding evaluation, but this was not significant. The subjects who would avoid medical evaluation were not different in age or score on Epworth Sleepiness Scale from those not discouraged by mandatory reporting.

**Conclusions:** The threat of mandatory reporting of their names to a driver's license agency discourages sleepy drivers from being evaluated for sleep apnea. The resulting failure to diagnose and treat sleep apnea would result in many preventable automobile crashes.

## 300.J

### CORRELATION OF OXIMETRY PARAMETERS WITH RESPIRATORY DISTURBANCE INDEX AMONG ADULT PATIENTS WHO UNDERWENT FULLNIGHT DIAGNOSTIC POLYSOMNOGRAPHY

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**Introduction:** Obstructive Sleep Apnea Syndrome (OSAS) is of increasing importance because of its high prevalence and danger of morbidity to untreated patients. With the cost and inconvenience of doing polysomnography (PSG), oximetry has been proposed as a tool in the diagnosis of OSAS. The aim of this study is to correlate Respiratory Disturbance Index (RDI) of 5, 20 and 30 with oximetry parameters among adult patients who underwent fullnight diagnostic polysomnography (PSG) and to compare these parameters in patients with and without OSAS.

**Methods:** Design: Retrospective, descriptive and analytical study  
Design: Retrospective, descriptive and analytical study  
Setting: St. Luke's Medical Center Sleep Center Materi-

als and Methods: Patients referred to the Sleep Center for PSG with symptoms suggestive of OSAS were investigated. Their clinical features and questionnaire responses were reviewed. RDI was calculated for all the patients and were classified as mild (RDI>5 events/hour), moderate (RDI>20 events/hour), and severe (RDI>30 events/hour). Oximetry parameters determined quantitatively and qualitatively from the strip chart recording include mean lowest oxygen saturation (MLSAT), lowest oxygen saturation (LSAT), and mean oxygen saturation (MSAT).

**Results:** Three hundred one patients (age, 47.04±13.6) were included. A total of 222(74%) OSAS patients were identified with RDI > 5 events/hr of which 24%(54/223) had mild OSAS, 10%(22/223) had moderate OSAS and 66%(146/223) had severe OSAS. Height, weight, body mass index (BMI) and neck circumference were significantly different between patients with and without OSAS at p<0.05. Comparison of the MLSAT, LSAT, and MSAT in patients with and without OSAS showed a significant difference using the Student's T-test at p<0.05. There was likewise a significant difference (p=0.000) in the above mentioned oximetry parameters between patients without OSAS and with mild, moderate, and severe OSAS computed independently. RDI had significant negative correlation with MLSAT (r=-0.441; p=0.000), LSAT (r=-0.247; p=0.003), and MSAT (r=-0.430; p=0.000) using Pearson's correlation.

Table 1

Comparison of Oximetry Parameters in patients with and without OSAS			
Oximetry Parameters	(-) OSAS N= 78	(+) OSAS N=223	P value
Mean lowest O2 Sat, %	93.0±2.60	85.4±6.78	0.000*
Lowest O2 Sat, %	89.5±4.25	65.3±17.76	0.000*
Mean O2 Sat, %	95.5±10.81	90.5±7.72	0.000*

\* significant at p&lt;0.05

**Conclusions:** Combined clinical evaluation and the use of overnight pulse oximetry would allow recognition of a patient with OSAS in the absence of PSG. It helps determine the severity of the disease and can be used as a cheaper alternative to detect sleep apnea.

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## 301.J

**OBSTRUCTIVE SLEEP APNEA SYNDROME AMONG CITY BUS DRIVERS: DIAGNOSTIC IMPLICATIONS AND DRIVING CAPACITY**Telakivi T,<sup>1,2</sup> Partinen M,<sup>1,2</sup> Hublin C,<sup>1,2</sup> Hirvonen K<sup>1,2</sup>

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**Introduction:** Excessive daytime sleepiness (EDS) of a professional motor vehicle conductor is a risk for traffic safety. Risk of an individual with obstructive sleep apnea syndrome (OSAS) to be involved in a traffic accident has been reported to be significantly greater than for controls. We reported a 20.3% prevalence of OSAS and 7.9% prevalence of severe OSAS with EDS (oxygen desaturation index, ODI4 > 30 and S1-latency in MWT < 12.9 minutes) in city bus drivers. We further analyzed these data for the implications on driving performance and clinical decision-making.

**Methods:** 421 bus drivers of the City Transportation Department, Helsinki, Finland answered to a modified Basic Nordic Sleep Questionnaire. 22 subjects with suspected OSAS (reported loud, intermittent snoring every or nearly every night and either sleep apneas > 1 night a week or snoring 20 years or longer with Epworth Sleepiness Scale (ESS) score > 8) and 16 age-matched controls (snoring once a week or less often, ESS < 8) were screened by all-night polysomnography, MWT and driving simulator test (STISIM, Systems Technology Inc., USA). Definitions: EDS: S1-latency < 12.9 minutes in MWT, OSAS: ODI4 > 10, severe OSAS ODI4 > 30. The subjects' history of traffic accidents in the past 10 years was reviewed.

**Results:** 17/22 with suspected OSAS and 4 /16 of subjects with no OSAS-suspicion had OSAS in the polysomnography. The performance of subjects with or without OSAS in the driving test and the past history of accidents did not differ. ESS score did not correlate significantly with ODI4. The S1-latency was shortest in those with OSAS and longest with no OSAS when ESS >10. The sensitivity and specificity of ESS > 10 were 60% and 66% and those of two items, self-reported snoring every day or almost every day and reported apneas at least once a week were 100% and 40%, respectively for severe OSAS with EDS. MWT sleep latency increased with age. ODI4 correlated significantly with reaction time ( $F = 4.498$ ,  $P = 0.042$ ), but the reaction times of subjects with OSAS and EDS did not differ significantly from those with OSAS but not with EDS nor with controls with EDS.

**Conclusions:** The results illustrate the difficulty of clinical conclusions concerning professional drivers with OSAS and/or EDS. Questions concerning habitual snoring and self-reported apneas > once a week did single out all drivers with severe OSAS and EDS, but there was a weak specificity. ESS >10 was not sensitive in differentiating OSAS patients from controls, nor the driving performance, or history. A significant correlation between ODI4 and the mean reaction time was found, but it did not differentiate those with or without EDS. Better tools to screen for sleep laboratory examinations and to estimate driving capacity in professional drivers are warranted.

**Research supported by The Finnish Work Environment**

## Fund

## 302.J

**EXECUTIVE DYSFUNCTION IN CHILDREN REFERRED FOR OBSTRUCTIVE SLEEP APNEA (OSA) EVALUATION**Beebe DW,<sup>1</sup> Groesz L,<sup>1</sup> Jeffries J,<sup>1</sup> Chini B,<sup>1</sup> Amin R<sup>1</sup>

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**Introduction:** The most consistent area of cognitive deficit in adults with OSA is executive dysfunction (1). Executive dysfunction is comprised of deficits in attention, inhibition, immediate working memory, behavior regulation, metacognition (e.g., planning and organization), and mental flexibility. In children, similar cognitive deficits and additional behavioral disturbances reminiscent of attention-deficit / hyperactivity disorder (ADHD) have been reported. However, no published study has targeted executive functioning in a pediatric population referred for evaluation for OSA. We hypothesized that, relative to published norms, such children would display deficits on tests of executive functioning, despite having normal basic verbal, nonverbal, and long-term memory skills.

**Methods:** We assessed consecutive children aged 6-12 who had been referred for evaluation of obstructive breathing during sleep. All were reported by their parents to snore loudly and chronically. Exclusion criteria included any other chronic medical condition or developmental delay. Children underwent overnight polysomnogram and, on a separate day, a 1.5 hour battery of validated cognitive tests begun between 2 and 3:30 p.m.: WISC-III Vocabulary, Block Design and Digit Span, NEPSY Visual Attention and Verbal Fluency, WRAML List Learning, Gordon CPT Omissions and Commissions. Parents also completed a validated executive functioning form (2). Subjects were classified as poor scorers on a test if their performance was <=16th percentile ( $z \leq -1$ ) compared to age-based norms. Statistical analyses included single-sample t-tests comparing group means to norms, and binomial tests assessing the likelihood of obtained poor performance rates.

**Table 1**

Construct	Mean (z-score)	Rate of poor scores
Vocabulary	-.33	33%
Block Design	-.22	33%
List Learning	.00	17%
Verbal Fluency	-.67*	25%
Sustained Attn.	-.91**	42%*
Selective Attn.	-.73**	58%**
Working Memory	-.53*	42%*
Impulsivity	-2.76**	67%**
Behav. Regulation	-.94**	50%**
Metacognition	-1.26**	50%**

\*p<.05, \*\*p<.01, one tailed. Group means expressed as z-scores, with negative scores indicating deficits compared to published norms.

**Results:** To date, 12 children (50% male; median age=7.5) have been enrolled. The results in Table 1 are consistent with predictions. Mean scores and rates of poor scorers in all three

non-executive areas (verbal memory, vocabulary, visual construction) did not differ from norms. In contrast, all areas of executive function (verbal fluency, sustained and selective attention, working memory, and impulsivity) yielded deficient mean scores or a high rate of poor scores. Parents also reported abnormal mean scores and poor performance rates in the behavior regulation and metacognition of their children. These deficits were present despite relatively mild respiratory pathology (all but one AHI < 5). AHI correlated only with sustained attention ( $\rho = -.58, p = .025$ ), but this may be related to the small sample.

**Conclusions:** These data suggest specific executive function deficits in children referred for evaluation for OSA. If future work supports these findings, they (a) could account for behavioral similarities with ADHD, a neurodevelopmental disorder that involves executive dysfunction, (b) would extend adult findings to the pediatric age, and (c) would support routine cognitive screening of children suspected of OSA. These data are in line with our recent theoretical model of the pathogenesis of cognitive morbidity in OSA, which posits that sleep and respiratory pathology differentially impact prefrontal brain regions, resulting in executive dysfunction (1). We are now expanding this sample and conducting longitudinal follow-up.

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**303.J**

**DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN A PRIMARY CARE POPULATION:**

*Confirmation with Polysomnography and Ambulatory Studies—Nichols DA,<sup>1</sup> Kushida CA,<sup>1</sup> Simon RD,<sup>1</sup> Grauke JH,<sup>2</sup> Brown JB,<sup>3</sup> Hyde PR,<sup>3</sup> Dement WC<sup>1</sup>*

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**Introduction:** The Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness of sleep disorders within the primary care community and to determine their prevalence within a specific primary care practice. In 2000, we reported that almost a fourth of the patients within a primary care population had symptoms of Obstructive Sleep Apnea (OSA) (1). These preliminary OSA diagnoses were based on patient responses from interviews and questionnaires. To demonstrate that symptomatology gathered from this study could provide information about the prevalence of OSA in primary care, it was crucial to solidify the diagnoses for the identified patients by either polysomnography or ambulatory studies.

**Methods:** A three-physician primary care practice in Moscow, Idaho was selected for the study. A total of 1,254 patients from the Moscow Clinic agreed to complete the consent form and four sleep questionnaires. Once the questionnaires were scored, a preliminary OSA diagnosis was assigned to any patient whose responses met criteria. Additionally, an OSA severity rating was assigned to each of the positive patients based on snoring, apnea, and fatigue questions as well as Epworth scores. Once a questionnaire-based OSA diagnosis was made, the primary care physician as well as the patient was notified. To encourage treatment, the patients were offered a complimentary Edentrace recording to screen for OSA. Polysomnography was recommended for patients with a positive screening test.

**Table 1**

OSA Severity (based on RDI)	Percent of Patients (Number of Patients)
Severe OSA (RDI ≥ 30)	28% (32)
Moderate OSA (RDI = 15–29)	28% (32)
Mild OSA (RDI = 5–14.9)	31% (35)
Minimal OSA (RDI = 1–5)	13% (15)

**Results:** A total of 296 patients from the original study had symptoms of OSA. Either a polysomnogram or an ambulatory study was performed on 114 (39%) of these patients. The severity based on the Respiratory Disturbance Index (RDI) from the overnight study is shown in Table 1. The groups formed by the questionnaire-based OSA severity rating are described in Table 2.

**Table 2**

OSA Severity Rating (based on questionnaire)	Percent of Patients	Mean RDI	Mean Epworth Score	Mean BMI
Severe	15%	49.1	12.0	29.9
Moderate	25%	34.7	9.2	29.2
Mild	60%	21.9	9.1	27.5

**Conclusions:** Our results indicate that the questionnaires used to screen the Moscow Clinic primary care population were effective in identifying patients with at least mild OSA. Strong evidence of OSA, as measured by an RDI of five or more, was present in 87% of the patients who underwent either polysomnography or a screening test. Additionally, all 15 patients with an RDI less than 5 had airflow limitation as evidenced by snoring, and 7 out of 15 had evidence of upper airway resistance syndrome by crescendo breathing. Therefore, sleep disordered breathing was found for all 114 patients who agreed to overnight testing. We attempted to study all 296

patients, yet the majority did not respond to our multiple offers for complementary screening tests. Upon evaluating the patients with an OSA severity rating, we found the RDI, the Epworth score, and the BMI were greatest for the severe group. The most important outcome is the overwhelming number of the patients identified by our questionnaires with evidence of OSA, suggesting that this sleep disorder has a high prevalence in primary care. Continued efforts to inform the primary care community about OSA are essential to insure treatment for the greatest number of patients.

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**304.J**

**DISCRIMINATING VALUE OF SIMPLE MORPHOMETRIC FEATURES AND EPWORTH SLEEPINESS SCALE IN PREDICTING APNEA PLUS HYPOPNEA INDEX ≥ 20 IN A SLEEP DISORDERS CENTER POPULATION.**

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**Introduction:** Several investigators have demonstrated significant association between morphometric features, measures of sleepiness and severity of obstructive sleep apnea (OSA), as determined by the apnea plus hypopnea frequency (AHI). We proposed to determine, if applied to a sleep disorders center population, could readily obtained morphometric features, subjective sleepiness as assessed by Epworth sleepiness scale (ESS) and simple assessment of oral pharyngeal aperture by Mallampati oral pharyngeal class (OPC) score be used to identify patients with severe OSA as defined by an AHI ≥ 20.

**Methods:** The study consisted of data prospectively collected on 222 consecutive patients referred to the sleep disorders center. All patients had comprehensive sleep consultations prior to polysomnography (PSG). 23 were deleted from analysis due to missing data points. Of the remaining 199 patients, 156 (78%) had PSG for suspected OSA (28 split night PSG) and the remaining 43 (22%) for nonapnic sleep disorders. Multiple linear regression was used to examine the relationship between AHI and neck circumference in inches (NC), body mass index in kg/m<sup>2</sup> (BMI), ESS and OPC. Using cut off points for NC ≥ 16, BMI ≥ 28, OPC of 3 and ESS ≥ 10, we calculated the specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) for these variables to predict AHI ≥ 20.

**Results:** Mean ± standard deviation for age, BMI, NC, OPC, ESS, AHI, % REM sleep and % sleep efficiency were 51.43 ±

13.4, 32.7 ± 8.99, 16.9 ± 1.62, 2.6 ± 0.6, 12.3 ± 6.28, 31.93 ± 31.8, 13.79 ± 7.89 and 80.62 ± 15.38, respectively. Multiple linear regression analysis showed statistically significant association (p < 0.05) between AHI and NC, BMI and ESS. The predictive value of the variables can be found in the table.

**Table 1**

Predictive indices					
	BMI	NC	OPC	ESS	All
Sensitivity	0.79	0.95	0.78	0.70	0.47
Specificity	0.38	0.19	0.52	0.46	0.79
PPV	0.59	0.57	0.65	0.59	0.71
NPV	0.62	0.78	0.68	0.57	0.57

All = BMI + NC + OPC + ESS

**Conclusions:** Using specific cut off points, all of the variables tested were highly sensitive but not specific for AHI ≥ 20. Combining the variables improves specificity and PPV. OPC, while not linearly related to AHI, improves specificity and PPV at predicting AHI ≥ 20. This data may be useful to sleep disorders centers when selecting patients for split night polysomnography. Since these variables were derived from a sleep disorders center population, they should not be extrapolated for use in general medical practice.

**References:**

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**305.J**

**EFFECT OF SURGICALLY INDUCED WEIGHT LOSS ON OBSTRUCTIVE SLEEP APNEA IN MORBIDLY OBESE PATIENTS.**

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**Introduction:** A high percentage of morbidly obese patients have Obstructive Sleep Apnea (OSA) (98%) (1). Obese patients with OSA may respond favorably to weight reduction. The aim of the study was to evaluate the impact of surgically induced weight loss on OSA in morbidly obese patients.

**Methods:** Eighteen morbidly obese patients were evaluated by nocturnal polysomnography and the daytime Multiple Sleep Latency Test (MSLT) before and 1-year after bariatric surgery. All patients completed the Sleep Disorders Questionnaire (SDQ) and the Epworth Sleepiness Scale the day after polysomnographic evaluation. Pulmonary systolic artery pressure (PSAP) by echocardiogram was also evaluated in 8 patients. Differences were analyzed using the paired t-Test. There were 8 men and 10 women with a mean age of 39.2±11.2 years. Performed surgical procedures were: VBG in 6 patients, RYGBP in 4 patients and dRYGBP in 8 patients.

**Results:** After 1-year of surgery, a decrease of 30% in the

excess body weight resulted in significant improvement of OSA and arterial blood gases, with a decrease in the level of reported snoring severity and reported level of sleepiness. There was not statistically significant change in pulmonary artery pressure nor objective measurement of sleep tendency during the day (see Table 1).

**Table 1**

Effect of Surgically weight reduction on OSA.

Variable	Before	After	P
BMI kg/m <sup>2</sup>	54±12	38±8	0.001
Snoring severity (1-5)*	4+1	2+1	0.001
Epworth Sleepiness Scale	12±7	6±5	0.009
Mean MSLT (min)	7+7	6+6	0.06
PSAP (mmHg)	58±17	46±14	0.07
<b>Awake</b>			
Mean % SaO <sub>2</sub>	87+8	93+2	0.01
EtCO <sub>2</sub> (mmHg)	43+7	37+5	0.01
<b>Sleep</b>			
Apnea/Hypopnea Index	43+35	17+24	0.001
Mean % SaO <sub>2</sub> in NREM	78±15	89±4	0.003
EtCO <sub>2</sub> in NREM (mmHg)	44+7	37+5	0.007
Mean % SaO <sub>2</sub> in REM	69±18	86±6	0.001
EtCO <sub>2</sub> in REM (mmHg)	44+9	40+7	0.18
Minutes of Oxygen Saturation <65%	75±110	2±5	0.01

All values are mean ± Standard Deviation;  
\* Sleep Disorders Questionnaire.

**Conclusions:** A weight loss of 30% after 1-year of surgery improves OSA and arterial blood gases in morbidly obese patients. However, despite the significant weight reduction, this group of obese patients is still at risk for OSA with a significant level of sleepiness determined by MSLT.

**References:**

(1) Valencia-Flores, Orea A, Castaño VA, et al. Prevalence of Sleep Apnea and Electrocardiographic Disturbances in Morbidly Obese Patients. *Obesity Res* 2000;8:262-269.

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**306.J**

**PREVALENCE OF DYSPNEA IN PATIENTS BEING ASSESSED FOR SLEEP DISORDERED BREATHING**

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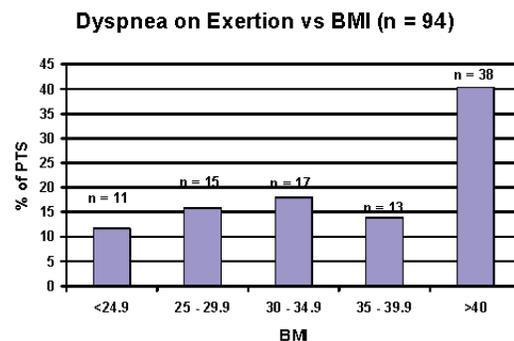
**Introduction:** Dyspnea is the term used for the subjective complaint of an uncomfortable sensation while breathing. Patients with sleep disordered breathing (Obstructive Sleep Apnea and Cheyne-Stokes Respirations) frequently have complaints of gasping for breath at night<sup>1</sup> and shortness of breath at various times throughout the day. Many of these patients have concomitant obesity that may contribute to the complaint of dyspnea. Dyspnea is commonly experienced by patients with cardiopulmonary disease but is also noted in normal healthy subjects<sup>2,3</sup>. To date, the prevalence of dyspnea in

patients being evaluated for sleep disordered breathing has not been well described. The purpose of this investigation was to: 1) Determine the prevalence of the complaint of dyspnea in patients being evaluated for sleep disordered breathing. 2) Ascertain the characteristics of the dyspnea complaint in this population. 3) Examine the impact of obesity on the complaint of dyspnea.

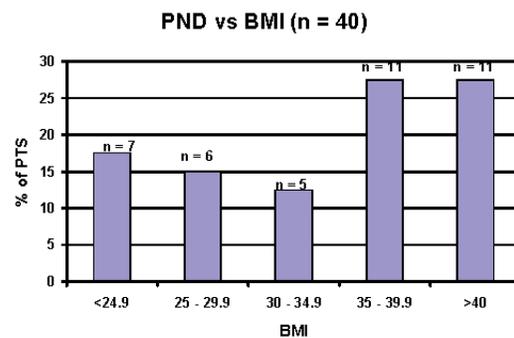
**Methods:** Prospective Case Series. 120 consecutive patients (58 men / 62 women) - to date. Inclusion Criteria: New male and female patients > 18 years of age referred to the Sleep Evaluation Center. A dyspnea questionnaire was administered to all new patients referred to the University of Pittsburgh Sleep Evaluation Center prior to an assessment by a sleep physician. The questionnaire asked if during the past month the patient was short of breath at rest during the daytime, short of breath with activity/exertion, short of breath when they first laid down (orthopnea) or awoke suddenly from sleep with shortness of breath (paroxysmal nocturnal dyspnea). If an affirmative response was obtained, they were questioned as to how many days a week they experienced the symptom. Descriptive statistics were utilized and the data was expressed as mean ± standard deviation.

**Results:** Age 46 ± 14; BMI 37.4 ± 12.3; 40% (48/120) had dyspnea at rest; 78% (94/120) reported dyspnea with exertion; 27.5% (33/120) reported orthopnea and 33.3% (40/120) reported paroxysmal nocturnal dyspnea (PND).

**Figure 1**



**Figure 2**



**Conclusions:** 1) The complaint of dyspnea is common in patients being evaluated for sleep disordered breathing. 2) Dyspnea at rest, orthopnea and dyspnea on exertion positively

correlated with obesity. 3) The complaint of PND was less frequent (33.3% of patients queried) and did not strongly correlate with the presence of obesity.

**References:**

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- (2) Harver A, Mahler DA, Schwartzstein RM, Baird J. Descriptors of Breathlessness in Healthy Individuals. *Chest* 2000;118:679-690
- (3) Manning H, Schwartzstein RM. Mechanisms of Dyspnea. *N Engl J Med* 1995; 333:1547-1553

**307.J**

**ANATOMICAL AND PHYSIOLOGICAL DIFFERENCES IN THE PHARYNX OF PRE VS POST-MENOPAUSAL WOMEN**

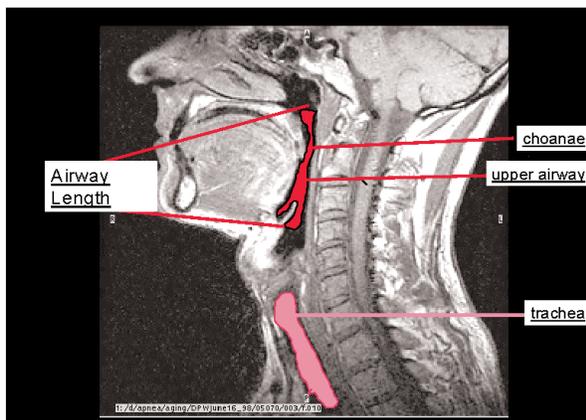
*Malhotra A,<sup>1,2,4</sup> Lazic SE,<sup>1,2,4</sup> Fogel RB,<sup>0</sup> Pillar G,<sup>1,2,4</sup> Stanichina M,<sup>1,4</sup> Jakab M,<sup>1,2,4</sup> White DP<sup>1</sup>*

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**Introduction:** Obstructive sleep apnea (OSA) increases in prevalence in women following menopause, for unclear reasons. The mechanism could be related to anatomical changes, development of pharyngeal muscle control abnormalities, or alterations in ventilatory control stability. This study examined differences in upper airway (UA) anatomy and physiology between pre and postmenopausal women that might contribute to the development of OSA in the latter group.

**Methods:** Twenty-two female subjects, between the ages of 27 and 80 were studied. All women under 50 had regular menses, while women over age 50 had secondary amenorrhea for at least 2 years. Each underwent standard overnight polysomnographic evaluation (with nasal pressure recording), UA physiology testing [awake genioglossal EMG (measured as a percentage of maximum activity), plus genioglossal responsiveness to negative pressure pulses and CO2 stimulation] and volumetric magnetic resonance imaging (MRI) analysis of multiple upper airway, soft tissue and bony features.

**Figure 1.**



**Results:** Postmenopausal women had a significantly longer airway (p=.012) as measured from the hard palate to the base of the epiglottis. In addition, the volume of the parapharyngeal adipose tissue deposits was larger in post-menopausal (i.e. fat pads; p = .047) than pre-menopausal women (even when BMI normalized p=.06). Apnea Hypopnea Index (AHI) correlated significantly with fat pad volume (r = .491, p = .028) and with airway length (r=.432, p=.06). None of the measured physiological variables (GGEMG, response to negative pressure pulses, pharyngeal resistance, or response to CO2) was different between pre and postmenopausal women.

**Conclusions:** Airway length and fat pad volume (independent of BMI) may be important anatomical variables in the development of OSA in postmenopausal women. These differences are not likely due to aging alone as there was no significant difference in airway length or fat pad volume between younger and older men (n=27) that underwent the same experimental protocol.

**Research supported by**

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**308.J**

**ROLE OF GABA-A RECEPTOR MECHANISMS IN THE CONTROL OF HYPOGLOSSAL MOTOR OUTFLOW TO GENIOGLOSSUS MUSCLE IN NATURAL REM SLEEP**

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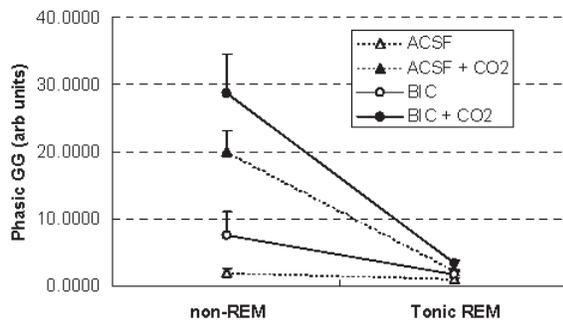
**Introduction:** The genioglossus (GG) muscle of the tongue is important for the maintenance of an open airway and effective breathing. Rapid eye movement (REM) sleep recruits powerful neural mechanisms that can abolish GG muscle activity, even during strong reflex respiratory stimulation by elevated CO2. Such suppression of GG activity during sleep can lead to upper airway narrowing or closure, and the clinical syndrome of obstructive sleep apnea. However, the mechanisms mediating the major suppression of GG activity in natural REM sleep are unknown, particularly the potential role of inhibitory neural mechanisms such as GABA. Indeed, controversy arises from studies in a pharmacologically induced REM-like state produced by pontine carbachol in which there is both evidence for (1) and against (2) post-synaptic inhibition of hypoglossal motoneurons. However, the carbachol model does not fully reproduce REM sleep neural events, particularly the effects on breathing. Accordingly, we have developed a model to chronically manipulate neurotransmission at the hypoglossal motor nucleus using microdialysis across natural sleep-wake states in rats (3). The present study tests the hypothesis that microdialysis perfusion of the GABA-A receptor antagonist bicuculline into the hypoglossal motor nucleus will prevent the suppression of GG muscle activity in REM sleep during both room air and CO2 stimulated breathing.

**Methods:** Six male Wistar rats were implanted with electrodes to chronically record sleep-wake states from electroencephalogram (EEG) and neck muscle (EMG) activities, and

respiratory activity of the GG and diaphragm muscles. Microdialysis probes were implanted into the hypoglossal motor nucleus for perfusion with artificial cerebrospinal fluid (ACSF) or 100uM bicuculline. In initial studies we showed that this dose of bicuculline blocks the inhibition of hypoglossal motor output by GABA-A receptor stimulation with muscimol. The effects of ACSF and bicuculline were tested during both room air and CO<sub>2</sub> stimulated breathing (6.5-7.5% inspired CO<sub>2</sub>).

**Results:** Microdialysis probes were successfully implanted in the hypoglossal motor nucleus in each rat as determined from post mortem histology. Respiratory-related GG activity decreased from non-REM to tonic REM sleep with this change being especially prominent during CO<sub>2</sub> breathing (P=0.002, see Figure) but unaffected by GABA-A receptor antagonism at the hypoglossal motor nucleus (mean decreases = 89.1 and 88.3% for ACSF and bicuculline respectively). Of importance, compared to ACSF, antagonism of GABA-A receptors at the hypoglossal motor nucleus did not increase GG activity in tonic REM sleep during room air (P=0.34) or CO<sub>2</sub> breathing (P=0.19).

Figure 1



**Conclusions:** We conclude that GABA-A receptor mechanisms at the hypoglossal motor nucleus do not play a major role in the inhibition of GG muscle activity during tonic REM sleep. Given that GABA-A receptors are present on hypoglossal motoneurons and are blocked by 100uM bicuculline (see Methods), we conclude that GABA pathways inhibiting GG activity may be recruited in behaviors other than REM sleep. Further studies will determine the role of other neurotransmitters in the major suppression of hypoglossal motor outflow in natural REM sleep. Determination of such mechanisms may lead to the development of new treatment strategies for obstructive sleep apnea.

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sis perfusion of 5-HT into hypoglossal motor nucleus differentially modulates genioglossus activity across natural sleep-wake states in rats. *J Physiol.* 2001; 532:467-81.

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**309.J**

**SNORING PREVALENCE AMONG PRESCHOOLERS AT-RISK FOR LEARNING DIFFICULTIES: A PRELIMINARY REPORT.**

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**Introduction:** Previous research from our laboratory supports the notion that cognitive development in school-age children may be compromised by the presence of sleep-disordered breathing and fragmented sleep (1). However, the prevalence of sleep-disordered breathing (SDB) among preschool-age children who are developmentally or financially disadvantaged is unknown.

**Methods:** Parents of children ages 3-5 years attending Jump Start preschool classes in Jefferson County, Kentucky, were administered a previously validated, 5-point Likert-scale questionnaire (1) to identify those children who may have sleep-disordered breathing.

**Results:** Thus far, information on 341 children (52% male) has been collected. Snoring was very frequent, such that 56% of children (53% males) were reported to snore > 1 night/week. Furthermore, habitual snoring (>3 nights/week) was present in 15.5%. Of all the snorers, 37% were reported to snore from "medium loudly" to "extremely loudly". Although we did not find a significant difference between males and females in their frequency of snoring (Chi-square=4.2, df=4; p>0.05), males were reported to have more severe levels of snoring (Chi-square=17.6, df=4, p<0.01).

**Conclusions:** In a population of preschool children who are at risk for lower school achievements, an unusually high proportion will be reported to snore by their parents. Since SDB may adversely impact on neurobehavioral development, identification of at-risk groups for SDB coupled to an early intervention program may result in improved cognitive development and school-related performance.

**References:**

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**Research supported by NIH Grant HL-65270 and Department of Education Grant H324E011001**

**310.J****DO SUBJECTIVE SLEEPINESS MEASURES PREDICT DIFFERENCES IN OBJECTIVE MEASURES OF SLEEP APNEA BY GENDER IN THE SLEEP HEART HEALTH STUDY?**

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**Introduction:** The Epworth Sleepiness Scale has been the 'gold standard' for assessing subjective daytime sleepiness. Male gender has been associated with higher Epworth scores, however, even after adjusting for confounders (1). In the Sleep Heart Health Study (SHHS), the distribution of Epworth scores and sleepiness items from a Sleep Habits Questionnaire (SHQ) also differed by gender (2). The intent of this study is to determine whether differences in the Epworth and SHQ are reflected in gender differences in objective measures of sleep apnea.

**Methods:** SHHS participants (n=6,185; 52.7% women) completed the Epworth scale and a measure of sleepiness that combined two SHQ items. No gender differences were noted for age or BMI. Epworth scores <sup>3</sup>11 were defined as daytime sleepiness. SHQ questions (daytime sleepiness and insufficient sleep) were dichotomized such that 'almost always' and 'frequently' indicated daytime sleepiness, while 'sometimes', 'rarely', or 'never' indicated its absence. Both measures served as independent variables, and were compared across objective continuous dependent variables related to sleep apnea, including respiratory disturbance index (RDI), time in desaturation below 90%, sleep architecture, stage shifts, systolic and diastolic blood pressure (SBP/DBP), and naps per week. Skewed variables were log transformed. Bivariate analyses were used controlling for gender.

**Results:** Daytime sleepiness prevalence rates assessed by the Epworth were higher for men than women (29.7% vs. 20.8%), but higher for women as assessed by the SHQ (19.3% vs. 24%) (each p<0.0001). Significant gender interactions were noted with the SHQ, but not the Epworth, for desaturation and DBP respectively. Specifically, men positive for sleepiness using the SHQ spent a greater percent of their time in desaturation below 90% (interaction p<0.05). Men positive for sleepiness showed elevated DBP compared to men without sleepiness with the SHQ, whereas women showed no such differences (interaction p<0.01). After adding gender as a main effect, the Epworth was not associated with percent time spent in sleep stages 2 and 3/4, suggesting gender acted as a confounder. The Epworth, SHQ, and gender (males higher) were independently associated with RDI and mean number of naps per week (each p<0.0001).

**Conclusions:** Results suggest that the SHHS SHQ measure may not only serve as a salient and parsimonious subjective measure of sleep apnea-related daytime sleepiness, but also appears to show less gender bias. The Epworth, SHQ, and gender were independently associated with RDI, a key objective sleep apnea variable. Gender acted as a confounder using the Epworth, however, for percent time spent in some sleep stages. In addition, more men scored <sup>3</sup>11 on the Epworth, sug-

gesting bias toward identifying sleepiness in males, as reported elsewhere (1). Additional studies are required to assess further any gender differences, as well as concordance rates between the Epworth and SHQ measures.

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**311.J****AUTOMATED CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT FOR SLEEP DISORDERED BREATHING IN CHILDREN**

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**Introduction:** This study will attempt to determine the effectiveness of an automated or "smart" nasal continuous positive airway pressure device (AutoSet Tä) in children with sleep disordered breathing in an attended setting. (1,2). These type of devices are available for adults but have not been previously tested in children. This is the first report using automated CPAP in children

**Methods:** Our institution's review board for human subject research approved the study. Subjects were recruited from children previously diagnosed with sleep disordered breathing who were scheduled for conventional CPAP titration. After CPAP mask selection, the children were monitored with a polysomnogram (EEG, EOG, EMG, EKG, airflow, respiratory effort and oximetry). The titration was initiated using an automated CPAP device in automatic mode. The sleep technologists continuously monitored the child during the titration in automatic mode. If during the recording there was any evidence of the device not correcting the subject's respiratory events the technologist were instructed to switch to a conventional manual CPAP titration. The raw data was reviewed to determine the optimal CPAP pressure. The children were then prescribed conventional nasal CPAP for home use based on the data collected

**Results:** Ten children were studied. (Means: age 7.7 years old, range: 8 months-12 year; BMI: 19.2 kg/m<sup>2</sup>). The AHI showed a significant decrease from baseline (mean 12.9 events/hour, range:2.3-40.6) after titration (1.9 events/hour, range:0- 5.9) (p > .05). There was an improvement in the oxygen saturation nadir from 87.6%(range: 74-100) to 91.6% (range: 88-100) that did not reach statistical significance. The mean pressure prescribed was: 7.9 cm H<sub>2</sub>O (range 5-12 H<sub>2</sub>O). All children, except for one, were able to tolerate automated CPAP in automatic mode during the study. That child was unable to tolerate CPAP even when it was later being titrated manually. During the study the technologists needed to sometimes adjust the

children's masks to minimize air pressure leak. Minimizing the air leak was the most common problem during the study. This was due in part to relatively few number of CPAP masks styles and sizes available for this age group. When the air leaks were controlled with a better fitting mask the automated CPAP was able control the obstructive respiratory events.

**Conclusions:** For a child, automated CPAP can be effective and safe in an attended setting to determine the optimal CPAP pressure. It is essential to have proper fitting mask for the device to work properly. Greater availability of child size masks would be beneficial for children needing CPAP. Further research is needed to test the suitability of automated CPAP in an unattended home setting.

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**312.J**

**THE RELATIONSHIP BETWEEN SLEEP DISORDERED BREATHING AND GASTROESOPHAGEAL REFLUX**

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**Introduction:** The presence of significant Gastroesophageal reflux (GER) has been reported in adults with Sleep Disordered Breathing (SDB)(1). However the relationship between GER and SDB in children is unknown. The aim of the study is to determine the prevalence of GER in a cohort of otherwise normal children with suspected SDB and to investigate the relationship of GER and the severity of SDB.

**Methods:** Children with a history of snoring and possible apnea who were referred to a tertiary care Children's Hospital to rule out SDB were included in this study. Patients with craniofacial malformations, neuromuscular diseases, genetic syndromes or patients with a prior history of surgery for Gastroesophageal Reflux Disease were excluded from the study. All patients underwent overnight polysomnographic study in conjunction with 24 hr dual pH probe monitoring. Patients were considered to have SDB if 1) Apnea Hypopnea Index (AHI) is greater than 1 or 2) Et CO<sub>2</sub> >47 torr for greater than 70 % of the total study time(obstructive hypoventilation OH). A pH value <4 occurring for greater than ≥12% of the study time in infants and ≥6% in older children was considered as pathological reflux (2). Patients with SDB were sub- categorized into mild (AHI 1-5), moderate (AHI 5-10), and severe (AHI >10).

**Results:** Over a twenty-four month period 45 children were included in the study. (mean age of 4.5 ± 0.6yrs. M/F 27/18). Thirty children (66%) were diagnosed with SDB (mean AHI 5.9). Pathological reflux was identified in 56% patients with SDB (17of 30). In contrast, 20% of the children without SDB

(3 of 15) had pathological reflux (Chisq = 5.44, p= 0.019). There was no relationship between severity of SDB and GER (Table 1). Interestingly children with OH seem to have higher incidence of GER. In children with pathological reflux and SDB, 79 % of the episodes were noted during wakefulness vs 21 % during sleep.

**Table 1**

**Relationship between Severity of OSA and GER**

	Apnea Severity				Patients with SDB (AHI ≥ 1)	Patients with no SDB
	Mild (AHI 1- 5)	Moderate (AHI 5-10)	Severe (AHI> 10)	OH		
n	10	6	8	6	30	15
Age (yr)	3.9 ± 1.2	5.2 ± 1.2	4.6 ± 1.7	3 ± 0.9	4.2 ± 0.7	5.1 ± 1
Mean AHI	2.1 ± 0.2	5.8 ± 0.4	15 ± 1.6		5.93 ± 1.1	0
Pts with GER (%)	5	3	4	5	17 (56%)	3 (20%)

Data represent mean ± SEM

**Conclusions:** This preliminary analysis suggests that children with SDB have a higher prevalence of GER than control subjects. However there is no relationship between the severity of SDB and presence of GER. Children with OH appear more likely to have GER in the small group of patients studied. The majority of the reflux events are noted during wakefulness and visual analysis of the polysomnogram reveal no temporal relationship between Obstructive Sleep Apnea (OSA) events and reflux episodes. Thus the role of SDB in the pathogenesis of GER is unclear and needs additional studies to establish the cause and effect relationship.

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**313.J**

**THE RELATIONSHIP BETWEEN CEPHALOMETRIC CHARACTERISTICS AND OBSTRUCTIVE SITES IN OBSTRUCTIVE SLEEP APNEA SYNDROME**

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**Introduction:** Although it has been widely reported that

patients with obstructive sleep apnea syndrome (OSAS) have characteristic dentofacial features, the sites of obstruction differ greatly. The purpose of this study was to investigate the dentofacial characteristics of OSAS patients with respect to the obstructive sites.

**Methods:** The subjects consisted of thirty Japanese adult male OSAS patients and were divided into three groups; (1) obstruction at the retropalatal and retroglossal region (Rp+Rg group), (2) obstruction at the retropalatal region (Rp group), (3) obstruction due to tonsillar hypertrophy (tonsil group). The number of each group was ten. To identify the Rp+Rg and Rp group, dynamic MRI was used. To identify the tonsil group, Mecklenzie fs classification, axial MRI, and the weight of the tonsils were used. The control group was comprised of ten Japanese adult males showing no symptoms suggestive of OSAS. Lateral cephalometric radiographs were taken for the all subjects and ANOVA was performed for the 46 cephalometric parameters.

**Results:** Among the many dentofacial characteristics of OSAS patients, the tendencies for retrognathia, micrognathia, and skeletal Class II were most closely related to the Rp+Rg group and somewhat related to the Rp group. The tendency for a long face was dominant in the tonsil group and the presence of a long soft palate was strongly related to the Rp group. All groups shared the characteristics of having an inferior position of the hyoid bone.

**Conclusions:** In the current study, we could conclude that many features of OSAS are specifically related to each obstructive type of OSAS.

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### 314.J

#### PARTITIONING OF INHALED VENTILATION BETWEEN THE NOSE AND MOUTH DURING SLEEP IN NORMAL SUBJECTS.

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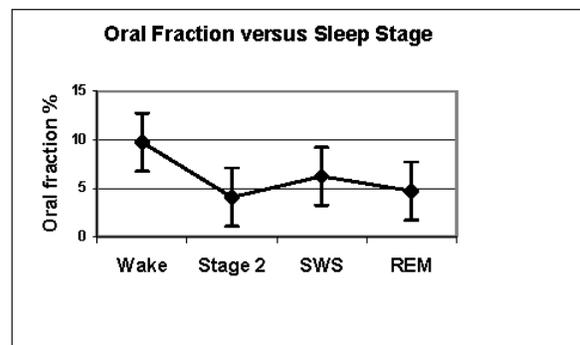
**Introduction:** It is not clear how normal humans partition inhaled ventilation between the nose and mouth during sleep. This is important to understand for two practical reasons: (1) the nasal cannula pressure transducer, which is rapidly becoming the standard method of airflow measurement for clinical sleep studies, may not include any measurement of oral ventilation; and (2) there is considerable evidence that mouth-breathing increases the propensity to obstructive sleep apnea.

**Methods:** Volunteers were first screened by questionnaire to exclude subjects with systemic or respiratory illness, regular use of medication, nasal obstruction or allergic rhinitis, and cigarette smokers. Subjects meeting inclusion criteria were further screened by (a) acoustic rhinometry, to rule out anatomic nasal obstruction, and (b) by spirometry and flow-volume loop to verify normal lung function. Each subject underwent a single overnight sleep study. A two-compartment

facemask with sealed oral and nasal compartments was employed to enable independent measurements of oral and nasal ventilation. An identical research pneumotach system was attached to each of the two mask compartments to simultaneously record oral and nasal ventilation. The pneumotach data was interfaced on-line with the other routine polysomnographic data to permit simultaneous visualization of sleep stage and breath-by-breath inhaled ventilation throughout the overnight sleep recording. Subjects: 9 healthy subjects (5M, 4F) aged (mean)  $37 \pm$  (sd) 13 years (range 22-63y), BMI  $23 \pm 2$  kg/m<sup>2</sup> (range 22-28 kg/m<sup>2</sup>).

**Results:** All subjects had normal nasal resistance (mean)  $1.84 \pm$  (sem) 0.2, range 1.0-3.0 cmH<sub>2</sub>O/l/s. Nasal ventilation [% Total inhaled ventilation (%VI)] was significantly greater than oral ventilation during wakefulness ( $90 \pm 7\%$  vs  $10 \pm 7\%$ ;  $p < 0.001$ ) and sleep ( $95 \pm 3\%$  vs  $5 \pm 3\%$ ;  $p < 0.001$ ). The oral fraction of inhaled ventilation (% VI) during wakefulness ( $10 \pm 7\%$ ) was higher than that during sleep ( $5 \pm 3\%$ ;  $p < 0.001$ ). However, there was no significant difference in the oral fraction between sleep stages [stage 2 ( $4 \pm 3\%$ ); stages 3&4 ( $6 \pm 3\%$ ); REM sleep ( $5 \pm 3\%$ )  $p=0.33$ ].

Figure 1



**Conclusions:** Recumbent normal subjects inhale primarily through the nose during wakefulness and sleep. Mouth-breathing decreases with the transition from wakefulness to sleep. Once asleep, the oral fraction in normal subjects does not change significantly between sleep stages.

**Research supported by Ontario Thoracic Society Block term Grant.**

### 315.J

#### SLEEP APNEAS AND SLEEP HYPOPNEAS DURING PERIODS OF MICROSLEEP OR TRANSITIONAL SLEEP WITHIN 30-SECOND EPOCHS SCORED AS WAKEFULNESS

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**Introduction:** Clinically significant sleep apneas and sleep hypopneas may occur during periods of microsleeep (also called transitional sleep) within 30-second epochs scored as

wakefulness according to R&K criteria (>15 seconds of alpha, beta, or muscle artifact). Such microsleep respiratory disturbances present a scoring conundrum for calculating the respiratory disturbance index: Should such events be included in an RDI using a denominator of total sleep time or sleep period time? The sleep period time refers to the period of time from the first epoch of sleep to the final epoch of sleep, inclusive. The EEG changes during the transition from wakefulness to sleep have been well documented and consist of a dropout of alpha and a generalized slowing of the EEG.<sup>1,2</sup> The question arises as to whether or not to score sleep apneas or hypopneas within epochs scored as awake in which such EEG slowings (microsleeps) and obvious respiratory disturbances have occurred. It has also previously been recognized that EEG frequency changes, specifically a slowing of the EEG frequencies from alpha to theta, occur during sleep apnea episodes.<sup>3</sup>

**Methods:** Three patients from a clinical sleep disorders center were selected to illustrate the occurrence of sleep apneas and hypopneas during microsleep. The RDI figures are compared between using total sleep time versus sleep period time in the denominator for the RDI calculation.

**Results:**

PSG #	Polysomnogram Number:		
	#520	#548	#1203
Total Sleep Time (min.)	12.5	60.0	29.5
Time in Bed (min.)	100.5	430.5	461.0
Sleep Efficiency (TST/TIB x 100)	12.4%	13.9%	6.4%
Number of Apneas	21	282	104
Number of Hypopneas	73	18	439
RDI Calculated Using TST(A+H/hr TST)	451	300	1104
Sleep Period Time (min.)	125.5	283	454.4
RDI/SPT Calculated Using SPT (A+H/hr SPT)	44.9	63.6	71.7

**Conclusions:** In certain patients with extremely severe obstructive sleep apnea/hypopnea the respiratory disturbances may occur during repetitive hypnagogic or transitional periods of sleep as defined by brief periods of time of relatively low voltage, mixed frequency EEG or sometimes even during periods of just alpha attenuation. In such patients, the duration of the EEG patterns defining sleep is so short (less than 15 seconds) that it must be called a period of microsleep. This presents a conundrum for calculating the RDI. This paper has shown that in such cases it is better to determine a RDI/SPT in terms of the number of apneas or hypopneas per hour of sleep period time rather than the number of apneas or hypopneas per hour of total sleep time.

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**316.K**

**SECONDARY NARCOLEPSY WITH NORMAL CSF HYPOCRETIN (OREXIN) LEVELS**

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**Introduction:** Secondary narcolepsy has been associated with processes near the third ventricle and cerebrospinal fluid (CSF) hypocretin deficiency (1,2). We report a case of secondary narcolepsy with normal hypocretin levels after treatment of a pineal region tumor.

**Methods:** At the age of 28, a woman with no prior history of sleep complaints developed headache and diplopia. A MRI of the head revealed a cystic pineal tumor later demonstrated to be a metastatic choroid plexus carcinoma. Treatment commenced with neurosurgery (resection plus placement of a reservoir in the inferior aspect of the third ventricle), local external beam radiation (60 Gy to the pineal, hypothalamus and pituitary region) as well as intrathecal chemotherapy. She entered full remission from her malignancy but required thyroid replacement. Immediately after surgery, she developed an irregular sleep/wake rhythm, initial insomnia (2-3 hours) and middle insomnia. The patient had an Epworth Sleepiness Score (ESS) of 15. She denied cataplexy, sleep paralysis and hypnagogic hallucinations. Over 2 years, over 15 unsuccessful medication trials (including melatonin and barbiturates) plus sleep hygiene training were undertaken. Eventually all hypnotic medications were discontinued for two weeks and, after obtaining IRB approval, comprehensive sleep testing was conducted at the GCRC.

**Results:** Actigraphy revealed an irregular sleep/wake cycle within the context of the patient carrying out her parental responsibilities. Polysomnography showed a brief ISL of 0.5 min, initial REM latency of 5.0 min, increased total percentage of REM sleep (38.4%) with a TST of 503 min. Serum melatonin levels measured every 30 minutes were normal with a dim light melatonin onset at 20:00 with a peak level of 47.6 pg/ml. MSLT demonstrated 3/4 SOREMs with a median ISL of 4 minutes. The SOREM's were not accounted for by sleep deprivation or the abnormal sleep/wake cycle. CSF hypocretin 1 level collected at 2 pm was 518 pg/ml. HLA DQ B1\*0602 testing was negative. She subsequently responded well (less insomnia, ESS 8) to treatment with methylphenidate 100 qd in three divided doses.

**Conclusions:** Despite an extensive resection, sufficient pineal tissue remained to produce melatonin. Instead of finding the suspected melatonin deficiency associated with insomnia (3), narcolepsy was diagnosed based on multiple SOREM's. Narcolepsy likely resulted from the intracranial radiotherapy or the instrumentation in the third ventricle disrupting hypothalamic functioning rather than the pineal resection. In this case, monosymptomatic narcolepsy developed in the absence of hypocretin deficiency. It is unclear whether narcolepsy was induced through dysfunction of some other aspect of the hypocretin system, such as receptor dysfunction as seen in canine narcolepsy, or through another as yet undiscovered neuromodulating system. The effects of neurosurgical procedures and radiotherapy on the diencephalon region need further study in patients with and without sleep complaints.

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**317.K****COMPLICATIONS OF HIGH DOSE STIMULANT USE IN THE TREATMENT OF DISORDERS OF EXCESSIVE SOMNOLENCE**

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**Introduction:** A subgroup of patients with narcolepsy or idiopathic hypersomnia requires stimulant therapy at doses that exceed published guidelines in order to achieve adequate alertness. It is controversial whether such doses are associated with unacceptable risks. Among 11 narcoleptics receiving 100 mg or more of methylphenidate daily for at least 5 years, 2 developed psychoses and 54% showed evidence of depression or dysthymia[1]. We performed a retrospective study to determine the effects of high dose stimulants in a population of patients with narcolepsy or idiopathic hypersomnia.

**Methods:** We used the Mayo Narcolepsy Research Center database to identify all patients treated between 1950 and 2000 with stimulants at dosages greater or equal to 120% of the maximum recommended by the ASDA Standards of Practice Committee [2]. The minimum daily doses for inclusion were: methylphenidate 120 mg, dextroamphetamine 120 mg, methamphetamine 100 mg, pemoline 180 mg. Patients' records were reviewed and the data abstracted and analyzed.

**Results:** Fifty-eight patients were identified, 31 male and 27 female. Forty-seven (81%) had narcolepsy with cataplexy, 9 (16%) narcolepsy without cataplexy, and 2 (3%) idiopathic hypersomnia. Fifty-seven patients had used methylphenidate, 2 dextroamphetamine, 5 methamphetamine and 3 pemoline in doses above the inclusion limits. The median highest daily dose of methylphenidate was 200 mg (range 120-1,400 mg). Patients used up to a daily maximum of 375 mg dextroamphetamine, 225 mg methamphetamine and 300 mg pemoline. The median duration of high dose methylphenidate use was 5.9 years (range <1 month- 39 years). Forty patients (69%) received one or more psychiatric diagnosis. These included psychoses in 7 (12%), paranoia or disordered thinking in 6 (10%), depression in 24 (41%), alcohol or polydrug abuse in 10 (18%), anxiety in 26 (45%) and obsessive-compulsive disorder in 3 (5%). One depressed patient committed suicide, 3 attempted suicide and one experienced suicidal ideation. Twelve (21%) needed psychiatric hospitalization at least once, 3 were arrested and 4 demonstrated drug seeking behavior

(multiple sources or alleged lost prescriptions). Twenty-one patients (36%) were hypertensive, 6 (10%) experienced supraventricular tachyarrhythmias and 8 (14%) developed cardiac or cerebrovascular disease. Eleven (19%) experienced loss of appetite or weight.

**Conclusions:** The high frequency of psychiatric disorders in these patients is alarming. Almost a quarter experienced psychoses or thought disorder, while over 40% were diagnosed with depression, a fifth of whom considered or attempted suicide. Drug abuse, unrelated to their prescribed stimulants, was common. Over a third were diagnosed with hypertension and 10% developed tachyarrhythmias. Various interpretations of these findings are possible. The disorders described may have been induced by the drugs, may be associated with narcolepsy, or may be risk factors predisposing to the need for higher doses of stimulants. Whatever the explanation, clinicians should prescribe these higher doses only with considerable caution. A history of prior psychiatric disorders should be obtained. Patients should be carefully monitored for psychosis, thought disorder, depression, anxiety, substance abuse, hypertension and cardiovascular disease.

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**Research supported by Mayo Foundation (Piscopo Funds)**

**318.K****CSF HYPOCRETIN (OREXIN) LEVELS IN NARCOLEPSY WITH AND WITHOUT CATAPLEXY**

*Krahn LE,<sup>1</sup> Oliver LK,<sup>1</sup> Pankratz VS,<sup>1</sup> Boeve BF,<sup>1</sup> Silber MH<sup>1</sup>*

(1) Mayo Clinic

**Introduction:** Human narcolepsy with cataplexy is associated with hypocretin 1 (also known as orexin A) deficiency based on undetectable CSF levels and absent hypocretin neuronal expression in post mortem brains (1,2). To date relatively few studies have been published expanding on these significant findings by looking at important variants and including patients without cataplexy or HLA DQB1\* 0602 (3). We hypothesized that CSF hypocretin 1 levels will be undetectable (< 40 pg/ml) in narcoleptic patients with cataplexy and the DQB1\* 0602 allele compared to other variants.

**Methods:** This ongoing study examines hypocretin 1 CSF levels in narcoleptic patients divided in to four groups subdivided by presence of cataplexy and HLA type. Narcolepsy was diagnosed based on the Mayo Narcolepsy Research Criteria. Cataplexy was confirmed using a clinical interview and cataplexy questionnaire. Hypocretin values were also determined for 10 control patients undergoing lumbar punctures for indications other than sleep, infectious or possible autoimmune diseases.

**Results:** As seen in Figure 1, 6 out of 7 subjects with cataplexy and the DQB1\*0602 allele (86%) had undetectable hypocretin



vating effect of BHT-920 was attenuated by VNS.

**Conclusions:** VNS significantly modified cataplexy in narcoleptic dogs. We have previously demonstrated that dopaminergic D2/D3, adrenergic alpha-2 and muscarinic M2/3 receptor systems are critically involved in the occurrence of cataplexy (1). The results of the drug challenge may suggest that VNS modulate the central adrenergic neurotransmission and significantly modify cataplexy. This interpretation is also consistent with the results of previous animal experiments suggesting the involvement of changes in activity of LC neurons for the mediation of the VNS effects (2). The opposite effect of VNS on cataplexy in these two animals may be due to the differences in the VNS stimulation parameters. Considering the fact that VNS was reported to have opposite effects on sleep depends on stimulation parameters (3), it may be possible that we are able to find stimulation parameters that significantly improve cataplexy by adjusting the VNS frequency, and further experiments are in progress.

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### 320.K

#### HOW VALID ARE THE ICSD CRITERIA FOR NARCOLEPSY?

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**Introduction:** Criteria for the diagnosis of Narcolepsy have been proposed and are widely used (1) but there is little evidence regarding their validity (2). The aim of this study is to assess to what extent the physiological criteria apply to a group of patients with a definite clinical diagnosis of Narcolepsy.

**Methods:** All patients attending the Papworth Hospital Sleep Centre, Cambridge, UK with a definite clinical diagnosis of Narcolepsy were studied. All patients were HLA DQB1\*0602 positive, had cataplexy and excessive daytime sleepiness. They underwent polysomnography (Psg) and next day multiple sleep latency tests (MSLT) off stimulant medication. The sleep latency and presence of sleep onset REM during Psg and sleep latency and number of sleep onset REMs during MSLT were recorded.

**Results:** Sixty-Six patients were studied. The age range was 24 to 92 years. There were 30 males and 36 females. No differences were found between the physiological measurements for sex. Polysomnographic and MSLT results are shown in Table 1. Psg alone supported the clinical diagnosis of Narcolepsy in 82% of patients, while MSLTs alone supported the diagnosis in 88% of patients. At least 1 of the 4 ICSD physiological criteria were present in 64 patients. When Psg and MSLT findings were used together 97% of patients with a clinical diagnosis met the ICSD criteria.

**Table 1**

	Number of Patients	% Population	ICSD Diagnostic Criteria
Psg, SL < 10 min	45	68	Yes
Psg SOREM (<20 min)	30	45	Yes
Mean MSLT SL < 5 min	51	77	Yes
≥ 2 SOREM MSLT	54	82	Yes
Only 1 SOREM MSLT	7	11	No
Psg and only 1 MSLT SOREM	4	6	Yes
Psg criteria (any one)	54	82	Yes
MSLT criteria (any one)	58	88	Yes
Psg or MSLT criteria	64	97	Yes

**Conclusions:** All the subjects had well-established clinical diagnostic criteria and supporting HLA type for the diagnosis of Narcolepsy (3). The agreement between the clinical diagnosis and physiological findings are improved when both Psg and MSLT criteria are used emphasising the importance of scheduling both investigations when assessing patients for narcolepsy.

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No financial or other support has been provided for this study.

### 321.K

WITHDRAWN

### 322.K

#### ADDING A MID-DAY DOSE OF MODAFINIL SUSTAINS WAKEFULNESS IN NARCOLEPSY PATIENTS WITH RESIDUAL EVENING SLEEPINESS DESPITE SATISFACTORY DAYTIME EFFICACY

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(1) Integris Southwest and Baptist Medical Centers, Oklahoma City, OK, (2) Cephalon Inc, West Chester, PA,

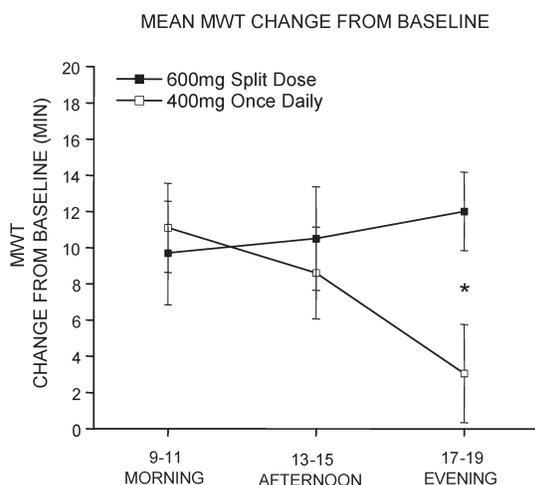
**Introduction:** Some patients treated with modafinil for excessive daytime sleepiness experience late-afternoon/evening sleepiness despite satisfactory treatment earlier in the day. For these patients, physicians are faced with the decision to add a

short-acting stimulant, increase the dose of modafinil, or add another dose of modafinil. We evaluated the effects of adding a second dose of modafinil at midday for maintaining wakefulness throughout the entire waking day.

**Methods:** Twenty-four narcolepsy patients reporting a positive daytime response to modafinil with residual late-afternoon/evening sleepiness were enrolled in this randomized, double-blind, parallel design study. At screening, all patients had a Clinical Global Impression (CGI) of Severity rating with respect to late-afternoon/evening sleepiness of at least moderate severity. Patients were randomized to one of two 3-week treatment regimens, 400 mg once-daily (400 mg at 0700h) and 600 mg split dose (400 mg at 0700h and 200 mg at 1200h). The 3-week treatment period was preceded by at least a 1-week, single-blind, placebo washout period. Efficacy was evaluated using modified Maintenance of Wakefulness Testing (MWT) consisting of 30-minute MWTs every 2 hours from (0900h to 2100h). The Clinical Global Impression of Change scale was used to evaluate overall clinical condition with respect to evening sleepiness. Adverse events were recorded. (A portion of these results are presented in a separate abstract with data from a similar protocol.)

**Results:** Both modafinil treatment regimens significantly improved mean sleep latency at week 3 compared with baseline ( $P<0.01$ ). As depicted in Figure 1, the mean improvement from baseline in evening sleep latency was significantly greater for the 600-mg split-dose regimen than for 400-mg once-daily regimen ( $P<0.05$ ). With respect to evening sleepiness, the percentage of patients rated as 'much improved' or 'very much improved' was significantly greater for those receiving 600 mg split dose (92%) than for those taking 400 mg once-daily (75%) ( $P<0.05$ ). The percentage of patients rated as 'very much improved' in the evening was greater for those receiving 600 mg split dose (50%) than for those taking 400 mg once-daily (8%). The most common adverse events possibly attributable to modafinil were headache (8%) and emotional lability (8%). All adverse events were mild in nature. All patients completed the study.

**Figure 1**



**Conclusions:** The addition of a 200 mg dose of modafinil at lunch significantly improved late afternoon/evening wakefulness as measured by the MWT and the CGI. The 600 mg dose of modafinil was well tolerated. Some narcolepsy patients with late-afternoon/evening sleepiness despite satisfactory daytime treatment may benefit from an additional 200 mg dose of modafinil taken at midday. The 600 mg dose was well tolerated.

Research supported by Cephalon, Inc., West Chester, PA.

### 323.K

#### DOSE RESPONSE AND DOSE REGIMEN EFFECTS OF MODAFINIL FOR SUSTAINING WAKEFULNESS IN NARCOLEPSY PATIENTS WITH RESIDUAL EVENING SLEEPINESS

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**Introduction:** We previously reported that 400 mg given either once daily or as a split dose at breakfast and lunch, when compared with 200 mg given once daily in the morning, significantly improved alertness throughout the entire waking day in narcolepsy patients with late-afternoon/evening sleepiness despite satisfactory treatment earlier in the day. We present the combined results of two investigations designed to compare the effects of 3 daily doses of modafinil (200 mg, 400 mg and 600 mg) and 2 dosing strategies (once daily vs split dosing) for maintaining wakefulness throughout the entire waking day.

**Methods:** Fifty-four narcolepsy patients reporting a positive daytime response to modafinil with residual late-afternoon/evening sleepiness were tested in two investigations employing randomized, double-blind, parallel designs. All patients had a Clinical Global Impression (CGI) of Severity rating with respect to late-afternoon/evening sleepiness of at least moderate severity at screening. Patients were randomized to one of four 3-week treatment regimens, 200 mg once daily (N=11), 400 mg once daily (N=23: 400mg at 0700h), 400 mg split dose (N=10: 200mg at 0700h and 200mg at 1200h), and 600 mg split dose (N=12: 400mg at 0700h and 200mg at 1200h). The 3-week treatment sequence was preceded by at least a 1-week, single-blind, placebo washout period. Efficacy was evaluated using modified Maintenance of Wakefulness Testing (MWT) consisting of 30-minute MWTs every 2 hours from (0900h to 2100h). Adverse events were recorded. (A portion of these results are presented with data from another protocol in a separate abstract.)

**Results:** All modafinil doses and dosing regimens significantly improved the total daily mean MWT sleep latency at week 3 compared with baseline ( $P<0.01$ ). Modafinil 600 mg split dose was significantly better than 400 mg at improving wakefulness. The percentage of patients who were able to sustain wakefulness for at least 20 minutes on both of the MWT tests at each time point are presented in Figure 1a. These results

demonstrate predictable time of day and dose response effects. With respect to late afternoon/evening sleepiness, the mean improvement from baseline in MWT sleep latency was significantly greater ( $P < 0.05$ ) for each of the two split-dose regimens than for each of the two once-daily regimens (Figure 1b). The most common adverse events potentially attributable to modafinil during the three treatment periods were nausea (4.5%) and headache, dizziness, insomnia, nervousness, and emotional lability (2.3% for each). In these patients the 600 mg split dose was well tolerated. All adverse events were mild to moderate in nature.

Figure 1a

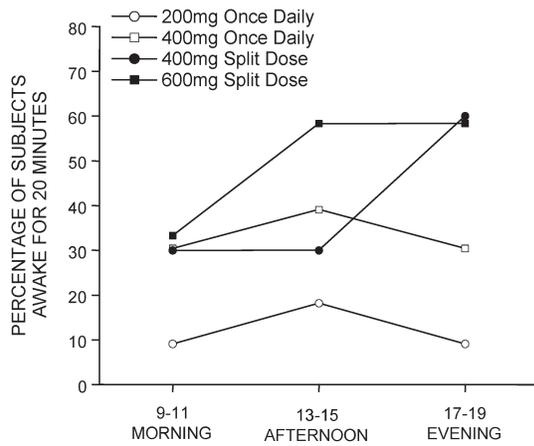
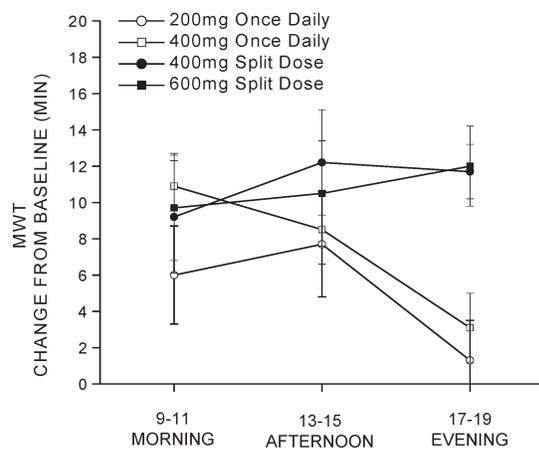


Figure 1b



**Conclusions:** Modafinil demonstrates predictable dose-response and dose regimen effects with respect to time of day. In narcolepsy patients with late-afternoon/evening sleepiness despite satisfactory daytime treatment, a split-dose regimen preferentially sustains wakefulness throughout the entire day whether it is administered at 600 mg or 400 mg total daily dose.

Research supported by Cephalon, Inc., West Chester, PA.

324.L

INSOMNIA DIAGNOSES AND HYPNOTIC USAGE IN THE NATIONAL AMBULATORY MEDICAL CARE SURVEY FROM 1990-1998

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**Introduction:** Primary insomnia is the second most common type of chronic insomnia (1), and it is the diagnosis most often included in hypnotic medication clinical trials. This investigation estimates the frequency of outpatient visits in the U.S. for different forms of insomnia and tabulates the diagnoses associated with use of hypnotic medications.

**Methods:** Estimates were derived from the National Ambulatory Medical Care Survey (NAMCS) from 1990 through 1998.(2,3) The NAMCS collects outpatient visit data from nonfederal physicians of all specialties, except anesthesiology, pathology, and radiology. The NAMCS uses sophisticated sampling techniques to produce estimates that reflect global U.S. practice patterns. Diagnoses were coded according to the International Classification of Disease-Clinical Modification-9th Edition (ICD-9-CM).

**Results:** 296,169 physician-patient encounters were analyzed for 1990-1998, corresponding to 4.9 billion office visits nationwide. Only 418 of the 296,169 encounters were associated with an insomnia code, and only 4 of these were for primary insomnia (ICD-9-CM code 307.42). Hypnotic medications encounters were twice as likely to be associated with a psychiatric code than with a diagnostic code for insomnia. Primary insomnia did not appear among the diagnoses most commonly associated with a hypnotic prescription.

**Conclusions:** Although primary insomnia is the second leading cause of chronic insomnia in sleep centers and in community samples, it was infrequently coded in a representative sample of U.S. outpatient practices. Hypnotics were more commonly associated with a psychiatric diagnosis than with the symptom of insomnia. As a result, it is unclear whether clinical trials data derived from samples of primary insomnia can be extrapolated to the patients that most commonly receive these medications. This represents a critical knowledge gap in the treatment of insomnia.

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### 325.L

#### A META ANALYSIS OF SLEEP CHANGES ASSOCIATED WITH PLACEBO IN HYPNOTIC CLINICAL TRIALS: METHODOLOGIC AND ETHICAL IMPLICATIONS

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**Introduction:** These effects associated with placebo (EAP) have been incompletely described in clinical trials of insomnia treatment. We conducted a meta-analysis of insomnia medication trials for the purpose of estimating the magnitude of sleep EAP after two weeks of placebo administration.

**Methods:** We performed a literature review using Medline for the period of 1966 through 2000 to gather data for the meta-analysis (1). The subject heading of insomnia restricted to the subheading of drug therapy was crossed against the results of a search on the subjects heading placebo and text word placebo. We selected only papers that examined primary insomnia, incorporating both placebo and active medication therapies in a randomized, double-blind, parallel-group design. We required that treatment results be reported for 1, 2, 3, or 4 weeks of treatment, and that the outcome variable be reported in hours/minutes.

**Results:** Only five papers satisfied our requirements for eligibility, comprising 213 patients receiving placebo for a two-week interval. Subjective sleep latency demonstrated a significant reduction (mean + s.e.) of 13.1 + 2.0 minutes (95% CI 9.2, 17.0) for the placebo group after combining the data across studies. Subjective total sleep time demonstrated a significant increase of 13.5 + 3.2 minutes (95% CI 7.0, 19.6). Polysomnographic sleep latency demonstrated a non-significant reduction of 2.5 + 4.3 minutes (95% CI -5.9, 10.9).

**Conclusions:** These results are consistent with the general finding in the insomnia literature that the magnitude of subjective complaints and subjective response to treatment are greater than PSG measurements. Our present findings have practical and perhaps ethical ramifications. If we had found no EAP, then it could be argued that an 'equivalence design' could be employed for testing the efficacy of new medications against a proven standard treatment in primary insomnia, without a placebo control. Instead, the presence of EAP in primary insomnia supports the idea that new medications be contrasted against placebo. The strongest arguments against placebo are ethical ones. The World Health Organization's 1964 Declaration of Helsinki effectively prohibits the ethical use of placebos in clinical trials when a proven therapeutic method exists. The ethical dilemma would seem to be solved by appealing to the principal of freely-given informed consent, allowing patients to make their own choices. Yet the strongest antagonists of placebo use in clinical trials have questioned whether freely-given and fully-informed consent ever exists. However, if placebo-controlled studies are abandoned in favor of an 'equivalence design', the effects size will likely be smaller, requiring the enrollment of more study participants and potentially greater exposure to an ineffective new treatment.

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### 326.L

#### SLEEP DYNAMIC THERAPY FOR POSTTRAUMATIC INSOMNIA

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**Introduction:** Posttraumatic insomnia is a complex disorder often comprising the triad of psychiatric distress, psychophysiological conditioning, and physiological sleep fragmentation [e.g. sleep-disordered breathing (SDB)](1). We have developed an integrative, evidence-based, Sleep Dynamic Therapy (SDT) program to address "complex insomnia." SDT aims to increase awareness of the multifactorial nature of sleep disturbance in the aftermath of trauma by emphasizing six basic components: (1) sleep quality self-assessment; (2) cognitive-behavioral therapy (CBT); (3) sleep hygiene; (4) sleep-related emotional processing; (5) imagery rehearsal therapy (IRT); and (6) sleep physiological self-assessment. The core therapeutic aim of SDT is to educate the patient on the value of a rigorous and candid assessment of sleep quality through which one might estimate the degree that distress, conditioning, and physiological sleep disruption cause or exacerbate insomnia. Because trauma survivors are often inculcated with the belief that distress is the primary cause of insomnia, SDT starts with sleep quality, CBT, and sleep hygiene principles to quickly demonstrate that insomnia responds to standard sleep medicine therapies regardless of distress symptoms. Then, sleep-related emotional processing examines how anxiety and depression exacerbate insomnia, and IRT is taught to decrease nightmares. In the last session, sleep physiological self-assessment prepares the patient for a night of polysomnography to assess sleep breathing or movement disorders.

**Methods:** In a pilot study, SDT was administered to a group of disaster survivors (n=66), evacuated during the Cerro Grande Fire in Los Alamos, NM (May, 2000). SDT was delivered in six weekly sessions to the entire group (on average, 8 patients attended makeup sessions each week). The Insomnia Severity Index (ISI, range 0 to 28) assessed insomnia at 8 points: intake; immediate pre-treatment (7.5 weeks after intake); weeks 2, 3, 4, and 5 of treatment; posttreatment; and 12-weeks from treatment initiation. Repeated measures ANOVA was conducted and Cohen's d effect sizes were calculated.

**Results:** ISI showed a small decrease from intake to pre-treatment (d = .32) indicative of spontaneous recovery. Additional substantive improvement occurred at posttreatment (d = .62) (F(7,59) = 11.97, P = .0001) with maintenance of change at 12-week follow-up. Forty-nine patients improved, 11 worsened and 6 reported no change in insomnia. Forty participants' post-treatment ISI scores fell below non-clinical levels (scores ≤ 10)(2).

**Conclusions:** SDT was successfully delivered to a single group of disaster survivors. In the early post-treatment follow-up, there was a highly significant, medium-sized decrease in

insomnia severity. Additional treatment effects among patients pursuing SDB treatment with CPAP or oral appliances will be forthcoming. Although this study was uncontrolled, spontaneous recovery was small during a lengthy pre-treatment assessment period. Moreover, all the techniques comprising SDT have been found effective in controlled studies. Therefore, it is likely that SDT played an important role in the changes reported by these patients. Given the current need to assist disaster and other trauma survivors, SDT may be a very pragmatic approach for the treatment of posttraumatic insomnia in large groups of patients.

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### 327.L

#### BRAIN MUSIC THERAPY FOR TREATMENT OF INSOMNIA AND ANXIETY

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**Introduction:** The close relationship between insomnia and anxiety is well established. Anxious patients have difficulties maintaining sleep, they spend less time in deep sleep and their sleep is more fragmented than that of normals. Traditional approaches have emphasized pharmacological treatment of insomnia. Benzodiazepines have become the most widely prescribed of all pharmaceuticals. Concern has been expressed however about their potential to cause dependency associated with self-dosing management. A non-pharmacological method – “brain music therapy” has been recently developed for treatment of some psychosomatic symptoms. This method allows establishing the most effective rhythmic and tonal parameters creating meditative conditions in patients by influencing the bioelectrical brain activity in the process of music therapy depending on the individual EEG. Subsequently EEG patterns are converted into unique music recorded on a personalized compact disc with listening instructions catered to each individual. Brain music therapy because of its more favorable side-effect profile may represent a possible alternative for therapeutic management of insomnia and anxiety. The purpose of the present study was to assess the effectiveness of brain music therapy for treatment of insomnia in anxious patients using objective actigraphic measures and psychometric testing.

**Methods:** Eighteen volunteers who had complained of symptoms of insomnia of at least two years duration and who had

scored above 50 on the Zung Self Rating Anxiety Scale were recruited for participation in the study. Patients were divided into two groups on a double-blind randomized basis. Experimental group I comprised ten insomniacs (7 females and 3 males, aged 41.6.0±5.8) who were provided with their authentic “brain music” (computerized or composed during neuro-feedback session). Placebo group II consisted of eight patients (5 females and 3 males, aged 42.8±7.8) who received compact disks with brain music of a different subject. The duration of the treatment, which entailed listening to the music on a daily basis, was four weeks. Athens Insomnia Scale and actigraphy were used for assessment of subjective and objective quality of sleep. Forty eight-hour actigraphic recordings were performed before and after 4 weeks of brain music therapy. Average sleep onset latency (SOL), total sleep time (TST), and amount of intervening wakefulness were determined. Affective status of the patients was controlled by using the CES-Depression Scale. Participants from both groups had slightly elevated scores (19.6±3.8 and 20.1±5.4 respectively;  $p > .05$ ). Statistical analysis was performed using the independent samples’ t-test in the SPSS statistical software package with significance set at  $p < 0.05$ . Bonferroni correction was used for multiple variable analysis.

**Results:** Both authentic and placebo brain music reduced anxiety scores with more pronounced effects observed in the experimental group (58.1±2.8 vs.31±4.6 and 60±5.6 vs. 46.5 ±6.1 respectively,  $p < .01$ ). There was a dramatic improvement in sleep quality as judged by the Athens Insomnia Scale ( $p < .001$ ). However there was no significant difference between the effects of authentic and placebo brain music. Interestingly some actigraphic parameters characterizing insomnia in anxious patients were found to be significantly improved only in the experimental group of patients who were using authentic brain music therapy. Amount of intervening wakefulness was significantly less following brain music therapy ( $p = .02$ ). The patients had a significant increase in TST ( $p = .004$ ). SOL remained unchanged before and after brain music treatment ( $p > .05$ ).

**Conclusions:** In this study a 4 week regimen of brain music therapy was shown to be of value in reducing symptoms of anxiety and insomnia as evidenced by psychometric testing. Objective actigraphic measures of insomnia have been improved in the group of anxious insomniacs treated with endogenously generated brain music. Brain music therapy is a useful alternative to pharmaceutical therapy for treating these conditions.

### 328.L

#### PRELIMINARY RESULTS OF A PILOT STUDY EVALUATING YOGA AS A TREATMENT FOR INSOMNIA

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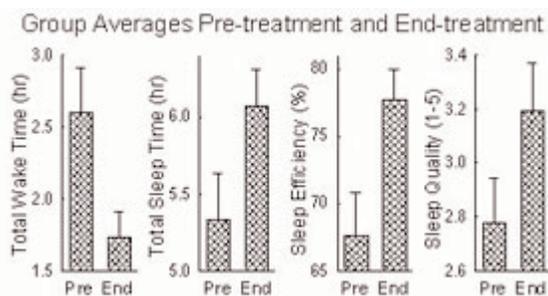
**Introduction:** There is good evidence that cognitive and/or physiological arousal, including sustained elevated sympathetic balance, is a characteristic of chronic primary insomnia. Furthermore, relaxation treatments such as progressive relaxation and meditation, which reduce arousal, have been found to be effective insomnia treatments. Numerous research stud-

ies have documented the effectiveness of yoga in reducing autonomic arousal and in the treatment of specific medical disorders. Although yoga has been clinically recommended for the treatment of insomnia, its effectiveness in treating insomnia has not been thoroughly tested (1,2). The aim of this pilot study is to evaluate the feasibility of applying a daily yoga treatment for chronic insomnia of various etiologies.

**Methods:** Individuals with an insomnia complaint were recruited primarily from physician referrals. Following informed consent and a sleep history interview, study participants kept daily sleep-wake diaries. Following a 2-week baseline evaluation, participants were individually taught a 30-minute sequence of Kundalini yoga (as taught by Yogi Bhajan) including breathing exercises, static postures, and meditation, which they practiced daily at home for 8 weeks. One in-person follow-up meeting confirmed proper practice of the exercises with additional contact by telephone. For quantifying the subjective degree of insomnia, daily values of total wake time, total sleep time, sleep efficiency, and subjective sleep quality on a scale of 1 to 5 were averaged over the 2-week baseline period and over the last 2 weeks of the treatment.

**Results:** To date, 10 female participants aged 33 to 64 have completed the 10-week protocol. Initially, all of the participants complained of sleep maintenance insomnia, and 7 of them also reported sleep onset insomnia. Only one participant had evidence of a sleep disorder other than insomnia (RLS), three had some evidence of anxiety disorder and one had major depression. Two participants reported occasional hypnotic use during the protocol. Qualitative analysis of subjective sleep diary characteristics over the course of the treatment revealed gradual improvements in the degree of insomnia and decreases in day-to-day variability for 8 of the 10 participants. Averaged values for all 10 participants comparing pre-treatment baseline and end-treatment periods are plotted with standard errors, and show a decrease of 0.9 hr in total wake time ( $p = 0.02$ , t-test), an increase of 0.7 hr in total sleep time ( $p = 0.07$ ), an increase of 10% in sleep efficiency ( $p = 0.02$ ), and an increase of 0.4 on the sleep quality scale ( $p = 0.12$ ). In general, most of the participants exhibited a high degree of compliance in performing the daily treatment and reported no difficulties in executing the exercises.

Figure 1



**Conclusions:** The yoga treatment applied was well tolerated and the majority of participants reported some degree of benefit. These preliminary data suggest that the effectiveness of

this treatment is worthy of further evaluation with a larger sample size in a randomized controlled study incorporating additional objective outcome measures.

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**329.L**

**SCREENING FOR SLEEP-DISORDERED BREATHING IN COMPLEX INSOMNIA PATIENTS**

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**Introduction:** Polysomnography (PSG) is not routinely indicated for insomnia patients. However, the presumed boundary between insomnia and sleep-disordered breathing (SDB) has become less distinct (1,2). Accordingly, it may prove useful to screen appropriate insomnia patients for SDB prior to undergoing PSG. The Autoset II Plus (AS) (ResMed, Australia) is an ambulatory device that performs a diagnostic sleep study by automatically analyzing an airflow tracing from a nasal cannula. Previous studies have validated the AS apnea/hypopnea index (AHI) for obstructive sleep apnea (OSA)(3). Additionally, the AS measures flattening of the flow-time curve that is displayed on an arbitrary scale of 0 to .3 in which a cut-off ( $\leq .15$ ) implies flow limitation (i.e. RERAs). The flattening index (FI) is the percentage below the cut-off. Anecdotally, a FI  $\geq 20\%$  appears consistent with UARS when the AHI is low. Therefore, we hypothesize that the AS might successfully screen for UARS in diagnostic mode using the FI. As a preliminary step prior to a formal validation of the AS, we collected data on a series of patients who underwent PSG after having screened positive with an elevated FI.

**Methods:** Thirty-five consecutive crime victims seeking treatment for insomnia who had an AHI  $\leq 10$  and a FI  $\geq 20$  were evaluated for SDB with PSG at various sleep labs in Albuquerque, NM. Some labs utilized thermistor/thermocouples while others used airflow pressure transducers to assess sleep-breathing disturbance. All diagnoses were based on the individual sleep specialist's interpretation of the PSG. Eight patients in the sample were diagnosed by the second author.

**Results:** SDB was diagnosed in 32 of 35 (94%) patients. Of those with SDB, 50% had OSA, 47% had UARS, and one borderline UARS. Of the OSA patients, 69% technically qualified as OSA (i.e. AHI  $\geq 5$ ) but had predominantly UARS type events. An additional 12 patients, not meeting this study criteria (AHI  $< 10$  and a FI  $< 20$ ), reported clinical symptoms highly suspicious for SDB. All 12 were referred for PSG and diagnosed with SDB (2 OSA and 10 UARS).

**Conclusions:** AS was evaluated and found to be useful as a screening tool for SDB in crime victims with insomnia. However, there are limitations with respect to false negative AS

studies. In the 12 excluded patients with false negative AS, it was found that 1) the FI was artificially lowered by the use of total recording time instead of total sleep time, and 2) the flattening and FI cut-offs may have been overly conservative estimations for screening purposes. Notwithstanding, a rigorous interpretation of the raw AS data including SaO<sub>2</sub> desaturations, increased respiratory effort, snoring, and visible flattening can mollify these limitations until further studies validate definitive cut-offs. In the interim, AS appears useful for screening insomnia patients with suspected UARS or UARS-predominant SDB cases.

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**330.L**

**DAYTIME TESTING AFTER LABORATORY AND HOME POLYSOMNOGRAPHY**

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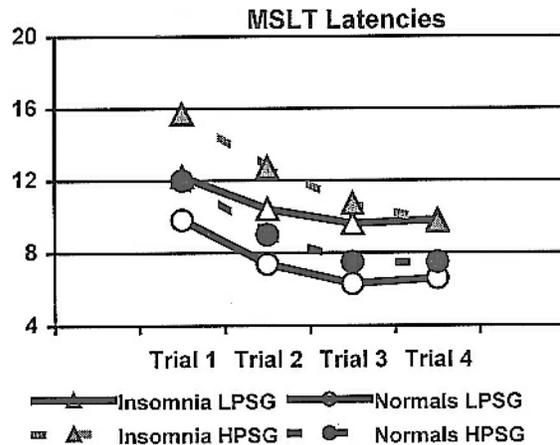
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**Introduction:** Insomnia sufferers have shown themselves to be paradoxically alert and devoid of marked performance deficits in many studies examining their daytime functioning. Such findings suggest insomnia sufferers exhibit a chronic state of hyperarousal that masks or offsets their endogenous diurnal sleepiness or performance decrements.<sup>1,2</sup> However, the studies leading to this impression all conducted daytime comparisons of insomnia sufferers and normal sleepers following one or more nights of laboratory polysomnography (LPSG). The current study was conducted to determine if similar results would be obtained following home-based PSG (HPSG).

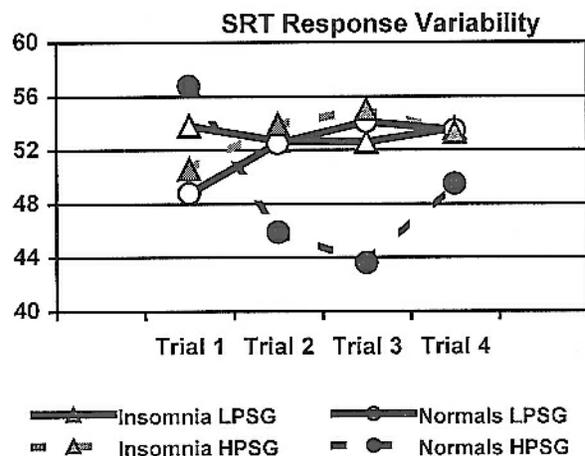
**Methods:** Through careful screening via medical exam and structured sleep and psychiatric interviews, 33 (17 women) middle-aged ( $M_{sAgeS} = 49.9$  yrs.,  $SD = 5.8$  yrs.) individuals meeting criteria<sup>3</sup> for Primary Insomnia and 35 (18 women) non-complaining normal sleepers ( $M_{sAgeS} = 46.5$  yrs.,  $SD = 5.0$  yrs.) were recruited. Roughly ~ of the participants in each sample were randomly assigned to complete three consecutive LPSG nights prior to completing a four-trial diurnal MSL T coupled with four trials of computer-administered reaction time tasks; the remaining participants underwent three consecutive nights of HPSG prior to this daytime testing. Dependent measures extracted from daytime testing included sleep onset latencies (SOLs) from each MSLT trial as well as within-trial

SD's for participants' response latencies to each of four types of reaction time tasks administered. An hierarchical linear statistical model (HLM) was used in the analyses of each of the study's five dependent measures.

**Figure 1**



**Figure 2**



**Results:** Results of HLM analysis with the MSLT data showed a significant ( $F_{s3,196S} = 2.97, p = .03$ ) overall main effect in the comparisons of the study's subgroups of participants. Post-hoc, Bonferroni comparisons showed that the SOLs of insomnia sufferers who underwent HPSG were significantly higher across MSL T trials than were those of the normal sleepers who underwent LPSG prior to their daytime testing (see Figure 1). Subsequent exploratory analyses showed that inclusion of nocturnal sleep onset latency as a covariate in our HLM analysis of the MSL T data led to the elimination of the previously observed significant differences among our subgroups. HLM analyses of performances on a relatively non-stimulating simple reaction time test (SRT) showed a significant ( $F_{s3,181S} = 3.08, p = .03$ ) subgroup x trials quadratic effect. Post hoc tests showed that only the insomnia sufferers and normal sleepers who underwent HPSG showed statistically distinct

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response profiles across SRT trials (see Figure 2). Among these individuals, the insomnia group showed a relatively "flat" pattern of response variability (i.e., attentional lapses) across trials whereas the normal sleepers tended to show declining response variability, particularly across the first 3 SRT trials. Contrary to the MSL T results, subsequent exploratory analyses for SRT data showed no relationships between nocturnal sleep measures and the performance test findings.

**Conclusions:** Findings suggest that heightened MSL T latencies of insomnia sufferers are related to a general sleep onset difficulty that plagues these individuals both at night and in the daytime. However, the home sleep environment may exacerbate this presumed index of endogenous hyperarousal. Despite the alertness implied by their MSL T data, insomnia sufferers do show some evidence of daytime fatigue (e.g., attentional lapses) particularly after sleeping in their homes prior to daytime testing. Thus, future studies of insomnia sufferers' daytime functioning should consider the effects of the prior night's sleep setting on the results of the daytime measures obtained.

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**331.L**

**THE CONSEQUENCES OF SITUATIONAL INSOMNIA**

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**Introduction:** Patients with Psychophysiological Insomnia have been found to suffer from hyperarousal. Despite poor nocturnal sleep, these patients may be significantly more alert than normals on tests of objective alertness during the following day. Recently, Situational Insomnia (SI) has been shown to be a reliable phenomenon. However, it is not known whether individuals who are prone to SI are more similar to patients with Psychophysiological Insomnia (i.e., have elevated arousal which protects them from sleepiness in response to poor sleep) or are more similar to normal sleepers, who have specific residual consequences in response to reduced sleep. In the current study, objective daytime alertness was compared in good sleepers and in participants with SI after baseline nights and nights with sleep advanced by 3 and 6 hours.

**Methods:** Participants to date have been 26 normal young adults (age 22). Subjects slept in the lab for a screening night followed by a baseline night and an advanced sleep night (advance of normal bed time by 3 or 6 hours). In the follow-

ing week, Ss returned for another baseline and the other advanced sleep night. Ss remained in the lab for the day after each night for MSL T and performance evaluation. Ss with the best sleep (top 25%, n = 7) on the screening night were defined as the Good Group and the Ss with the worst sleep (bottom 25%, n = 6) became the SI Group.

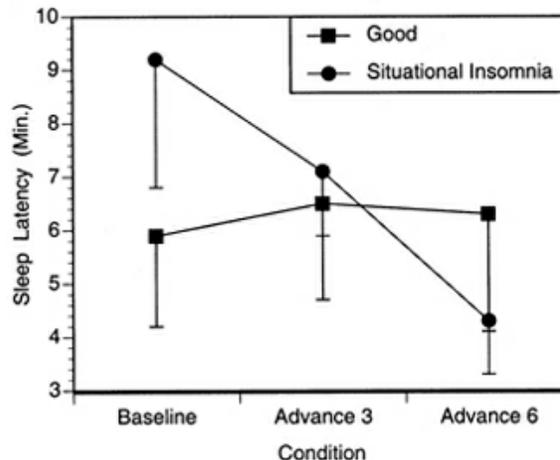
**Results:** The good sleepers did not demonstrate a significant decline in sleep efficiency from baseline to the 3 or 6 hour advances in sleep time (see Table). The SI did show a significant decrease in sleep efficiency from baseline to the 6 hour advance night. The SI also had significantly lower sleep efficiency than the good sleepers after the 6-hour advance. MSL T data for the groups is presented in the Figure. There was a significant Group by Condition interaction ( $F = 5.25, p < .01$ ). Neumann-Keuls pairwise comparisons indicated that the SI Group had a significant increase in sleepiness following the 6-hour advance as compared to their baseline. There was no change in objective sleepiness across conditions in the Good Group. This interaction could be explained by the fact that total sleep was reduced by almost 3 hours on the Advance 6 night in the SI Group as compared to their baseline while sleep was reduced by only about 1 hour in the Good Group on the Advance 6 night. It can also be seen that the SI Group had significantly longer sleep latencies on the MSL T following the baseline night as compared to the Good Group despite slightly (nonsignificant) reduced total sleep on the night before. Therefore, individuals with SI have longer MSL T latencies (like Psychophysiological Insomniacs) but also show residual sleepiness after a night of reduced sleep (like normals).

**Table 1**

Sleep Efficiency		
	Good	SI
Baseline	97.6	93.5
Advance 3	92.4	82.3
Advance 6	83.6	57.5*

F (Interaction) = 3.57; p < .05

**Figure 1**



**Conclusions:** These data indicate that individuals who have SI may display greatly reduced sleep time in a stressful situation that can result in significantly increased sleepiness after as little as one night.

**Research supported by a Merit Review Grant from the Department of Veterans Affairs, Wright State University School of Medicine, and the Sleep-Wake Disorders Research Institute.**

### 332.L

#### MENOPAUSAL METHYLTESTOSTERONE TREATMENT INDUCES CHANGES IN SUBJECTIVE SLEEP THAT CORRELATE WITH CHANGES IN MOTOR SPEED BUT NOT IN VIGILANCE

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**Introduction:** Healthy menopausal women on hormone replacement therapy (N = 34) were recruited to test the effects of testosterone replacement on affective measures and cognitive function. During two consecutive, randomized, double-blind, 8-week treatment periods, subjects took identically-appearing pills daily. The pills contained esterified estrogen 0.625 mg in both periods. During one of the periods, it also contained methyl-testosterone 1.25 mg. In a post-hoc analysis, we tested whether subjective sleep quality would correlate with objective measures of daytime cognitive function.

**Methods:** Subjective Sleep was measured by an index compounded of z-transformed scores for St. Mary's Sleep Questionnaire items (depth, satisfaction, how well one slept, clear-headedness in morning, number of awakenings, ease of falling asleep and trouble with early awakening). Daytime cognitive measures were taken at the end of both treatment periods. These included measures of complex verbal and associational fluency, motor speed (finger tapping), and vigilance (continuous performance response time, number of responses slower than normal [ $> 432$  msec; "lapses"], and response steadiness [standard deviation]) (Neurobehavioral Systems, Atlanta). Analyses were directed at finding whether subjective sleep was reflected in daytime cognitive measures. Stepwise regression (SAS, Cary, NC) was used to model subjective sleep index by cognitive measures during the estrogen alone condition, when not on methyltestosterone. Subjective sleep changes induced by added methyltestosterone were modeled by changes in cognitive measures between treatment conditions. To control for possible effects of independent co-variables, oophorectomy status, age and order of treatment were entered into the analyses.

**Results:** No significant relationship was found between self-reported sleep quality and cognitive variables in the estrogen alone condition. Testosterone replacement induced a trend towards improved sleep quality ( $p = .06$ ). Change in subjective sleep index after added methyltestosterone treatment correlated with change in cognitive measures (Model  $F = 7.2$ ;  $p = .01$ ). Of the three cognitive functions measured, motor speed changes accounted for 18% of the variance in sleep quality changes, but vigilance changes did not significantly correlate

with subjective sleep index changes.

**Conclusions:** We conclude that in menopausal women treated with estrogen alone, subjective sleep does not correlate with cognitive measures. However, methyltestosterone-induced changes in subjective sleep may correlate with motor speed. Hypothetically, this might occur because motor speed reportedly correlates with dopaminergic functions (1), which potentially affect sleep, and because dopamine may mediate some behavioral effects of testosterone (2).

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**Research supported by an unrestricted grant from Solvay Pharmaceuticals**

### 333.L

#### COMPARISON OF HOME AND LABORATORY ACTIGRAPHY IN YOUNG ADULTS WITH AND WITHOUT PRIMARY INSOMNIA

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**Introduction:** Recent research indicates that the setting in which sleep is measured (e.g., home vs. laboratory) may affect insomnia sufferers differently than normal sleepers (1) and is thus an important consideration in characterizing the sleep of insomnia sufferers. This study investigated setting differences in a sample of young adult insomnia sufferers using wrist actigraphy, an inexpensive and non-obtrusive objective means of estimating sleep patterns.

**Methods:** Participants were age and gender-matched samples of young adults with insomnia ( $n = 22$ ; 10 male, 12 female; M age = 29) and normal sleepers ( $n = 31$ ; 14 male, 17 female; M age = 28). Insomnia sufferers met ICSD diagnostic criteria for a chronic ( $> 6$  months) primary insomnia disorder. Normal sleepers had no history of sleep complaints and failed to meet criteria for any sleep disorder. All participants were screened for the absence of medical and/or psychiatric difficulties that could compromise sleep. Participants underwent 3 consecutive nights of laboratory PSG and 3 consecutive nights of home PSG (in a counterbalanced order) on separate weeks, as part of a larger research project investigating sleep-setting effects. On these six study nights (3 laboratory, 3 home) participants were also monitored with Actiwatch-L (Mini-Mitter Co., Inc., Bend OR) devices, the results of which are presented herein.

**Results:** The following sleep variables were estimated from actigraphy: total sleep time (TST), total wake time (TWT), sleep onset latency (SOL), sleep efficiency index (SEI), mean sleep bout time (MSBT; average length of blocks of continuous sleep), and mean wake bout time (MWBT; average length of blocks of continuous wake). Differences were analyzed in 2

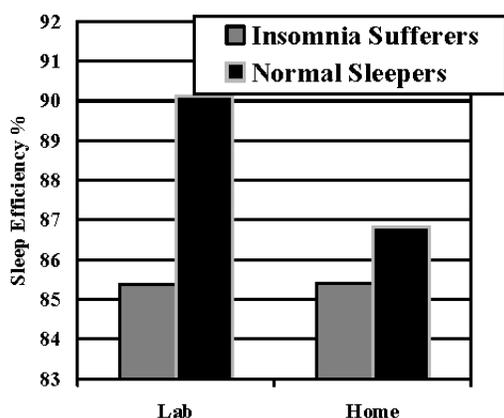
(Group: insomnia vs. normal sleepers) X 2 (Place: home vs. lab) ANCOVAs, controlling for gender, night (1 through 3), order (home or lab), and time in bed. Adjusted means are presented in Table 1. There were significant interaction effects for TST ( $F[1, 261] = 8.77, p < .01$ ), TWT ( $F[1, 261] = 5.47, p < .05$ ), SEI ( $F[1, 261] = 10.05, p < .01$ ), and MSBT ( $F[1, 261] = 9.66, p < .01$ ). Bonferroni-corrected post-hoc comparisons revealed that for all 4 of these sleep variables, normal sleepers experienced significantly worse sleep at home compared to the laboratory, whereas insomnia sufferers slept similarly in each environment. Figure 1 exemplifies these differences for sleep efficiency. These findings were supported qualitatively by post-study interviews with normal sleepers who reported sleeping better in the lab setting due to the minimization of environmental distractions.

Table 1

	Insomnia Sufferers		Normal Sleepers	
	Home	Lab	Home	Lab
	M (SE)	M (SE)	M (SE)	M (SE)
TST	386.7 (5.8)	387.2 (5.8)	393.6 (4.9)	408.4 (4.9)
TWT	56.7 (5.3)	57.5 (5.3)	49.4 (4.5)	39.5 (4.5)
SOL	14.5 (2.8)	16.7 (2.8)	11.8 (2.3)	8.7 (2.4)
SEI	85.4 (1.3)	85.4 (1.3)	86.8 (1.1)	90.1 (1.1)
MSBT	23.6 (2.8)	22.0 (2.8)	24.7 (2.3)	31.7 (2.3)
MWBT	2.0 (0.1)	2.0 (0.1)	1.9 (0.1)	1.8 (0.1)

Note. All values are in minutes except for SEI, which is %.

Figure 1



**Conclusions:** Estimates of sleep obtained from actigraphy showed no setting influences in young adults with insomnia. However, actigraphy monitoring of young normal sleepers suggested longer and more consolidated sleep in the lab compared to the home environment. We conclude that the low-stimulus (i.e., quiet, dark) lab environment maximizes the

sleep potential of young normal sleepers.

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**334.L**

**INSOMNIA AND HYPNOTIC USE IN BRAZIL**

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**Introduction:** To estimate the prevalence of the disorder of sleep initiation (DSI), sleep maintenance (DSM), and early arousing (DEA), and the use of hypnotics in the general population and to evaluate the effect of sex, age, social-economical class, schooling level, marital status, and occupation.

**Methods:** Design: Domiciliar interviews from the 3rd to the 8th of April 2001 in 7 urban regions of Campo Grande, Brazil, according to the use of structured questionnaire and with the consent from the interviewed subjects. Setting: The randomized sampling obtained through the method of cluster with quotas of sex, age and social-economical class according to survey data. Participants: 408 inhabitants being 18 years old or over. Interventions: N/A

**Results:** Results: The results are presented according to descriptive statistical methods and of inference based on parameters of binomial distribution, while for their analysis the qui-square (c2), and Fisher test were used. The significance level adopted was of 5% and the confidence interval (CI) of 95%. There is a general prevalence of insomnia 19.1% (sd=2.0%) mostly in women (p=0.0015) and people of low schooling level (p=0.0317) - sub type DSI (14.2%, p=0.0043) and chronic (p=0.7022). 6.9% (sd=1.3%) used hypnotics in the last month among which 68.1% over three times a week. In the life span 17.2% (sd=1.9%) among which 70.3% in the last 2 years, mostly insomniac (p<0.0001), women (p=0.0372 and p<0.0001) and people over 30 years of age (p=0.0536 and p=0.0091), with no prevalence of any insomnia sub type.

**Conclusions:** There is a high prevalence of chronic insomnia and high indices of hypnotic use in the urban population of Campo Grande.

**335.L**

**PRELIMINARY STUDY OF THE TEST-RETEST RELIABILITY AND CONCURRENT VALIDITIES OF THE PITTSBURGH INSOMNIA RATING SCALE (PIRS)**

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**Introduction:** The PIRS is a 65-item scale designed to rate the

severity of insomnia in clinical trials. Subjects rate items asking about subjective distress (Part 1 - 46 items), subjective sleep parameters (Part 2 - 10 items), and quality-of-life (Part 3 - 9 items) in the past week. The global score sums the items, each scaled 0-3. This preliminary study evaluated PIRS test-retest reliability and its correlations with the Pittsburgh Sleep Quality Index (PSQI) (1) and the Spielman Insomnia Symptom Questionnaire (SISQ) (2).

**Methods:** Adults with a primary diagnosis of an insomnia, depression, anxiety, or sleep apnea were eligible to participate. Subjects completed the PIRS, PSQI, and SISQ at baseline. Some completed a retest PIRS that was mailed to them. Missing data on the PIRS and the SISQ did not exceed 10% of items; average item values were imputed to missing items. PSQI scores were obtained using standard procedures (1). Pearson product-moment correlations were obtained between the two time points for the global PIRS score, as well as subpart scores. Correlations were also obtained between baseline global scores of the three questionnaires. Statistical testing of correlations utilized t-tests (3).

Figure 1

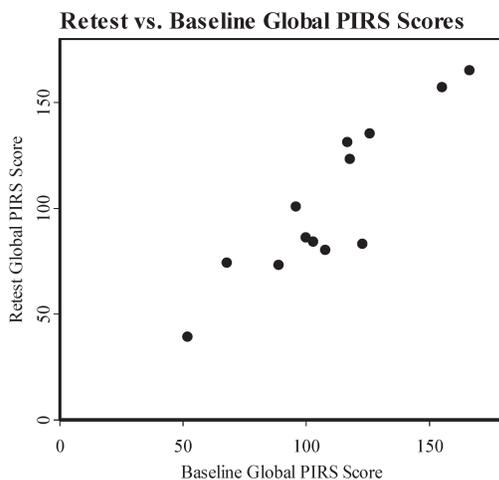


Table 1

		Baseline:Baseline and Baseline:Retest Correlations of the PIRS			
		BASELINE			
		Total	Part 1	Part 2	Part 3
BASELINE	Total	1.00			
	Part 1	0.98‡	1.00		
	Part 2	0.72‡	0.60†	1.00	
	Part 3	0.60†	0.50*	0.45*	1.00
RETEST	Total	0.90‡	0.86‡	0.70†	0.65*
	Part 1	0.90‡	0.89‡	0.60*	0.57*
	Part 2	0.56*	0.41	0.89‡	0.53*
	Part 3	0.71†	0.64*	0.53*	0.84‡

‡ p < 0.001 † p < 0.01 \* p < 0.05

**Results:** To date, 20 subjects (5 males, 15 females) have provided baseline data. The mean age was 43 (S.D. = 14). There was no missing baseline data for the PIRS or SISQ, but 4 subjects had missing data that prevented calculating a baseline PSQI score. Sixteen subjects provided retest completions, 13 within a 2-week period and with sufficient data. Nineteen subjects had a primary diagnosis of Primary Insomnia (18 Psychophysiologic Insomnia and 1 Idiopathic Insomnia), and 1 with sleep apnea. The global test-retest correlation ( $r = 0.90$ ) is shown in Figure 1. Correlations within the baseline PIRS and between the test and retest PIRS completions are given in Table 1. The PIRS:PSQI, PIRS:SISQ, and SISQ:PSQI correlations were  $r = 0.73$  ( $t = 4.00$ ,  $df = 14$ ,  $p = 0.0013$ ),  $r = 0.71$  ( $t = 4.27$ ,  $df = 18$ ,  $p = 0.00045$ ), and  $r = 0.56$  ( $t = 2.52$ ,  $df = 14$ ,  $p = 0.024$ ), respectively.

**Conclusions:** This preliminary psychometric study of the PIRS indicated that the PIRS has good test-retest reliability as a measure of insomnia severity in the past week. It does not have ceiling or floor effects for measuring insomnia severity. Lower, but significant between-subscale correlations suggest separate dimensions of insomnia are rated. It appears to have good concurrent validity with the PSQI and the SISQ. Further evaluation of the PIRS concurrent (i.e. between questionnaires) and discriminant (i.e. between clinical group) validities is needed. The PIRS may serve as a convenient, multidimensional global severity metric for insomnia symptoms in the past week.

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336.M

UNCONSCIOUS MOTIVATION FOR SLEEP-RELATED VIOLENCE: DREAMS AS EVIDENCE

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**Introduction:** Bonkalo's(1) guidelines for evaluating "impulsive behavior during the confusional state of a prolonged period of arousal from sleep" include: "the act (is) senseless, the victim anybody who happened to be present", "amnesia for the event", as well as "perplexity on full awakening without attempt to escape or cover up". These fit a recent case of a stabbing death of a "beloved" wife. With no evidence of prior hostility toward the victim and no other explanation, "unconscious motivation" is often invoked. Freud suggested that dreams are a source of information concerning the motives underlying dysfunctional behavior. Thus dreams may provide

the missing explanatory link between positive waking feelings and an act of sleep-related violence.

**Methods:** This is an uncontrolled, study of dreams of a 42 year old professional man, of reputed exceptionally good character and standing in his church and community, convicted of the death of his wife and sentenced to life without parole. The defense argued that there was no evidence of marital discord, and that the accused was not responsible for the attack which took place while in a state of non-conscious sleep-walking. Since his incarceration, the prisoner has kept a written record of dreams recalled on awakenings noting date and time of occurrence. There are 63 reports. These have been analyzed by roles of self and others, motives and repeating dream themes (2).

**Results:** 1. Frequency. The wife is the most frequent dream character appearing in 24% of reports. The daughter 19% and son 17%. Male authorities 16% and "bad men", (space aliens, enemy soldiers) 16%. The most frequent self roles are: husband and father 20%, someone physically threatened by others (enemies, huge machines) 20%. In 19% he is a rescuer-helper-protector. 2. Relationships. The husband-wife interactions are viewed as: a team, doing things with the children and for others. She is described as amused, encouraging, helpful, a companion, and he as happy, loving, protective, but also as worried, nervous, sensing danger, expecting a catastrophe. In recent dreams he becomes aware that she is absent and he misses her. 3. Motives, applying the 22 Jackson PRF, Most frequent are harm avoidance, and nurturance. The self character engages in only two acts of aggression; in one he hits a bad man who has captured a small boy, the other he hauls his son by the collar for being rebellious. 4. Two common themes: one positive: enjoying routine family activities, the other negative: fear of external physical danger. These appear to reflect his past life and current situation. There is no evidence of hidden antagonism toward the wife.

**Conclusions:** Although these data lack the usual controls they do not support the presence of unconscious hostility toward the wife.

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**337.M**

**ZOLPIDEM IS ASSOCIATED WITH AMNESTIC NOCTURNAL EATING**

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**Introduction:** Sleep related eating disorder (SRED) is more common in patients with insomnia and is often associated with restless legs syndrome (RLS), periodic limb movement disorder (PLMD), or obstructive sleep apnea syndrome (OSA). We evaluated five patients over an 11-month period in which

SRED either began, or worsened with zolpidem therapy. When the underlying sleep disorder was treated and zolpidem was discontinued, nocturnal eating stopped.

**Methods:** Case series of 5 patients with nocturnal eating and zolpidem use, who presented for evaluation with initial complaints of nocturnal eating (1/5), excessive daytime sleepiness (3/5), and parasomnias (1/5). On history, we elicited nocturnal eating and sleep onset or maintenance insomnia in 5/5. All patients had been started on zolpidem prior to referral for insomnia symptoms. Final diagnosis of the underlying sleep disorder(s) was suspected after history and physical in 5/5 patients, and confirmed with polysomnography in 4/5 patients.

**Results:** Demographic, historic, diagnostic, and treatment data are summarized in the table below. In each case, use of zolpidem was associated with onset (3) or worsening (2) of nocturnal eating and initial or worsening amnesia to nocturnal eating (5). Underlying sleep disorders diagnosed included RLS (5), OSA (3), sleepwalking (2), and psychophysiologic insomnia (1). One of our patients with sleepwalking fell down the stairs with fortunately only minor injury. In all cases, treatment of the underlying disorder and stopping zolpidem was associated with cessation of nocturnal eating and sleepwalking. Duration of follow up was a mean of 73.3 (median 61, range 40-157) days.

**Table 1**

Case	1	2	3	4	5
Gender	F	M	M	M	F
Age at presentation / onset of nocturnal eating	54/51	56/41	66/15	67/65	64/30
Age at start of zolpidem use	51	41	64	65	56
Effect of zolpidem on night eating behavior	Started	Started	Increased	Started	Increased
Amnesia with eating	Sometimes	Always	Increased after zolpidem	Mostly	2/3
Sleep Disorders other than SRED	RLS	RLS, OSA (RDI=76)	RLS, OSA (RDI=30)	RLS, OSA (RDI=18), Sleep Walking	RLS, Psych Ins, Sleep Walking
Treatment in addition to discontinuing zolpidem	clonidine, clonazepam	CBP, clonazepam	CBP, clonazepam	Paliperone, prazosin	prazosin, levamisole

**Conclusions:** SRED has been associated with RLS/PLMD and OSA, all disorders that increase nocturnal arousals. For this reason, many have suggested SRED is a disorder of arousal. Providing zolpidem, a medicine that has rarely been reported to cause transient amnesia, to patients with a disorder of arousal might be expected to occasionally lead to amnesia to arousal-induced behavior. Zolpidem has been previously associated with sleep walking [1, 2]. However, why SRED manifested de novo in some patients begun on zolpidem is uncertain, and suggests a novel association of nocturnal eating with zolpidem [1]. Zolpidem binding of GABA receptors reportedly does not elicit hyperphagia, but perhaps this assertion should be re-evaluated [3]. Nocturnal eating was not volunteered initially by 4/5 patients, and required specific question-

ing to elicit this symptom. Nocturnal eating is more common in those with insomnia than in the general population. For practicing sleep physicians, these cases highlight the importance of inquiring about nocturnal eating behaviors, especially in those taking zolpidem, and of arriving at an accurate diagnosis and appropriate treatment plan. Providing zolpidem for insomnia without seeking specific diagnoses may lead to unusual and potentially harmful nocturnal behaviors.

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### 338.M

#### POLYSOMNOGRAPHIC CHANGES IN PTSD AND IDIOPATHIC NIGHTMARE PATIENTS FOLLOWING IMAGERY REHEARSAL TREATMENT

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**Introduction:** Imagery Rehearsal (IR), a cognitive-behavioral technique for alleviating nightmares, is associated with subjective improvements in sleep quality (1-3). However, no independent replication of this effect has been conducted, and sleep improvements have not yet been assessed using polysomnography (PSG). This study addresses these limitations and investigates whether IR differentially affects PTSD and idiopathic nightmare (I-NM) patients.

**Methods:** Twelve nightmare patients completed prospective dream logs, measures of psychological distress, and underwent polysomnographic (PSG) recordings both prior to and 6-10 weeks after receiving the IR treatment. Six patients suffered from posttraumatic stress disorder and frequent nightmares (P-NM) and six suffered from I-NM. IR was provided during a single session in a small-group format. Pre-post treatment comparisons were made for dream logs, measures of psychological distress, and PSG recordings.

**Results:** Post-treatment, significant reductions in retrospective nightmare frequency ( $p = 0.007$ ), in prospective bad dream frequency ( $p = 0.03$ ), and in anxiety scores ( $p = 0.004$ ) were observed. Apart from an increased micro-arousal index ( $p = 0.04$ ), no changes in sleep structure were remarkable. Further, post-treatment sleep profiles were different for the two subgroups. Post-treatment, I-NM patients showed an increase in %S2 ( $p = 0.05$ ) and a reduction of periodic leg movements in REM sleep ( $p = 0.04$ ), whereas P-NM patients exhibited elevated micro-arousal indices ( $p = 0.01$ ).

**Conclusions:** These results independently replicate the effica-

cy of IR treatment for alleviating nightmares and other symptoms of psychological distress, but suggest that the effects may vary as a function of nightmare pathology. It remains possible that the reduction in disturbed dreaming and psychological distress precede the occurrence of significant objective sleep improvements. Further, the use of prospective dream logs in the present study indicates that bad dreams (unpleasant dreams that do not immediately awaken the sleeper), rather than nightmares (unpleasant dreams associated with awakenings), are a more sensitive measure of disturbed dreaming.

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Research supported by Canadian Institute of Health Research and Fonds de la Recherche en Santé du Québec

### 339.M

#### DOPAMINERGIC AND OPIATE THERAPY OF NOCTURNAL SLEEP-RELATED EATING DISORDER ASSOCIATED WITH SLEEPWALKING OR UNASSOCIATED WITH ANOTHER NOCTURNAL DISORDER

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**Introduction:** Nocturnal sleep-related eating disorder (NSRED) is a female-predominant disorder often associated with (or symptomatic of) another sleep disorder, esp. sleepwalking (SW), but also restless legs syndrome (RLS), periodic limb movement disorder (PLMD), insomnia, obstructive sleep apnea (OSA), narcolepsy, and circadian rhythm disturbances (including poor sleep hygiene). Various other conditions and their treatments/toxicity can be closely linked with NSRED. Nevertheless, NSRED can present as an idiopathic condition, or at least as a condition unassociated with another nocturnal disorder ("idiopathic NSRED"). Pharmacotherapy is a cornerstone of therapy, along with proper sleep-wake hygiene, daytime eating habits and stress-management skills. Whereas bedtime benzodiazepine therapy controls problematic—and even violent—SW in >80% of reported cases, benzodiazepine monotherapy is considerably less successful in controlling SW with problematic nocturnal eating (<50% of reported cases). In contrast, dopaminergic therapy (at times combined with opiate and/or clonazepam therapy) has been reported to be effective in controlling problematic nocturnal eating in patients with SW. The rationale for this therapeutic

approach in SW/NSRED was based on the successful control of problematic nocturnal eating in patients with RLS/PLMD/NSRED. Furthermore, this therapeutic approach (which is standard therapy for RLS/PLMD without nocturnal eating) may also be quite effective with idiopathic NSRED. We now report our center's cumulative experience in treating these two sub-groups of NSRED with dopaminergic and opiate therapy.

**Methods:** Over a 15 year period, 18 patients with NSRED associated with SW or unassociated with another nocturnal disorder ("idiopathic") were treated, by one of the authors, with dopaminergic and/or opiate therapy. This group comprised approximately 25% of all NSRED patients evaluated and diagnosed at our center during that time period. The SW patients with NSRED not included in this report had either responded to benzodiazepine (or other) therapy, had received treatment elsewhere, had refused therapy, or were lost to follow-up. All pts with SW had prior histories of SW involving non-eating behaviors, although at the time of presentation, most or all SW behaviors involved eating. All pts had undergone extensive clinical evaluations, including hospital-based polysomnographic (PSG) and audio-visual monitoring, with expanded EEG and EMG montages, utilizing standard methods of recording and scoring.

**Results:** All 18 pts had nightly eating episodes, with partial consciousness, and without perceived hunger, during arousals from sleep. PSG monitoring: 77.8% (14/18) had eating episodes from NREM sleep. No pt. had PLMD, clinical OSA, REM motor abnormalities or EEG epileptiform activity. 72.2% (13/18) of pts reported 75-100% control of NSRED with bedtime treatment (tabulated below). N=13 RESPONDERS: mean age, 38.2 ± 10.5 yrs; mean age, NSRED onset, 26.0 ± 9.9 yrs; females, 76.9% (10/13); mean duration, treatment follow-up, 2.5 ± 3.0 yrs (2-6 months, n=3; 1-2 yrs, n=7; 6-9 yrs, n=3). Currently, 69.2% (9/13) of responders are still being followed at our center (including all 3 pts with a 2-6 month follow-up interval). N=5 NON-RESPONDERS: mean age, 30.2 ± 16.6 yrs; mean age, NSRED onset, 18.6 ± 11.2 yrs; females, 60% (3/5); idiopathic NSRED, 60% (3/5); SW/NSRED, 40% (2/5).

**TREATMENT RESPONDERS I) SW-NSRED SUB-GROUP:** n=6 (females, n=4); mean age, 36.8 ± 7.2 yrs; mean age, NSRED onset, 19.0 ± 7.8 yrs. **II) IDIOPATHIC SUB-GROUP:** n=7 (females, n=6); mean age, 38.2 ± 10.5 yrs; mean age, NSRED onset, 26.9 ± 9.9 yrs. **TABULATION OF TREATMENTS (N=13)** N=2 (L-dopa or bromocriptine) N=2 (L-dopa & benzodiazepine) N=2 (L-dopa & codeine) N=1 (L-dopa & codeine & benzo) N=1 (L-dopa & trazodone) N=1 (bupropion & codeine) N=2 (L-dopa & bupropion/trazodone) N=1 (L-dopa & bupropion/codeine) N=1 (codeine & benzo) (3 pts took combined carbidopa/L-dopa and CR-carbidopa/L-dopa hs) (Benzodiazepines: clonazepam (n=2); alprazolam (n=1); estazolam (n=1) (L-dopa: Rxed as carbidopa/L-dopa or CR—controlled-release—tablets) (Bupropion: Rxed as regular or SR—sustained-release—tablets; dopaminergic anti-depressant (Codeine: Rxed in combination with acetaminophen: 325 mg acetaminophen per 30 mg codeine) (All medications were generally well-tolerated, with infrequent side-effects) **DOSE RANGES** Carbidopa/L-dopa (20/200—100/400 mg hs); carbidopa/L-dopa CR (25/100—100/400 mg hs) Bupropi-

on (n=1; 450 mg); Bupropion SR (n=3; 200-350 mg): taken as 2-3 split daily doses Codeine (30-60 mg hs); Trazodone (100-200 mg hs); Bromocriptine (2.5 mg hs) Clonazepam (0.5 mg; 2.0 mg); Alprazolam (0.5 mg); Estazolam (3.0 mg)

**Conclusions:** Our findings indicate that dopaminergic and opiate therapy of NSRED associated with SW or unassociated with another nocturnal disorder can be successful in the majority of treated patients. A benzodiazepine agent or trazodone may need to be included in the treatment regimen to control any persistent sleep disruption after control of nocturnal eating is achieved; these agents may also contribute to control of nocturnal eating. Our findings also call attention to dopaminergic and opioid mechanisms of control and dyscontrol of feeding behavior across sleep and wakefulness.

### 340.N

#### SLEEP STAGE SCORING METHODOLOGY WITH RHYTHMIC MASTICATORY MUSCLE ACTIVITY.

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**Introduction:** Rhythmic Masticatory Muscle Activity (RMMA) has been reported in 60% of normal sleepers and in patients with tooth-grinding during sleep, a condition known as sleep bruxism (Lavigne et al., 2001). The present study was conducted to describe the method that we developed to score sleep stages associated with RMMA episodes and to characterize sleep stage shifts occurring in close temporal association with RMMA.

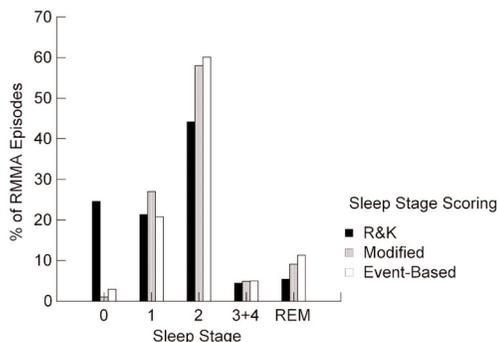
**Methods:** In this study, 20 moderate to severe bruxers were selected. Polysomnographic recordings were performed on two consecutive nights in a sleep laboratory. The first night was used for habituation to sleep laboratory conditions and to rule out other sleep disorders. RMMA episodes were scored as previously described (Lavigne et al., 2001). Sleep was recorded and first scored using the standard method of Rechtschaffen and Kales (1968, R&K) with 20-sec epochs. In the second analysis, all RMMA episodes scored wake with R&K were given the stage of the preceding epoch (modified scoring). As a third analysis, the sleep stage during the 20 sec before (B20) the beginning of the episode was scored (event-based scoring). The sleep stage during the 20 sec after (A20) the end of the episode, and during following 20 to 40 sec (A40) and 40 to 60 sec (A60) were scored. RMMA episodes separated by less than 100 sec were considered as being part of the same global episode (cluster) and sleep stages before and after the cluster were compared.

**Results:** With the R&K sleep stage scoring, 24.6% of RMMA episodes were scored as occurring in wake, while this decreased to 1.0% with the modified scoring (figure 1). A Cohen Kappa of 0.65 was observed between both methods, which indicates substantial agreement. The distribution of RMMA episodes (n=1107), over sleep stages, according to the modified scoring was 27.0% in stage 1, 58.0% in stage 2, 4.9% in 3+4, 9.1% in REM and 1.0% in wake. The distribution of RMMA episodes according to the event-based sleep stage scoring was 20.8% in stage 1, 60.1% in stage 2, 5.0% in 3+4,

11.3% in REM and 2.9% in wake. A Cohen Kappa of 0.78 was observed, which indicates substantial agreement between both scoring methods. A sleep stage shift occurred in 53.6% of episodes between B20 and A20. However, this decreases to 39.0% and 31.2% after 40 and 60 sec respectively. Episodes occurring in cluster were associated with sleep stage change in 56.8% of cases compared to 50.4% in isolated episodes ( $p=0.14$ ).

**Figure 1**

Distribution of RMMA episodes over sleep stages



**Conclusions:** These results show that the modified scoring and the event-based scoring give similar results. Moreover, approximately half of the RMMA episodes are associated with a transient sleep stage change immediately after the episode. The sleep stage then returns to its previous value in most episodes (69%).

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**341.N**

**AN OPEN-LABEL EXTENSION STUDY OF MODAFINIL FOR THE TREATMENT OF DAYTIME SLEEPINESS IN PATIENTS WITH PARKINSON'S DISEASE**

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**Introduction:** Excessive daytime sleepiness (EDS) and sleep

disorders are common complaints in patients with Parkinson's disease (PD). More than 15% of patients with PD experience EDS as compared with 1% of healthy elderly people. EDS and sleep disorders are among the most common causes of declining health-related quality of life in patients with PD. Modafinil, a novel wake-promoting agent, is effective for the treatment of EDS in narcolepsy<sup>1</sup> and obstructive sleep apnea,<sup>2</sup> and is potentially useful for treating EDS in patients with PD. Recently, we reported that modafinil was effective for the treatment of EDS in patients with PD who participated in a double-blind, placebo-controlled, study.<sup>3</sup> In this report, we extend our earlier observations to include results from a subsequent 4-week, open-label extension study.

**Methods:** Following completion of a 7-week, double-blind, placebo-controlled, study of modafinil and a 1-week washout period, 20 patients with idiopathic PD and EDS (ie, an Epworth Sleepiness Scale [ESS] score  $\geq 10$  at entry into the double-blind study) received modafinil 200 mg/d for 1 week and modafinil 400 mg/d for 3 weeks in a 4-week, open-label study. Efficacy was assessed using the ESS and patient- and physician-rated Clinical Global Impression of Change (CGI-C) scores. Other evaluations included scales for assessing fatigue, severity of PD, and activities of daily living.

**Table 1**

Assessment	Baseline	Endpoint
	Mean (SD)	Mean (SD)
ESS	15.6 (4.8)	12.2** (4.4)
FSS <sup>+</sup>	4.9 (1.5)	4.7 (1.8)
CGI-C Patient	0.00 (0.00)	0.85* (1.42)
CGI-C Physician	0.00 (0.00)	1.05 (1.36)

<sup>+</sup>FSS=Fatigue Severity Scale

\* $p=.02$

\*\* $p=.002$

**Results:** Mean (SD) ESS scores improved from 15.6 (4.8) at the postwashout baseline of the open-label study to 12.2 (4.4) after 4 weeks of treatment with modafinil ( $p = 0.002$ ). Improvements in wakefulness were also significant as assessed by patient- and physician-rated CGI-C scores ( $p = 0.015$  and  $p = 0.003$ , respectively). Mean scores on measures of fatigue, severity of PD, and activities of daily living remained relatively stable with respect to postwashout baseline values. Modafinil was well tolerated. Most adverse events (16 of 17; 94%) were mild to moderate in nature, and included two reports each of somnolence and abnormal dreaming. Four patients reported an increase in motor symptoms (ataxia, dyskinesia, hyperkinesia, or tremors), and two patients reported increased "OFF" time. There were no significant changes in mean diastolic or systolic blood pressure or mean pulse or respiration rates.

**Conclusions:** Treatment with modafinil significantly improved daytime wakefulness in patients with PD and EDS, and modafinil was well tolerated. The improvements in wakefulness observed in this open-label study were similar to those obtained in an earlier double-blind, placebo-controlled study.

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**342.N**

**PERIODIC LIMB MOVEMENTS DURING SLEEP IN PATIENTS WITH HEART FAILURE**

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**Introduction:** Periodic limb movements (PLM) is prevalent in several medical disorders as uremia, chronic myelopathies and anemia. Some patients may have asymptomatic PLM but it is usually associated with recurrent arousals from sleep leading to daytime sleepiness. Patients with congestive heart failure (CHF) usually have sleep complaints that can be related to both PLM and sleep breathing disorders (SBD). The objective of this study was to determine the prevalence of PLM in CHF patients with and without SBD.

**Methods:** We studied 31 patients with severe CHF with stable clinical condition and had left ventricular ejection fraction (LVEF) /leq 45 %. The etiologies of CHF were idiopathic (64.5% of total), Chagas' disease (19.4%), and ischemic (16.1%). Overnight polysomnography was performed using EMBLA equipment and all polysomnograms were performed and scored based on the guidelines for sleep studies. Daytime sleepiness was assessed by a subjective rating (Epworth Sleepiness Scale [ESS]). Significant differences between groups were analyzed by t test with p<0.05 considered significant. Of the 31 patients, 11 (35.5%) were women and 20 (64.5%) were men. The mean age was 60.8 (/pm 15.1) years with BMI of 20.5 (/pm 3.7) kg/m<sup>2</sup>. The LVEF was 35.6 (/pm 6.1)%.

**Results:** The sleep efficiency in patients without PLM was 85.9 (/pm 9.4) and with PLM was 71.7 (/pm 22.8). When just compared the polysomnographic characteristics of patients with SBD (Table 1), patients without PLM had higher TST, Sleep Efficiency, mean SaO<sub>2</sub> (p<0.05), and had lower AHI (p<0.05), compared with those with PLM. There are not differences between either age, BMI or LVEF. The ESS score

was 9.8 (/pm 6.3) in patients without PLM and 10.35 (/pm 5) in patients with PLM. These scores did not reach statistical significance.

**Table 1**

Polysomnographic Characteristics of the Patients with SBD

	<i>without PLM</i>	<i>with PLM</i>
<i>n° of patients</i>	<b>13</b>	<b>12</b>
<i>TST ( min)</i>	<b>361.2 ± 62.6</b>	<b>283.6 ± 103</b>
<i>sleep efficiency (%)</i>	<b>85.2 ± 9.5</b>	<b>68.5 ± 24.3</b>
<i>mean SaO<sub>2</sub> (%)</i>	<b>94 ± 1.8</b>	<b>91.6 ± 3.2</b>
<i>AHI</i>	<b>23.8 ± 14.7</b>	<b>49.3 ± 27.8</b>

**Conclusions:** This study suggests a high prevalence of PLM in patients with CHF, independently of the associated SBD.

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**343.N**

**ASSOCIATION OF RESTLESS LEGS SYNDROME WITH PARKINSON'S DISEASE, ESSENTIAL TREMOR, AND TOURETTE'S SYNDROME**

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**Introduction:** Patients with Parkinson's Disease (PD) have a 19.5% prevalence of Restless Legs Syndrome (RLS) (1) and patients with Tourette's Syndrome (TS) have a 59% prevalence of RLS (2). Because of this we did an opposite survey looking at the prevalence of PD, TS, and Essential tremor (ET) in RLS.

**Methods:** We looked at the prevalence of PD, TS, and ET in 120 patients with RLS. To eliminate referral bias patients who were referred for PD, TS or ET were excluded. Results were compared with prevalence rates of these 3 conditions from the literature using the Exact Binomial Test.

**Results:** The prevalence of PD in the general population for men in their 70's is .008. Four out of 14 men with RLS in their 70's had PD (P=.0001). For women in their 70's and men in their 80's the P value was <.05 for PD. Only one patient out of the 120 RLS patients had TS (P=NS). The prevalence of ET in the general population is .0042. Five out of our 120 RLS patients had ET (P <.00016.)

**Conclusions:** Putting together the results from the literature

and the current results we suggest that PD predisposes to RLS and RLS predisposes to PD. This may reflect the underlying dopaminergic deficit postulated for both conditions. Although TS and RLS are both responsive to dopaminergic drugs, TS appears to predispose to RLS whereas RLS does not appear to predispose to TS. The possible relationship of ET to RLS bears further exploration.

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### 344.N

#### AUGMENTATION WITH PRAMIPEXOLE IN THE LONG-TERM TREATMENT OF RESTLESS LEGS SYNDROME

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**Introduction:** Dopaminergic agonists have become first-line treatments for Restless Legs Syndrome (RLS). One of the great advantages of this class of agents appears to be the relative lack of "augmentation" (daytime rebound of symptoms), which can appear in 80% of L-Dopa treated patients. Montplaisir (2001) followed 7 patients for a mean of 7.8 months and did not find augmentation with pramipexole (mean dose 0.5 mg). Similarly, Ferini-Strambi et al. (2001) found that only 5 of 60 patients (8%) had augmentation with pramipexole (mean dose ~.5 mg). In all patients, pramipexole was given as a single dose at bedtime. We now report our longterm experience with use of pramipexole in patients with RLS.

**Methods:** All patients seen in a clinical practice given a diagnosis of RLS according to the IRLSSG criteria, who had been maintained on pramipexole for at least 6 months, were included. Augmentation was defined as an earlier appearance of RLS symptoms, requiring a change in the time of administration of pramipexole.

**Results:** Thirty-six patients (61 % female) were included, with a mean age of 59.6 yrs. (range 37-90). All but four patients were classified as primary RLS. Pramipexole had been taken continuously for an average of 21.6 months (range 6-41). Roughly 25% of patients were taking .125-.25 mg per day of pramipexole, 35% were taking .375-.5 mg per day, 20% were taking .75mg, and 20% were using 1.0 mg or more per day. Half (18/36) of the patients were taking the first daily dose of pramipexole at 6 pm or before. Nearly half (16/36) were taking pramipexole at least BID. Augmentation developed in 39% of patients (14/36). The precise time to the development of augmentation was unclear in many patients, and for some, this process continued to evolve over time. Augmentation did not necessitate discontinuation of pramipexole in any patient, and was generally managed with earlier dose administration or, occasionally, addition of other agents (gabapentin, opiates). In those for whom information was available, 88% (7/8) with

augmentation to pramipexole had previously developed augmentation to L-Dopa, whereas 58% (11/19) without augmentation to pramipexole had previous augmentation to L-Dopa. Most (25/36 or 69%) patients taking pramipexole were also taking one or more nocturnal sedative(s) to assist with sleep initiation or maintenance (trazodone=11, gabapentin=8, benzodiazepines=4, others=6). There was no statistically significant difference in age between those patients with and without augmentation, or in those receiving sedatives versus those not getting such agents.

**Conclusions:** We found much higher rates of augmentation than have previously been reported with pramipexole. The factors responsible for augmentation are unclear, and thus the causes for the disparity between our data and previous reports is unknown. However, two studies have noted augmentation in over one-quarter of RLS patients administered pergolide (Silber et al., 1996; Stiasny et al., 2001). Although augmentation was frequently observed in our patients, it was generally managed with earlier administration of pramipexole, or in unusual cases, addition of secondary agents. High rates of sedative-hypnotic use were found in our patients, suggesting that pramipexole may frequently be inadequate as a sole treatment for the sleep disruption in RLS.

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### 345.N

#### THE IMPACT OF RESTLESS LEGS SYNDROME (RLS) ON PATIENT QUALITY OF LIFE: RESULTS FROM A SURVEY OF RLS SUFFERERS

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**Introduction:** RLS is a sleep-related movement disorder in which a person during the transition between sleeping and waking experiences a strong urge to move usually associated with unpleasant sensations in the legs. This leads to severe sleep disruption. Whilst much research has shown the deleterious effects of sleep disorders on QoL (1), little research has been conducted to measure empirically the humanistic burden of RLS. The objectives of this study were to evaluate the validity of the new Restless Legs Syndrome Quality of Life (RLSQoL) questionnaire and to assess the impact of RLS on QoL among patients diagnosed with primary RLS.

**Methods:** The RLSQoL is an 18-item patient-report questionnaire that assesses the impact of RLS on daily life, sleep, emotional well-being, social life and work life. The RLSQoL was administered at baseline and 2 weeks later to 85 patients with primary RLS. The severity of RLS symptoms was assessed

using a patient-reported version of the RLS Rating Scale (RLSRS). Patients were also asked to report whether their symptoms improved or deteriorated over the 2-week period

**Results:** The majority of the sample (64.5%) were women and the mean age was 62.4 (SD, 14.0) years. The mean age at which RLS was first diagnosed was 36.6 (SD, 19.6) years. Four weeks prior to questionnaire completion, 67.1% of patients reported experiencing RLS symptoms almost daily. Patients not experiencing RLS symptoms daily had a mean symptom frequency of 7.54 ( $\pm$  6.3) days per month. Fifty-eight percent of patients reported that they experienced symptoms for 3 or more hours a day. The RLSQoL questionnaire yielded a single summary score of life impact that demonstrated acceptable internal consistency and test-retest reliability ( $\alpha=0.94$ ; intra-class correlation coefficient=0.75, respectively), satisfactory item-convergent and -discriminant validity, and excellent known-groups validity. QoL was significantly poorer for patients with more severe RLS symptoms, with at least a 10-point difference in RLSQoL scores between mild and moderate and between moderate and severe symptom groups. In addition, patients who reported that their symptoms had worsened over the 2-week period experienced a decrease in QoL, and those whose symptoms had improved showed an improvement in QoL. The effect sizes for the groups showing improvement (0.44) and deterioration (0.49) indicated a moderate change.

**Conclusions:** The RLSQoL questionnaire is a valid measure for evaluating RLS patients' QoL. The impact of RLS on patient QoL correlates with the severity of the disease, suggesting that treatment strategies aimed at improving or preventing RLS would have a significant effect on patient QoL. Instruments such as the RLSQoL can be used to evaluate further the humanistic burden of RLS and the benefits of therapeutic interventions on patient QoL.

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**346.N**

**MULTIPLE BLOOD DONATIONS AS A CAUSE OF IRON DEFICIENCY IN RESTLESS LEGS SYNDROME**

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**Introduction:** Iron deficiency has long been recognized as a predisposing factor for restless legs syndrome (RLS). Serum ferritin concentrations of <50 mcg/l correlate with increased severity of RLS [1]. Common causes of iron deficiency include menorrhagia, gastrointestinal blood loss and malnutrition. A less well-known mechanism is iron depletion from multiple blood donations. Serum ferritin concentration falls by 17-26% per donation and subjects donating 5 or more times in 2 years develop inevitable iron deficiency (ferritin <20 mcg/l) [2].

**Methods:** We identified 8 patients seen at the Mayo Sleep Dis-

orders Center in 2001 with RLS (International RLS Study Group criteria) and iron deficiency who were regular blood donors. Clinical and laboratory data was analyzed.

**Results:** Four were men; 4 premenopausal women (one with a hysterectomy, 3 with normal menstrual periods). Mean age was 47 years (range 40-59). RLS had been present for a year or less in 3 patients, for 7 years in one patient, and for 15 years or more in 4 patients. Two had family histories of first-degree relatives with RLS. No gastrointestinal causes of bleeding were identified. Patients had donated blood between 2 and 6 times a year (mean 4 times) for 3-25 years. RLS commenced after or at about the same time as the start of blood donations in 6/8 patients. Mean serum ferritin concentration was 8 mcg/l (range 3-15). Four patients were mildly anemic (hematocrits 31.9-37.3%). Two patients were treated with iron alone and 6 with iron and dopaminergic agents or opioids. Blood donation was stopped. Available follow up in 5 patients, including one treated only with iron and another who was able to discontinue pramipexole, revealed improvement in serum ferritin concentrations and excellent control of RLS.

**Conclusions:** We believe that iron deficiency from multiple blood donations either induced or helped perpetuate RLS in our patients. No other causes for iron deficiency were determined. Physicians treating RLS should question and counsel patients regarding blood donation. Staff of donor sites should be trained to question volunteers about RLS. Even if a screening hemoglobin concentration is normal, donations should not be accepted from RLS patients if their serum ferritin concentration is low. Donors should be prevented from suffering adverse clinical consequences of their altruism.

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**347.N**

**BRIEF NOCTURNAL BEHAVIOR OBSERVATIONS OF MOTOR ACTIVITY DISTINGUISH PARKINSON'S DISEASE FROM ALZHEIMER'S DISEASE**

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**Introduction:** The increased recognition of REM-dyscontrol in many neurodegenerative diseases such as Parkinson's Disease (PD) and Lewy Body Dementia and the development of PD in over a third of idiopathic REM Behavior Disorder cases leads to the prediction that motor activity in sleep is neither unexpected nor rare in PD. This study tested this hypothesis by conducting very brief observations (< 20 mins) of behavior during sleep in an unselected sample of inpatients with PD and a similarly hospitalized comparison group.

**Methods:** All patients were hospitalized in a specialized, subacute, tertiary care facility dedicated to geriatric patients (Wesley Woods Geriatric Hospital). Patients were hospitalized for a variety of reasons, but most typically for infections, injury or

medication adjustment. A total of 30 patients were studied, consisting of PD (n = 15) and other diagnoses (n = 15), the latter consisting of probable/possible Alzheimer's Disease (AD) (n = 9), major depression (n = 4), and generalized anxiety disorder (n = 2). Informed consent was obtained in all cases. Observations were made during behaviorally defined sleep between 0030 and 0500 and lasted between 7 and 35 minutes (X = 17.7 mins). Filming was made with a low light, audio-capable, second-by-second digital video camera placed on a tripod. Quantification of real-time observations was made by a second-by-second basis, with total seconds of movement observed for lower limbs, upper limbs, and body trunk computed separately. A fourth category, vocalization, was also recorded. Movement intensity for each behavioral category was defined on an ordinal scale (1) and then multiplied by time weights (5 12-sec intervals ranging from 0 - 60 sec). The summed score across categories was corrected for total # of seconds of observation. Higher scores thus reflected both pervasiveness and duration of movement, adjusted for duration of observation.

**Results:** The summed motor activity score was significantly higher in PD relative to AD/other patients (891.1 vs 205.7, Mann-Whitney Z = 2.94, p < .01). All four types of motor activity differentiated the groups, however there was some suggestion that the strongest differences occurred for the lower limbs. Among the PD patients, daily levo-dopa dose was positively correlated with motor activity score (rho = .53, p < .05), suggesting greater movement associated with more severe disease.

**Conclusions:** Use of these brief (but highly systematic) behavioral observations to detect motor activity in sleep in PD suggests very large effects. Given caregiver reports of disruptive nocturnal behavior in PD (2) and higher levels of overnight activity assessed with whole body actigraphy in PD (3), such effects cannot be considered altogether surprising. What is novel is their robustness based on the exceedingly short duration of such observations.

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**348.O**

**CLINICAL EXPERIENCE WITH VAGAL NERVE STIMULATION AND EXCESSIVE DAYTIME SLEEPINESS AS MEASURED BY THE EPWORTH SLEEPINESS SCALE**

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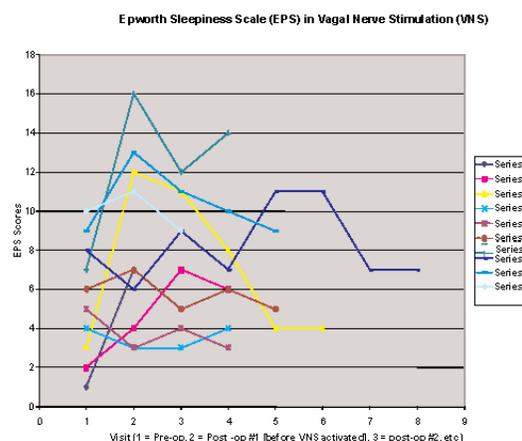
**Introduction:** Excessive daytime sleepiness is a common problem that may be associated with sleep loss (insomnia) or sleep fragmentation. Daytime sleepiness has been assessed using a tool called the Epworth Sleepiness Scale (ESS). The test consists of eight items and the patient is asked to gauge the chance of dosing on a 0-3 scale with 0 being would never dose

and 3 being high chance of dosing. Mean scores in normal subjects usually 5.9 with a range of 2-10. It was demonstrated by Zabara (2). Zabara demonstrated the anti-convulsant action of vagal nerve stimulation (VNS) in experimental animals. It was hypothesized that VNS could prevent or control seizures. The technique of VNS involves the implantation of a device in the left anterior chest wall. A subcutaneous generator sends an electrical signal to the left vagus nerve. VNS with the NCP system (Cyberonics). VNS with the NCP system utilizes an implantable, programmable bipolar pulse generator that stimulates the left vagus nerve with a bipolar lead. With a programming wand and software and a personal computer the pulse generator can be activated, interrogated and the character of the stimulation changed. VNS has been shown to be affective double blind studies and reduces seizure frequency overall a mean of 25% to 30% compared with baseline. A small sample open label study revealed that vagal nerve stimulation reduced the total in rapid eye movement sleep (3). For these reasons it was undertaken to have all patients treated for complex partial epilepsy with VNS in an outpatient Neurology/Sleep Medicine practice have serial EPS performed.

**Methods:** In a prospective fashion, patients referred for treatment by vagal nerve stimulation who had the clinical diagnosis of complex partial seizures were administered the Epworth Sleepiness Scale (1) preoperatively, postoperatively and then at intervals to see if there was any effect on daytime sleepiness in patients with epilepsy treated with vagal nerve stimulation. Fourteen patients have been enrolled. The results of the Epworth Sleepiness Scale given serially are presented graphically. Fourteen such patients were evaluated. Data is available on 10 patients. The study is ongoing.

**Results:** The results are seen in the accompanying table. Several patients manifest a trend toward reduction in daytime sleepiness. Large scale controlled studies may be helping in further elucidating whether VNS has a role in treating excessive daytime sleepiness. Confounding variables such as concomitant medication and seizure frequency should be evaluated.

**Figure 1**



POSTER PRESENTATIONS

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**349.O**

**MODAFINIL FOR TREATMENT OF DAYTIME SLEEPINESS IN PARKINSON'S DISEASE: A DOUBLE-BLIND PLACEBO CONTROLLED TRIAL**

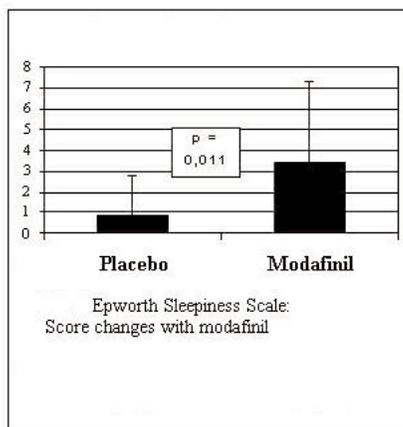
Högl B,<sup>1</sup> Saletu M,<sup>1</sup> Glatzl S,<sup>1</sup> Frauscher B,<sup>1</sup> Brandauer E,<sup>1</sup> Poewe W<sup>1</sup>

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**Introduction:** The goal of this study was to assess the therapeutic efficacy of modafinil in the treatment of increased daytime sleepiness in Parkinson's disease (PD).

**Methods:** 12 patients with idiopathic Parkinson's disease (9m, 3f, 65,0 +/- 7,6 years old, disease duration 6,8 +/- 4,1 years mean +/- standard deviation) and increased daytime sleepiness (Epworth sleepiness score ESS 10 or more) completed this double-blind, placebo controlled, randomized, crossover study. Patients with daytime sleepiness due to otherwise treatable causes (e. g. obstructive sleep apnea) were excluded. In two two-week treatment blocks patients received placebo or 200 mg modafinil (100 mg during the first treatment week) as a single morning dose in a randomized crossover order. Antiparkinsonian treatment was kept unchanged for the duration of the study. At baseline and at the end of each treatment block sleepiness was evaluated using subjective (ESS) and objective measures (maintenance of wakefulness test MWT, a variation of the MSLT).

**Figure 1**



**Results:** Epworth sleepiness scores were significantly improved with modafinil (mean score improvement 3,42 +/- 3,90) compared to placebo (0,83 +/- 1,99; p = 0,011, paired t-tests). Sleep latency in the MWT was marginally improved; before / after placebo 10,9 (3-40)/ 15,1 (2,5-40) minutes and before / after modafinil 12 (2,6-40)/ 17,8 (4,2-40) minutes (p = 0,139; n = 11, median, range).

**Conclusions:** The results of this study suggest, that modafinil is an effective treatment for daytime sleepiness in PD patients. However, otherwise treatable causes of daytime sleepiness have to be excluded.

**350.O**

**IMPACT OF L-DOPA ON SLEEP AND COGNITIVE PERFORMANCE IN PARKINSON'S DISEASE**

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**Introduction:** In Parkinson's disease (PD) up to 90 % of patients are sleep-impaired. Apart from additional diseases like sleep-apnea-syndrome, polyneuropathia or periodic-limb-movements the disease itself with its main symptoms akinesia, rigor and tremor may lead to disturbances of sleep. Finally, PD is affected by specific changes of sleep structure, e.g. sleep-fragmentation, reduced REM-sleep and sleep-efficiency. As a result, many patients with PD suffer from insomnia, daytime-sleepiness and impairment of cognitive functions. Treatment of PD can improve sleep but it can also have negative effects on sleep-structure, especially in higher doses.

**Methods:** To investigate the impact of l-dopa on sleep in PD, 20 patients with idiopathic Parkinson's disease, Hoehn and Yahr stage 2 to 4 and impairment of sleep, treated with l-dopa and dopamine agonists, underwent polysomnography (PSG) before and after addition of l-dopa in a slow-release preparation. Last medication was given at 10 p.m. The impact on motor performance in the morning after polysomnography was examined using the Unified Parkinson's Disease Rating Scale (UPDRS), part 3. To see the influence on cognitive performance, a battery of neuropsychological tests (Tower of London, Trail-making-test, Wechsler memory scale (WMS-R)), Mehrfach Wortschatztest (premorbid intelligence), Beck's depression inventory) was applied.

**Results:** Total sleep time, percentage of REM-sleep, sleep-efficiency, continuity- and fragmentation-index as well as duration of wake during sleep were seen as the main features of sleep-quality. The total sleep time of the first half of the night improved. Furthermore the patients showed decreased rigor and akinesia. Neuropsychological examination showed reduced depressive tendencies. A trend towards improvement of cognitive functions was observed.

**Conclusions:** Addition of l-dopa (slow-release) seems to show a positive effect on sleep-structure and daytime motor as well as cognitive performance. Late administration of l-dopa and dopamine agonists may improve sleep-structure. High doses of l-dopa or dopamine agonists on the other hand may lead to side effects like hyperkinesia, REM-suppression or vivid dreams with a deterioration of sleep-structure.

## 351.O

## MODAFINIL IS EFFECTIVE IN TREATING FATIGUE IN MULTIPLE SCLEROSIS: RESULTS OF AN OPEN-LABEL STUDY

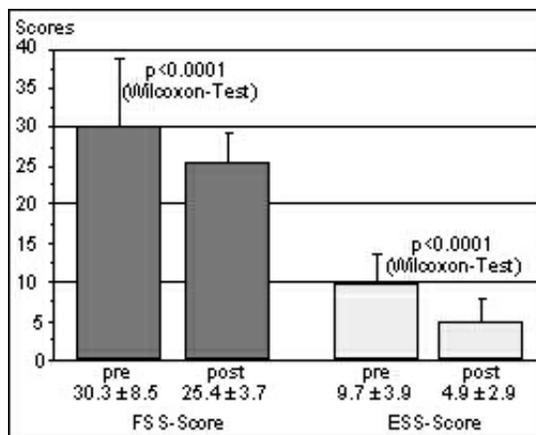
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**Introduction:** Fatigue is the most common symptom of multiple sclerosis (MS). Fifty to 60 % describe it as the worst symptom of their disease. Modafinil is a unique wake-promoting agent that is chemically distinct from traditional stimulants. It is effective in the treatment of excessive daytime sleepiness in patients with narcolepsy. The objective of this study is to establish the efficacy, safety and appropriate dose of modafinil in the treatment of fatigue and sleepiness in patients with multiple sclerosis.

**Methods:** A total of 50 patients diagnosed with MS (mean age  $40.4 \pm 10.3$  years, 30 females/20 males; MS type: 36 relapsing remitting, 1 primary progressive, 13 secondary progressive; mean disability level  $3.8 \pm 1.5$  on the Kurtzke EDSS) and complaining of chronic fatigue were enrolled in a prospective 3-month, two-center, open-label study. Efficacy was evaluated with the Fatigue Severity Scale (FSS, score range 0-42), the Epworth Sleepiness Scale (ESS, score range 0-24) and by subjective patient appraisal of change of fatigue, quality of life and overall satisfaction with treatment. Adverse effects (AEs) were recorded throughout the study. Treatment was started with a single daily dose of 100 mg in all patients. In non-responders the dose was increased by 100 mg increments up to a maximum daily dose of 400 mg.

Table 1



**Results:** Three patients discontinued modafinil because of AEs (nervousness, dizziness). Two patients (4%) were treated with 50 mg, 25 (50.0%) with 100 mg, 21 (42%) with 200 mg and 2 (4%) with 300 mg daily. No patient required 400 mg daily. Mean FSS scores were  $30.3 \pm 8.5$  at baseline and  $25.4 \pm$

$3.7$  at 3 months ( $p < 0.0001$ ). Mean ESS scores were  $9.7 \pm 3.9$  at baseline and  $4.9 \pm 2.9$  at 3 months ( $p < 0.0001$ ). Self-appraisal of change of fatigue showed clear improvement in 41 patients (87.2%), some improvement in 4 (8.5%) and no change in 2 (4.3%). Overall clinical condition was clearly improved in 43 patients (91.5%), somewhat improved in 1 patient (2.1%), and unchanged in 3 patients (6.4%).

**Conclusions:** Treatment with modafinil significantly improves fatigue and sleepiness is well tolerated by patients with MS. The interpretation of the results is limited by the open-label design of the study, and by the omission of objective sleep studies. But the very impressive outcome is a positive signal which should encourage further trials with a double-blind design, particularly as the drug is very well tolerated by MS patients.

## 352.O

## TRINUCLEOTIDE REPEAT COUNTS AND SELF-REPORTED DAYTIME SLEEPINESS IN MYOTONIC DYSTROPHY

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**Introduction:** Myotonic Dystrophy (DM) is an autosomally transmitted, multisystemic disease with muscular, cardiac, endocrine, and ocular involvement, as well as cognitive impairment. The molecular basis of the disease has been identified in an unstable base triplet (CTG)<sub>n</sub> repeat located in the 3' untranslated region of the myotonic protein-kinase gene on the long arm of chromosome 19. CTG repeat length broadly correlates with overall disease severity, yet a contribution of repeat count to brain versus muscle dysfunction has been established only for cognitive/memory (1). Sleepiness is an additional well-recognized symptom in DM (2) that may reflect either primary brain dysfunction or an epiphenomenon of disturbed sleep. In this study, we examined self-reported sleepiness, as measured with the Epworth Sleepiness Scale (ESS) and genetic loading for DM, as indicated by the number of CTG repeat sequences.

**Methods:** Thirty-four DM patients ranging in age from 15 to 72 (mean = 42.8, SD = 15.6) completed the ESS and underwent genetic analysis of CTG repeat counts. All had counts greater than 50 (median = 383, range 64 to 1201). Several underwent nocturnal polysomnography and Mean Sleep Latency Testing (MSLT) to document sleepiness objectively.

**Results:** Mean ESS score was 9.5 (SD = 5.3, range 1-20), indicating a modest level of sleepiness for the group as a whole. ESS scores were unrelated to CTG counts ( $\rho = .08$ , NS). Older age was associated with lower CTG count ( $\rho = -.45$ ,  $p < .01$ ), probably reflecting selective survivorship in which higher genetic load predisposes greater medical burden at an earlier age. Partialled effects of age did not effect the absence of the relationship between ESS and CTG count. Of note was an identical twin pair (ages 51) who had extremely low ESS scores (3/3) and very high CTG repeat counts (1201/1177). Even with this pair excluded, the correlation between ESS and CTG count was not significant.

**Conclusions:** The present results fail to associate CTG expan-

sion with differential manifestations of state control (i.e., sleepiness). The most parsimonious explanation is the unreliability of self-reported sleepiness; given poor correlation of the ESS and MSLT described in many sleep disorders population (3). However, the modestly high mean ESS for the group as a whole argues against this explanation. Another reason for this may be that sleepiness in DM may not reflect a single gene effect but rather a more complex trait determined by sleep apnea, medications, disturbance of sleep wake schedule and "trait sleepiness".

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**353.O**

**QUANTITATIVE EEG ANALYSIS OF WAKEFULNESS AND REM SLEEP IN PD PATIENTS WITH AND WITHOUT DEMENTIA, AD PATIENTS AND CONTROLS**

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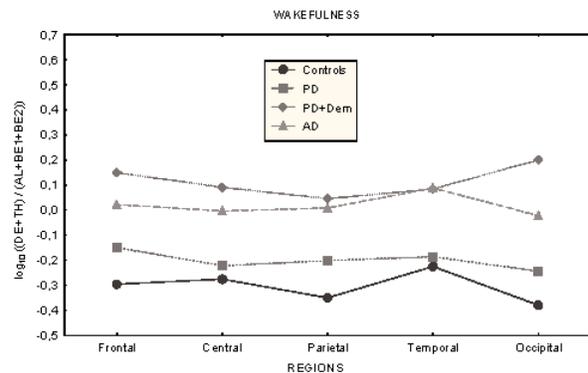
**Introduction:** Several studies have shown a slowing of the EEG during both wakefulness and REM sleep in Alzheimer's disease (AD) as well as a difference in the topography of the slowing between the two states (1). Patients with Parkinson's disease (PD) also show an EEG slowing during wakefulness, especially PD patients with dementia (2). The present study will thus investigate the topography of EEG slowing in both wakefulness and REM sleep in PD patients compared to both AD patients and controls.

**Methods:** The study included a group of 16 AD patients (71.1 /pm 5.5 yrs), 14 PD patients without dementia (63.2 /pm 6.6 yrs), 5 PD patients with dementia (76.8 /pm 3.2 yrs) and 23 control subjects (68.0 /pm 3.6 yrs). Absolute power in frontal, central, parietal, temporal and occipital regions was calculated for wakefulness and REM sleep from a total sample of 96 seconds of artifact-free EEG sections. Five frequency bands, delta (0.75-4.0 Hz), theta (4.0-8.0 Hz), alpha (8.0-13.0 Hz), beta1 (13.0-22.0 Hz), beta2 (22.0-31.0 Hz) and a ratio of activity in slow frequencies (delta+theta) over that in fast frequencies (alpha+beta1+beta2) were defined. Data were log-transformed prior to assessment by ANOVAs.

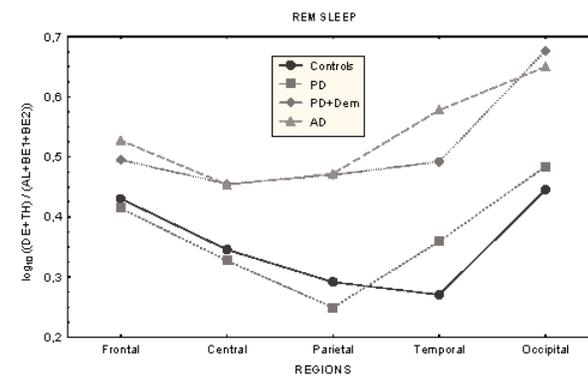
**Results:** In wakefulness, the ANOVA revealed a Group effect ( $F(3,54)=4.35$ ;  $p=0.008$ ). Specifically, a significant EEG slowing (ratio) was found in AD patients ( $p<0.004$ ) and PD patients with dementia ( $p<.01$ ) compared to controls in all five regions. Moreover, PD patients without dementia did not have a slowing of the wakefulness EEG compared to controls. A Group by Band interaction ( $F(12,216)=2.86$ ;  $p<0.0011$ ) indicated that delta and theta activity were higher for AD and PD patients with dementia compared to both controls and PD patients without dementia. In REM sleep, the ANOVA produced a sig-

nificant Group by Region interaction ( $F(12,216)=3.57$ ;  $p<0.0001$ ) indicating a slowing of the EEG in parietal, temporal and occipital regions in both AD and PD patients with dementia compared to both controls and PD patients without dementia. A Group by Band interaction ( $F(12,216)=2.84$ ;  $p<0.0012$ ) was also found, demonstrating that, in general, all bands except for beta2 contributed to the higher ratios in AD patients and PD patients with dementia.

**Figure 1**



**Figure 2**



**Conclusions:** Quantitative EEG in PD patients without dementia was similar to that of controls for both wakefulness and REM sleep. Conversely, PD patients with dementia presented an EEG slowing that was significant compared to controls and even similar to that of AD patients. This was true for both states. In fact, a state-related difference in the topography of EEG slowing was demonstrated in both AD patients and PD patients with dementia. Only the REM sleep EEG from the temporal region distinguished these two groups; it was slower in AD patients. These preliminary results should be interpreted with caution because of the small sample size of the PD with dementia group and because of significant differences between the two groups of PD patients in both age and PD severity.

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### 354.O

#### THE EFFECT OF MELATONIN TREATMENT ON SUBJECTIVE APPRAISAL OF NIGHTTIME SLEEP AND DAYTIME SLEEPINESS IN PATIENTS WITH PARKINSON'S DISEASE

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**Introduction:** Melatonin treatment in patients with age-related insomnia has been reported to improve a variety of objectively measured sleep parameters (e.g., sleep latency, sleep efficiency). Most investigations have not included subjective evaluations of nighttime sleep and daytime sleepiness. There is, however, at least one report in which objective improvements did not coincide with subjective self-reports (Hughes, Sack & Lewy, 1998). As part of a larger multicenter trial to examine the effects of melatonin at two different doses (5mg and 50mg) versus placebo to treat sleep complaints in patients with Parkinson's disease (PD), participants provided their subjective appraisals on various sleep and sleepiness related parameters.

**Methods:** The clinical design was a placebo-controlled, double cross-over trial. Subjects received each treatment (placebo, 5mg, 50mg) for a 2-week time period with a 1-week washout between treatments. The General Sleep Disturbance Scale (GSDS) (Lee, 1992) was used to assess participants' subjective sleep disturbances, daytime sleepiness and level of function over the past 1-week time period. The GSDS consists of 21 items related to difficulty getting to sleep, waking during sleep, waking up too early from sleep, quality and quantity of sleep, fatigue and sleepiness, and use of substances to help induce sleep. Subjects completed the GSDS for each of the 2 treatment weeks and results were averaged to achieve a single score for each treatment period.

**Results:** Thirty subjects (mean age=64 years, range=53-76) with PD (median Hoehn & Yahr scale score=2.5; mean=3.5±0.7) and without primary sleep pathology completed the experimental protocol. Wilcoxon signed ranks analyses of the GSDS results (see table) revealed a significant improvement (decrease) ( $p<.005$ ) in total score in the 5mg melatonin treatment condition compared to placebo. Further analyses of GSDS subscales revealed that the improvement in total score reflected significant improvements in reports of sleep quantity ( $p<.01$ ), mid-sleep awakening ( $p<.04$ ), early awakening ( $p<.007$ ) and daytime sleepiness ( $p<.001$ ). No significant differences were found in the use of sleep aids, sleep quality or difficulty initiating sleep. There was also improvement ( $p<.04$ ) in total GSDS score in the 5mg melatonin treatment

condition compared to the 50mg condition. This improvement reflects a significantly ( $p<.006$ ) lower daytime sleepiness rating in the 5mg condition compared to 50mg but not significantly different from placebo. No other significant differences were found in GSDS subscale scores. Subjects were also asked to identify during which treatment period they felt they slept "best." Eighty-four percent of the subjects identified the melatonin treatment periods as "best" (42% 5mg, 42% 50mg) compared to only 16% for placebo.

Table 1

General Sleep Disturbance Scale Scores						
	Mean score (SD)			Wilcoxon z (p - value)		
	placebo	5mg	50 mg	5mg - placebo	50mg - placebo	50mg - 5mg
Total	62.0 (13.1)	55.6 (14.5)	59.4 (15.0)	-2.8 (.005)	-1.3 (ns)	-2.1 (.04)
Substances to aid sleep	1.3 (2.5)	1.5 (2.6)	1.7 (3.2)	-0.7 (ns)	-0.9 (ns)	-0.6 (ns)
Sleep quality	12.6 (4.9)	11.0 (4.7)	11.6 (4.7)	-1.8 (ns)	-1.3 (ns)	-0.8 (ns)
Sleep quantity	12.1 (1.9)	11.3 (2.0)	11.5 (2.3)	-2.5 (.01)	-1.4 (ns)	-1.3 (ns)
Difficulty initiating sleep	1.9 (2.3)	1.5 (2.1)	1.6 (2.1)	-1.6 (ns)	-0.9 (ns)	-1.0 (ns)
Mid sleep awakening	6.4 (1.5)	6.2 (1.5)	6.1 (1.5)	-2.0 (.04)	-1.2 (ns)	-0.1 (ns)
Early awakening	5.2 (2.0)	4.2 (2.3)	4.6 (2.0)	-2.7 (.007)	-1.4 (ns)	-1.1 (ns)
Daytime sleepiness	23.2 (7.5)	19.9 (8.2)	22.3 (8.8)	-3.2 (.001)	-1.8 (ns)	-2.8 (.006)

**Conclusions:** Compared to placebo, a 2-week treatment with melatonin in this sample of patients with PD resulted in improved subjective reports of sleep disturbances, daytime sleepiness and level of function. Future analyses will compare these subjective reports to objectively measured parameters.

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### 355.P

#### SLEEP PATTERNS IN PRADER WILLI PATIENTS ON AND OFF MEDICATIONS

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**Introduction:** Prader Willi syndrome is a congenital disorder characterized by neonatal hypotonia, life-threatening obesity from childhood and onward, hyperphagia, hypopentia, hypogonadism, characteristic dysmorphic facial features, and short stature. Excessive daytime sleepiness (EDS) is a well-

known feature of Prader Willi syndrome. This study was conducted to determine if changes in sleep patterns could account for this EDS.

**Methods:** Fourteen Prader Willi patients ranging in age from 5 to 36 years were referred to The Sleep Research Unit with complaints of EDS. Six patients were on psychotropic and/or neuroleptic medications (fluoxetine, risperidone, methylphenidate, buspirone, benztropine, chlorpromazine, valproic acid, lithium and perphenazine) and 8 were medication-free. Patients underwent two overnight polysomnographic studies and daytime testing - Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) on successive days.

**Results:** There were no differences in the sleep architecture between the non-medicated and medicated groups but as a whole the Prader Willi patients had a significantly reduced percentage of REM sleep as compared to age-matched population normal values from the literature. The average REM percentage in the medicated group was  $12.2 \pm 5\%$  and in the non-medicated group was  $14.7 \pm 5\%$ , (not significantly different,  $p=0.4$ ). A diagnosis of sleep apnea was made in one patient (RDI = 42) from the medicated group, and two patients, one from each group, had elevated RDIs during REM sleep. The medicated patients had more severe daytime sleepiness as measured by the MSLT ( $9.3 \pm 6$  mins versus  $13.8 \pm 3$  mins in the non-medicated group,  $p<0.05$ ) and a greater occurrence of REM intrusions on the MSLT.

**Conclusions:** Our study found reduced amounts of REM sleep in Prader Willi patients that was independent of medication effects. We did not find a high frequency of sleep apnea or other sleep disturbances in our patients to justify the complaints of EDS, although patients on medications had more severe EDS. The psychotropic and neuroleptic medications commonly used to treat the behavioural and mood disturbances may particularly exacerbate sleepiness in this population. Further studies need to be conducted to determine if pharmacological intervention can help alleviate the EDS and if there are alternative medications that have less sedating action compared to the commonly used psychotropics and neuroleptics.

### 356.P

#### CHANGES IN SLEEP BELIEFS AND PRACTICES FOLLOWING SURGERY

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**Introduction:** One purpose of this study was to explore whether sleep beliefs and sleep promotion practices change during a stressful life event. Patients electing coronary artery bypass graft (CABG) surgery were selected for study because they are exposed to many of the factors known to generate short-term insomnia including hospitalization for a frightening and painful procedure. The surgical procedure itself has a major effect on circadian rhythms, thus disturbing sleep-wake patterns.

**Methods:** Elective CABG patients (N=25) completed ques-

tionnaires related to their sleep beliefs and sleep promotion practices pre-operatively and at 6-weeks post-operatively. The subjects were predominantly Caucasian men treated at a Mid-western USA medical center. Ages ranged from 47-82 years (M=64.5, SD=10.09). Sleep beliefs were measured by an 18-item Short-Form of the Floyd-Medler Sleep Belief Scale designed for use in clinical settings (1). It measures beliefs about (a) Next-Day Consequences, (b) Health Consequences, (c) Sleep Need, (d) Sleep Regularity, and (e) Coping. The Sleep Hygiene Awareness and Practices Scale (SHAPS) was used to measure sleep promotion practices (2). Two-tailed alpha was set at .05 for significance and .10 for trends.

**Results:** Sleep belief scores increased for all five factors, but none were significantly different from baseline. There were trends for beliefs about Sleep Need ( $t(24) = 1.98$ ) and Next-Day Consequences ( $t(24) = 1.75$ ) to increase following surgery. Only three sleep promotion practices were used more than 3 times/week and they did not change significantly in frequency of use pre- to post-operatively, see Table 1. Two related sleep hygiene practices changed following surgery: (a) There was a significant increase in worries while preparing for bed about being unable to sleep ( $t(24) = 2.31$ ) and (b) a trend toward increased worries during the day about being unable to sleep ( $t(24) = 1.72$ ). Subjects with strong pre-operative beliefs about Coping were significantly more likely following surgery to worry while preparing for bed about being unable to sleep,  $r=.44$ . Subjects with strong pre-operative beliefs about Sleep Need and the negative Next-Day Consequences of poor sleep were more likely to exercise during the day post-operatively,  $r=.45$  and  $r=.72$ , respectively. Also, subjects with strong pre-operative beliefs about Next-Day Consequences were likely to report post-operatively that they exercised vigorously within two hours of bedtime,  $r=.62$ .

**Table 1**

Most Frequently Used Sleep Promotion Practices

Sleep Hygiene Practice:	Mean Days / Week	
	Pre-Op:	Post-Op:
Had a comfortable nighttime temperature in bedroom	5.8	5.6
Set aside time to relax before bedtime	4.6	4.5
Slept approximately the same length of time each night	4.4	4.2

**Conclusions:** Although some practices adopted by this sample were positive, others, such as worrying about their ability to sleep and doing strenuous exercise close to bedtime are counterproductive. Overall, subjects in this sample used few of the sleep hygiene practices believed to promote sleep. There is partial support for the premise that adults' sleep beliefs may change during stressful life events and that beliefs about sleep may be related to sleep promotion practices adopted at those times. It remains to be demonstrated whether some beliefs about sleep protect or predispose adults to develop and maintain chronic insomnia during periods of stress.

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**357.P**

**REPORTED SLEEP-WAKE COMPLAINTS IN GENERAL PRACTICE PATIENTS: AN EPWORTH SLEEPINESS SCALE AND ATHENS INSOMNIA SCALE BASED STUDY**

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**Introduction:** The prevalence of sleep-wake complaints in the general population and in psychiatric patients is well documented. However within the health system as it is organized in Belgium, general practitioners are most likely the first to be confronted with these complaints. As we do not exactly know if physicians routinely question their patients about their sleep quality, we performed a one-day data collection on sleep-wake behavior and quality in a large group of patients consulting their general physician regardless of the reason.

**Methods:** 110 general practitioners agreed to participate in this study. During one day (a Wednesday in spring 2001) they presented following questionnaires to all successive patients that came for a consultation: The Epworth Sleepiness Scale (ESS), the Athens Insomnia Scale (AIS) and 10 short demographic and life style questions. 1343 patients (56% female, 44% male) agreed to participate.

**Results:** ESS: 228 patients (or 17%) had a score = 10 which is considered a significant risk for falling asleep during the day. Of these 228 patients, 64% were female, so slightly more than the 56% in the whole sample. The age group most represented (28%) are the 30 to 40 year old females. Further analysis is needed to find out if this finding is related to sleep disorders or to a possible sleep debt associated with life style and duties? AIS: A score = 4 on the first 5 AIS-items (questions on sleep) is considered as indicative of a sleep disturbance. The last 3 items of the AIS sample the quality of daytime functioning. 555 patients (or 41%) reached the cut-off of 4 on the AIS-5. Sixty two percent (343 patients) were females. There is a positive correlation between the 2 aspects assessed with the AIS. The higher the sleep scores (poorer sleep), the higher the complaints about poor daytime functioning. Regarding age, the highest prevalence of sleep complaints (39.3%) was found in patients within the 40-60 years group. Finally, relating the AIS and ESS scores we find an increasing percentage of patients with an ESS score = 10 as the AIS scores increase, as can be seen in the table below:

**Table 1**

AIS-8 score	ESS score $\geq$ 10
$\geq$ 6	25 %
$\geq$ 8	25 %
$\geq$ 9	33 %
$\geq$ 12	43 %

**Conclusions:** Forty-one percent of the patients consulting their primary physician present with sleep-wake complaints that may need some attention and further investigation, whereas seventeen percent have significant problems with maintaining daytime alertness as evidenced by well-validated questionnaires. Based on these findings, general practitioners should be encouraged to inquire more routinely about the sleep of their patients.

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**358.P**

**QUALITY OF SLEEP FOLLOWING BURN INJURIES: A SIX MONTH FOLLOW-UP.**

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**Introduction:** Sleep disturbances are frequently reported in burn victims. Disturbances during hospitalization, such as poor sleep quality and nightmares, are often reported, and have been known to persist for months or years (1,2). The purpose of this study was to evaluate sleep quality six month following hospitalization for severe burn injuries and to identify variables related to enduring sleep disturbances.

**Methods:** Twenty-eight oriented and non-ventilated patients (24M, 4W), between the ages of 17 and 50 years (mean = 34.8  $\pm$  = 10) were interviewed during five consecutive days within the first week of hospitalization and again (N = 18) at 6-month follow-up. During morning interviews, patients reported perceived quality of sleep (10cm visual analogue scale (VAS), #hours, #awakenings, #nightmares) and pain intensity (0-10 numerical scale). Patients also completed the Impact of Event Scale (IES) to determine posttraumatic stress symptoms and the Sleep Questionnaire for Adults to assess pre and post-hospitalization insomnia symptoms. Quality of sleep, pain intensity and medication ratings were averaged within subjects to produce single scores. Paired samples t-tests and McNemar tests were used to compare sleep measures at both times. Pearson correlations were used to evaluate the relationship

between measures.

**Results:** During hospitalization, patients' VAS scores averaged 5.4 (SD = 2.6) for sleep quality. Patients reported sleeping an average of 6 hours a night with frequent awakenings (mean = 4.3 ± 4.7). Eleven patients (39%) reported at least one nightmare. Six months following their injuries, patients reported sleeping an average of 7.5 hours a night with an average quality score of 6.6 on the VAS (SD = 2.3). Four patients reported at least one nightmare at follow-up. Five patients exceeded clinical criterion for posttraumatic stress symptomatology during hospitalization, whereas only one did at follow-up. Patients reported significantly better sleep on all measures and less posttraumatic stress symptoms at follow up (Table 1). Insomnia symptoms did not differ from pre-hospitalization to follow up (P = 0.45). Low scores on the sleep quality VAS at follow-up was significantly related to more nightmares (r = 0.68), more awakenings (r = 0.60), high pain intensity (r = 0.49) and high scores on the IES during hospitalization (r = 0.74, all Ps < 0.05).

**Table 1**

Comparison of sleep quality and posttraumatic stress scores during (H), and six months following (FU) hospitalization. Data are presented as means and (SD).

	H	FU	t	P ≤
VAS scores	5.1 (1.4)	6.6 (2.3)	-2.83	.011
Awakenings	4.6 (2.8)	1.4 (1.2)	5.76	.000
Hours	5.9 (0.9)	7.3 (1.1)	-4.95	.000
Nightmares	0.8 (0.8)	0.3 (0.6)	2.70	.000
IES scores	21.6 (17.3)	2.6 (3.6)	4.67	.015

**Conclusions:** Quality of sleep improved significantly from the first week of hospitalization to six months following burn injuries. Also, patients' reports of insomnia symptoms at follow-up were no different than they were prior to their injuries, suggesting that sleep disturbances during hospitalization did not persist. Whether they improved after discharge or gradually over time is not known. Still, the present results show a relationship between poor sleep quality at follow-up and anxiety related variables during hospitalization suggesting that, although their sleep has improved, anxious patients may still have difficulty sleeping in the months following their injuries.

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**359.P**

**SLEEP COMPLAINTS ARE ASSOCIATED WITH DISEASE SEVERITY AND INCREASED TNFA SOLUBLE RECEPTORS IN CONGESTIVE HEART FAILURE**

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**Introduction:** Congestive heart failure (CHF) is accompanied by complaints of fatigue and excessive daytime sleepiness<sup>1</sup>. The presence of Cheynes-Stokes respiration or central sleep apnea in many CHF patients may partially explain this phenomenon. However, the cytokine abnormalities associated with CHF<sup>2</sup> could also contribute to sleep complaints, as cytokines are known to affect sleep<sup>3</sup>. The purpose of this study was to determine whether the sleep complaints of CHF patients are positively correlated with pro-inflammatory cytokines and CHF severity.

**Methods:** This is a secondary analysis from a study of cytokines, depression, and CHF in patients at the UW Heart Failure Clinic. A majority (77%) of the 132 subjects reported here were male. Average age was 53 (range 19-74). New York Heart Association (NYHA) functional class rating of CHF severity ranged from 1 to 4, with 41% rated as NYHA 2, and 50% as NYHA 3. For analyses, CHF severity was defined by NYHA class and by 6-minute walk distance. Sleep information was extracted from sleep-related questions on the Hamilton Depression Scale and Hamilton Anxiety Scale. A Sleep Complaint score (range 0-3; 0 indicates no sleep complaints) was assigned to each subject, based on the combination of answers to these questions. Cytokines were measured by standard techniques in a daytime blood sample collected after supine rest. Analyses focused on the pro-inflammatory cytokines interleukin 6 (IL6), tumor necrosis factor alpha (TNFα), and the two soluble receptors for TNFα (sTNFα1 and sTNFα2). Cytokine data were available for only 81 subjects. As depression and sleep interact, all analyses were performed twice: once with the primary variables of interest, and again with a depression measure (score on SCL Depression Scale, after removing a sleep-related question) in competition with Sleep Complaint.

**Table 1**

Sleep Complaint	0	1	2	3
6-min walk (ft)	1310 \pm 250	1331 \pm 316	1226 \pm 197	967 \pm 367
NYHA class	2.6 \pm 0.6	2.5 \pm 0.7	3.0 \pm 0.7	3.0 \pm 0.6
sTNF\alpha1 <sup>a</sup>	2.94 \pm .28	2.96 \pm .29	3.11 \pm .44	3.12 \pm .26
sTNF\alpha2 <sup>a,b</sup>	3.52 \pm .32	3.53 \pm .17	3.64 \pm .23	3.57 \pm .19

Values are means ± standard deviations.

<sup>a</sup> Values have been log-transformed.

<sup>b</sup> Men only; regression analysis included age.

**Results:** Sleep complaints were positively correlated with CHF severity as indicated by NYHA class ( $p=.001$ ; table) and 6-min walk distance ( $p=.001$ ). Sleep complaints were also positively correlated with levels of sTNF $\alpha$ 1 ( $p=.015$ ). In men only, sleep complaints were positively correlated with sTNF $\alpha$ 2 ( $p=.043$ ). Though depression was significantly related to several variables, its inclusion in the analyses did not change the nature or significance of the sleep relationships.

**Conclusions:** Recent studies indicate that cytokines play an important role in the development and progression of CHF. Concurrently, sleep laboratories are finding that cytokines may play a role in the regulation of sleep. The results presented here provide preliminary support for the hypothesis that some of the excessive daytime sleepiness experienced by CHF patients may be due to CHF-related changes in cytokines.

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### 360.P

#### MULTIDIMENSIONALITY OF FATIGUE IN OBSTRUCTIVE SLEEP APNEA, INSOMNIA, AND CANCER: PRELIMINARY REPORT.

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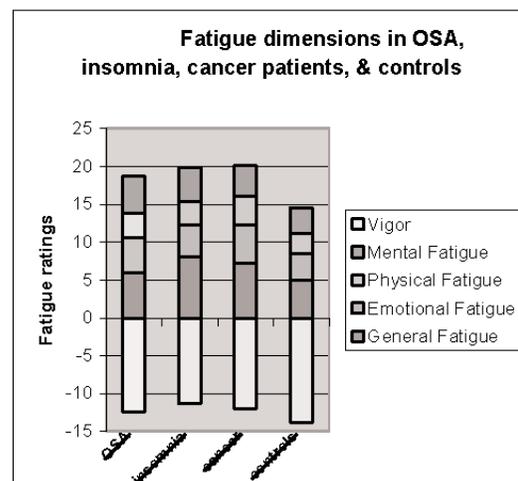
**Introduction:** Fatigue is a term that is understood only vaguely. It is a prominent and troublesome component of a variety of medical conditions, including cancer and most sleep disorders. Cancer-related fatigue is a complex and unique clinical phenomenon that was recently conceptualized as encompassing multiple domains or dimensions: i.e., physical, emotional, mental, general, and motivational/vigor(1). Compared to healthy subjects, cancer patients report significant fatigue in each of these dimensions. It is unknown at present how these dimensions may relate, if at all, to the frank sleepiness associated with sleep disorders such as obstructive sleep apnea. We previously reported the dimensions of fatigue experienced by 27 primary insomniacs; compared to published normative data, insomniacs reported significantly more General Fatigue and significantly less Vigor(2). In the present report we sought to quantify and describe the profile of fatigue dimensions in patients with obstructive sleep apnea.

**Methods:** 14 subjects (2F, 12M) age 30-65 years ( $49.3 \pm 9.5$ , mean  $\pm$ SD) in good physical health were recruited into an ongoing treatment study for OSA. Each subject was screened by physician interview and polysomnography (RDI > 15/hr

and filled out the 30-item short-form of the Multidimensional Fatigue Symptom Inventory (MFSI)(1), a validated fatigue assessment tool. The 30 items collapse into the following subscales or fatigue-dimensions: General, Emotional, Physical, and Mental, which are added together for a total fatigue score. Range of possible scores for the individual subscales is 0 to 24, higher numbers indicating more severe fatigue. Scores on the Vigor subscale are presented in negative values here, so that larger numbers also indicate worse fatigue. Because there were an insufficient number of observations, planned comparisons to published normative data were underpowered. Hence, the only data presented here are descriptive and qualitative.

**Results:** Figure 1 shows the mean fatigue subscale scores from: OSA patients (n=14), our previously reported insomnia patients (n=27), as well as previously published data from breast cancer patients (n=275) and normative comparison subjects (n=57)(1). Though total mean fatigue scores in each condition are higher than healthy comparison fatigue scores, the profile of the fatigue or the composition of total fatigue by its component dimensions may be distinct.

**Figure 1**



**Conclusions:** Though these data are clearly preliminary, they indicate the powerful conceptual utility of a survey instrument like the MFSI to parse out the contribution to overall fatigue by its component parts, across a variety of medical conditions. There is reason to suspect each of these domains may be perturbable by sleep loss or may be ameliorated by restored sleep. Fatigue is likely not a unitary phenomenon. Our notion of fatigue may require broadening, i.e., the term fatigue is not interchangeable with sleepiness. If there is a relationship between these dimensions and frank sleepiness, it remains to be seen.

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**361.P**

**IMPACT OF PAIN AND OPIOIDS ON SLEEP IN MEDICAL ONCOLOGY PATIENTS**

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**Introduction:** Pain and opioid analgesic use each independently interfere with nocturnal sleep and daytime wakefulness. However, some of our previous work suggests that opioids also have a net beneficial effect on nocturnal total sleep time due to their pain relieving properties.<sup>1</sup> Therefore, associations among pain, opioids, and sleep are complex, and the possibility that pain and its treatment have synergistic or interactive effects on sleep has not been well studied. Medical oncology patients receiving opioids for cancer-related pain not only report nocturnal sleep-related complaints despite treatment but also complain of daytime sleepiness, suggesting that research in this area is warranted. The purpose of this ongoing descriptive-correlational study is to examine relationships among pain, opioids, and day and nighttime sleep in medical oncology patients.

**Methods:** Subjects are male outpatients with solid tumor cancer diagnoses who are in some phase of a chemotherapy regimen and have a Karnofsky Performance Status (KPS) score of greater than or equal to 50. In addition, subjects must have at least one active opioid analgesic prescription or an average daily pain rating of greater than or equal to 2, as measured by the Brief Pain Inventory (BPI). Subjective daytime sleepiness is measured by the Epworth Sleepiness Scale (ESS). Patients receiving radiation therapy are excluded from participation. Activity and rest patterns are objectively assessed over a seven-day period in the subjects' normal environments using wrist actigraphy.

**Table 1**

Selected Characteristics of the Sample (N = 11)	
PARAMETER	Mean (+ SD)
Age in years	60.3 (9.4)
Karnofsky Performance Status score	75.45 (10.36)
BPI "worst pain in last week" (0-10 scale)	7.82 (1.54)
ESS total score	10.1 (3.67)
<b>Nighttime Actigraphy Measures:</b>	
Time in bed (hrs:mins)	8:48 (3:06)
Total sleep time (hrs:mins)	6:44 (1:23)
Sleep efficiency (%)	74.26% (9.88)
Sleep latency (hrs:mins)	0:36 (0:21)
Wake time during night (hrs:mins)	1:09 (0:29)
# of wake bouts (≥ 30 seconds)	35.04 (7.05)
<b>Daytime Actigraphy Measure:</b>	
Average daily nap time (hrs:min)	3:30 (1:28)

**Results:** Data from the eleven subjects recruited thus far (see Table 1) indicate that medical oncology patients with pain have poor nighttime sleep characterized by decreased nocturnal total sleep time, increased intervening wake time during the night, and decreased sleep efficiency. Subjects also report excessive daytime sleepiness and spend an average of 3 ½ hours napping during the day (see Table 1). However, those subjects taking a strong opioid (e.g., morphine) sleep an average of 4 ½ hours during the daytime in comparison to subjects taking a weak opioid (e.g., codeine) or no opioid who sleep an average of 2½ hours (see Table 2).

**Table 2**

Opioid Use And Hours Slept (N = 11)		
Opioid Use	Hours Slept-Night* Mean (± SD), Range(hrs:mins)	Hours Slept-Day* Mean (±SD) Range(hours:mins)
Weak/ No Opioid** n = 6	6:49 hrs (1:50) Range: 3:25-8:12	2:35 hrs (1:19) Range: 00:30-4:33
Strong Opioid n = 5	6:38 hrs (00:45) Range: 5:46 – 7:39	4:36 hrs (00:39) Range: 4:06-5:37

\* = Unadjusted means

\*\* = Only one subject reported no opioid use

**Conclusions:** These preliminary results are consistent with previous findings that both pain and opioid use have negative and fragmentary effects on nighttime sleep and daytime wakefulness. In particular, treatment with strong opioids appears to increase daytime sleep. While our results are not yet conclusive due to the small number of patients currently enrolled, as we enroll more subjects, we will be able to characterize these relationships more definitively. This work will permit a more detailed examination of the possible interactive effects of pain and opioid use on sleep. Ultimately, this work will provide a basis for the development of population-specific treatments to maximize pain relief while minimizing sleep-disrupting side effects.

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**362.P**

**EXCESSIVE DAYTIME SLEEPINESS IN MYOTONIC DYSTROPHY**

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**Introduction:** Myotonic dystrophy type 1 (DM) is an autosomal

mal dominant progressive disease characterized by muscular wasting, myotonia, endocrine dysfunction, and cataracts. Many patients affected by DM describe excessive daytime sleepiness (EDS) as the most incapacitating symptom of their condition. EDS associated with DM show clinical and neurophysiological traits similar to those seen in narcolepsy, namely disturbed nocturnal sleep, sleep-onset REM periods, frequent daytime napping and over representation of specific HLA DQ haplotypes.(1) The objectives of the present study were to estimate the prevalence of the classic symptoms of the narcolepsy tetrad in DM patients and to assess the relationship between EDS and sleep disturbances.

**Methods:** A sleep questionnaire based on the Sleep Questionnaire and Assessment of Wakefulness (2) was completed by 196 adult DM patients followed at the Neuromuscular Clinic of the Complexe Hospitalier de la Sagamie and by 26 controls. Mean age was 36.1 and 33.0 years, respectively (n.s.). A sleepiness scale was developed from 5 questions and scores varied between 0 and 15. The subjects indicated whether each brief descriptor always, often, sometimes or never applied. Sleep disturbances and other narcolepsy symptoms were dichotomized by the pairing of choices always/often and sometimes/never. Group differences in prevalence were analyzed with Chi-square tests. Bonferroni corrections for multiple comparisons (n=21) were applied.

**Table 1**

**Prevalence of Narcolepsy Symptoms in DM (%)**

	<b>DM</b>	<b>Controls</b>	<b>Significance</b>
EDS	43.1	3.8	<i>p</i> <.001
CP	17.0	0	<i>p</i> <.001
SP	4.7	4.3	<i>n.s.</i>
HH	6.2	3.8	<i>n.s.</i>

**Results:** An acceptable level of internal consistency between the sleepiness scale questions was found ( $\alpha=.79$ ), and factor analysis revealed that they measure a common factor. DM patients reported a higher sleepiness score than controls (6.14 vs. 1.85,  $p<.001$ ): they more often had sudden sleep attacks during daytime, felt less healthy during daytime, had more difficulty staying fully awake after meals, fell asleep more often while watching TV/or movies and took more naps. The 95th percentile value of controls on the sleepiness scale was 6.65: a score  $\geq 7$  was thus considered as indicative of EDS. EDS and cataplexy (CP) were more frequent in DM patients than in control subjects (43.1% vs. 3.8%, and 17.0% vs. 0%, respectively) while sleep paralysis (SP) and hypnagogic hallucinations (HH) did not differ between groups (Table 1). On the other hand, DM patients with EDS reported more frequent SP (10.3% vs. 0.9%) and HH (12.8% vs. 0.9%) than those without EDS ( $p<.002$ ). Finally, DM patients with EDS reported more difficulty remaining still for long periods, more difficulty staying up late in the evening, more respiratory disturbances during sleep, more pain during nocturnal sleep and felt less refreshed and less receptive in the morning compared with those without EDS ( $p<.003$ ).

**Conclusions:** This study reports a high prevalence of EDS in a large sample of DM patients. The presence of many clinical

traits indicative of hypersomnolence suggests a possible dysfunction of central sleep regulation in this condition. Since DM shares many physiological features of disordered arousal encountered in narcolepsy, the involvement of hypocretins should be assessed. (3)

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**363.P**

**ENVIRONMENTAL, DEMOGRAPHIC, AND ILLNESS-RELATED CORRELATES OF SLEEP QUALITY IN THE ACUTE CARE HOSPITAL**

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**Introduction:** Acute care hospitalization is known to be associated with disturbed sleep. Past research has implicated characteristics of the patient care environment (noise, lighting, patient care interactions), patients' demographic characteristics, and illness/treatment-related factors as correlates of sleep quality during hospitalization.(1) Yet, little is known about the relative contributions of these variables to sleep quality. The purpose of this study was to examine the relationships between environmental characteristics (noise, private vs. non-private room, hospital unit), demographics (age, gender,race), illness/treatment characteristics (type of diagnosis: medical, surgical, post-partum or antepartum and symptoms: pain, fatigue, anxiety) and self-reported sleep quality in hospitalized adults.

**Methods:** We surveyed 97 hospitalized patients (M age = 57,SD = 18.6 years, 50% women) who had spent the previous night in a 450-bed acute care hospital. The sample included 53(55%) medical, 32 (33%)surgical,and 12 (12%)antepartum and post-partum patients. The sample was 80% white, 10% black, 4% Hispanic, 3% Native American, and 2% Asian. Study participants completed questionnaires that included demographic and illness/treatment and environmental characteristics, and numeric rating scales (0-10, 0 = lowest, 10 = highest) of sleep quality, anxiety, pain, fatigue, noise, annoyance due to noise, and satisfaction with care.

**Results:** Descriptive statistics appear in the table. Overall levels of satisfaction with care were high. Participants reported more fatigue than anxiety or pain. There were no statistically significant correlations between age, gender, type of patient room (private vs. non-private), type of diagnosis (medical, surgical, maternity), pain, satisfaction with care, and sleep quality.

ty. Non-white patients reported better sleep quality ( $M = 7.3, SD = 1.6$ ) than white ( $M = 5.3, SD = 3.1$ ) patients,  $t(80) = -2.02, p < .05$ ). There were negative correlations between anxiety ( $r = -.34, p = .001$ ), fatigue ( $r = -.215, p < .05$ ), perceptions of noise during the night ( $r = -.21, p < .05$ ), annoyance with noise during the night ( $r = -.30, p < .01$ ) and sleep quality. Regression analysis demonstrated that race, anxiety, and annoyance with noise at night explained 23% of the variance in sleep quality. Race explained 6% of the variance in sleep quality, and anxiety and annoyance with noise explained 17%. Inspection of the beta weights revealed that the most salient correlates of sleep quality were anxiety ( $\beta = -.31$ ), annoyance with noise ( $\beta = -.29$ ), and race ( $\beta = -.22$ ). Pain, fatigue, and satisfaction with care did not explain a significant portion of the variance in sleep quality when included in the regression equations with the other variables.

Table 1

Variable	Numeric Rating		
	M	SD	Range
Pain	3.47	2.91	0-10
Fatigue	5.28	2.83	0-10
Anxiety	3.40	2.46	0-10
Sleep Quality	5.74	2.98	0-10
Satisfaction with Care	8.79	1.45	4-10
Noise	2.33	2.17	0- 9
Annoyance with noise	2.45	2.32	0- 9

**Conclusions:** These findings suggest that the most relevant correlates of sleep quality during hospitalization are affective: anxiety and annoyance with levels of noise. Environmental characteristics were not correlated with sleep quality. Further study of the role of perception and affectivity as influences on sleep quality in the acute care hospital is needed. The finding of differences between white and non-white patients was unexpected and warrants further study.

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**364.Q**

**HEART RATE VARIABILITY DURING SLEEP IN PATIENTS WITH PSYCHOGENIC ERECTILE DYSFUNCTION**

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**Introduction:** Regarding the etiology of erectile dysfunction (ED), besides a number of known organic causes, psychological factors play an important role in many patients. However, the neurobiological mechanisms underlying the so-called "psychogenic" ED are not yet understood. On the assumption that psychogenic ED is based on distinct disturbances of the central nervous system, heart rate variability (HRV) was studied with the aim to identify possible functional alterations of

the central autonomic activity as a neurobiological substrate of psychogenic ED. The study was carried out during different sleep stages, where cognitive and emotional influences were excluded to a great extent.

**Methods:** 24 male patients, 25-57 years old, with psychogenic ED participated in the study. They had no lifetime diagnosis of any other psychiatric disorder. Based on detailed case history, comprehensive clinical examination, laboratory parameters including hormones as well as assessment of nocturnal erections, there was no evidence of organic factors relevant for sexual function. In addition, an age-matched control group consisting of 24 healthy male volunteers, 26-56 years old, without sexual dysfunctions was also studied. None of the subjects had sleep disturbances. Each subject spent three successive nights in the sleep laboratory. After an adaptation night, two polysomnographies (EEG, EOG, EMG) were performed over 8 hours for each subject with registration of the electrocardiogram (ECG), which was sampled by 400 Hz. Off-line, after automatic detection of the QRS complexes, HRV was computed from the distances between successive RR intervals. Sleep EEGs were scored visually according to the criteria of Rechtschaffen and Kales.

**Results:** HRV was analyzed both in the time domain and the frequency domain during different sleep stages (1). For that, time segments of 10 minutes duration were selected from stage II, SWS and REM sleep, which were free of artifacts and movements. For most parameters, significant differences between sleep stages were found, pointing to different functional autonomic states during sleep. Particularly, SWS was characterized by a predominance of the parasympathetic over the sympathetic tone, whereas during REM sleep the autonomic balance was shifted in favor of the sympathetic activity. However, comparing patients and controls, no significant differences were found for all parameters.

**Conclusions:** Although in psychogenic ED a disturbance of the central nervous system including autonomic pathways has to be assumed, we could not prove any norm deviation of HRV, which is an important parameter reflecting central autonomic control of the heart. However, this is consistent with animal studies (2), which could demonstrate that autonomic activations can reveal regionally very different patterns. Therefore, our results with unchanged HRV do not exclude possible functional disturbances in other subsystems of the autonomic nervous system.

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365.Q

**SLEEP IN ALCOHOL DEPENDENT PATIENTS DURING ACUTE AND SUBACUTE WITHDRAWAL**

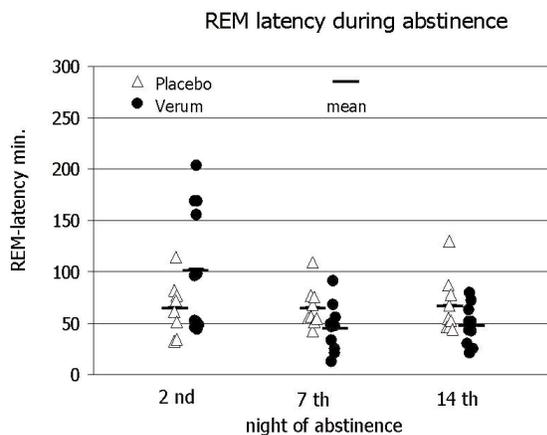
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**Introduction:** In recent years it has been shown by several authors that sleep in alcohol dependent patients during subacute withdrawal (after 2 to 3 weeks of abstinence) is characterized by disturbances of sleep continuity, reduced slow wave sleep and an increased REM pressure including a shortened REM latency, increased REM time and increased REM density (Gillin et al., 1994; Gann et al., 2001). In the present study sleep was investigated not only during subacute withdrawal, but also during acute withdrawal under a placebo condition versus treatment with clomethiazol (a thiazol derivate similar to thiamine). The study aimed at elucidating the course of REM sleep abnormalities during the withdrawal period.

**Methods:** To be included patients had to fulfill DSM-IV criteria for primary alcohol dependency. Only patients were included who had no prior history of severe withdrawal reactions, like for example seizures. Twenty patients completed the protocol (15 males, 5 females). Mean age of the sample was 42.0 + 8.3 years. Eleven patients were randomized to treatment with clomethiazol for five days and 9 patients were randomized to placebo treatment. Patients were investigated directly upon admission for 2 nights in the sleep laboratory. Patients were reinvestigated during night 6 and 7 and again during nights 13 and 14 after cessation of alcohol consumption. All sleep recordings were made according to standardized criteria and scored visually.

Figure 1



**Results:** For statistical analysis only the second night of each of the three pairs of nights was retained for analysis. As a primary parameter for data analysis REM latency was used. Results for REM latency in both patient groups during the first 14 days of abstinence are depicted in figure 1. REM latency was slightly prolonged in the clomethiazol group in the second night during the withdrawal period and shortened significant-

ly (p=0.05) in the seventh night. ANOVA over the three nights was not significant (p = 0.119). The group effect (clomethiazol vs. placebo) reached a p = 0.713.

**Conclusions:** When analyzing data for REM latency, for both groups taken together no significant change occurred over the first 14 days of abstinence, suggesting that shortened REM latency is a stable phenomenon during acute and subacute withdrawal. The data indicate that shortened REM latency during withdrawal in alcohol abstinent patients is not a mere rebound phenomenon of cessation of alcohol consumption.

366.Q

**SLEEP HABITS IN MIDDLE-AGED, NON HOSPITALIZED PATIENTS WITH CHRONIC SCHIZOPHRENIA**

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**Introduction:** Most studies on sleep disturbances in schizophrenia have been performed in small samples using polysomnography (1, 2). The aim of this study was to evaluate sleep quality in a large group of patients with schizophrenia using a questionnaire.

**Methods:** The study included 80 outpatients with schizophrenia (51 men, 29 women, aged 44.05 ± 5.9) and 36 healthy individuals (16 men, 20 women, aged 45.11 ± 6.35). Healthy participants were free from sleep disorders and personal or familial (first degree) history of psychiatric or neurologic disorders. All participants were asked to fill a questionnaire on sleep habits.

Table 1

Sleep variables in patients with schizophrenia in comparison to healthy individuals. (ξ ± SEM)

Variables	Sz	Ctl	P
Go to bed (weekdays) <sup>a</sup>	10.3±0.2	10.8±0.2	0.04*
Get out of bed (weekdays) <sup>a</sup>	8.1±0.2	6.5±0.1	<0.001*
Alarm clock (weekdays) <sup>b</sup>	0.2±0.0	0.5±0.1	0.002*
Go to bed (week-end) <sup>a</sup>	11.1±0.2	11.8±0.2	0.01*
Get out of bed (week-end) <sup>a</sup>	8.7±0.2	7.9±0.2	0.01*
Alarm clock (week-end) <sup>b</sup>	0.1±0.0	0.0±0.0	0.53
Naps (weekdays) <sup>b</sup>	0.5±0.1	0.2±0.1	0.02*
Duration of nap (weekdays) <sup>a</sup>	69.9±7.3	45.6±15.8	0.08
Naps (week-end) <sup>b</sup>	0.4±0.1	0.3±0.1	0.11
Duration of nap (week-end) <sup>a</sup>	80.2±9.3	39.3±12.6	0.01*
Time to fall asleep <sup>a</sup>	36.4±4.1	13.5±1.9	<0.001*
Number of awakenings <sup>a</sup>	1.4±0.2	1.5±0.2	0.23
Duration of awakenings <sup>a</sup>	14.1±3.9	6.4±1.0	0.74
Feeling of restfulness <sup>a</sup>	3.1±0.1	3.0±0.1	0.63
Sleep satisfaction <sup>a</sup>	0.8±0.0	0.8±0.1	0.86
Total sleep time <sup>a</sup>	8.9±1.8	7.5±1.2	<0.001*
Sleep efficiency index <sup>a</sup>	97.6±6.0	97.3±4.9	0.34

Notes : \* = significant; <sup>a</sup> = Mann-Whitney test, <sup>b</sup> = Chi<sup>2</sup> test.

**Results:** (See Table 1) Patients with schizophrenia showed the following characteristics: 1) They spend more time in bed : going to bed earlier and getting out of bed later than controls; 2) They took more time to fall asleep and used less frequently an alarm clock (on weekdays only); 3) They napped more fre-

quently during weekdays and duration was longer on weekends. The two groups did not show significant differences on feelings of restfulness and sleep satisfaction.

**Conclusions:** Patients with schizophrenia report increased sleep latencies, but also increased total sleep time. Their sleep efficiency, feeling of restfulness and sleep satisfaction are equal to that of controls. It is proposed that middle-aged patients with schizophrenia can make up for some sleep disorders by increasing time in bed and total sleep time, countermeasures that may not be possible for healthy controls.

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**367.Q**

**REPORTED SLEEP PATTERNS IN OLDER MEN AND WOMEN WITH SCHIZOPHRENIA**

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**Introduction:** Schizophrenia is associated with objectively disrupted sleep and complaints regarding sleep quality and daytime sleepiness. Sleep complaints are also common with advancing age in non-psychiatric adults. We recently reported older schizophrenia patients have disrupted circadian activity rhythms and a high prevalence of sleep disordered breathing.(1,2) We hypothesized older schizophrenia patients (SCZ) would report more disrupted nighttime sleep and more daytime sleepiness compared to similarly-aged normal comparison subjects (NCs). We also explored interactions between diagnosis (SCZ vs. NCs) and age, gender and depression with sleep reports.

**Methods:** In a larger late-life psychosis study, 137 SCZ (DSM-III-R; 69% male, M age =57.8, sd=9.7, M years since symptom onset=27; 81% taking neuroleptics) and 101 NCs (39% male, M age =64.0, sd=11.4) between ages 45-84 completed a battery of clinical measures including structured interviews about nighttime and daytime sleep patterns over the previous week, and the Hamilton Depression Rating Scale (sleep items removed for analyses; HAM-Ds) at study admission. MANOVA was used to examine effect of group (SCZ vs. NCs), gender, age and HAM-Ds, on sleep reports (with Bonferroni-corrected follow-up tests).

**Results:** Overall, final awakening time (FAT) was significantly later for SCZ than NCs ( $F_{s, 1,187} = 6.10, p=.014$ ); however, there was a significant groupXgender interaction ( $F_{s, 1,187} = 5.27, p=.023$ ; see Table). There was a significant groupXage interaction for FAT ( $F_{s, 1,187} = 4.72, p=.031$ ). Older

age was associated with later FAT within NCs only ( $F_{s, 1,187} = 5.36, p=.023$ ). There was no group main effect ( $F_{s, 1,187} = .43, p=.52$ ), but there was a significant groupXgender interaction ( $F_{s, 1,187} = 4.78, p=.030$  see table) for weekly frequency of falling asleep during sedentary daytime activities. SCZ were 3.3x more likely to complain of insomnia than NCs (see table). There were no other significant group effects or interactions.

**Table 1**

	SCZ		NCs	
	men	women	men	women
Final Wake Time	06:47h (114m)	07:22 <sup>a</sup> (82m)	6:43 (144m)	6:08 <sup>a</sup> (66m)
Fall Asleep in Activities	2.1 (3.9)	0.8 <sup>b</sup> (1.7)	2.1 (3.4)	2.5 <sup>b</sup> (3.2)
% Reporting Insomnia	25% <sup>c</sup>	39% <sup>c</sup>	6% <sup>c</sup>	13% <sup>c</sup>

<sup>a</sup>  $F_{1,187} = 6.45, p=.013$ ; <sup>b</sup>  $F_{1,187} = 7.60, p=.007$ ; <sup>c</sup> for SCZ vs. NCs,  $W_1 = 9.56, p=.0020$

**Conclusions:** Overall, SCZ report differences in sleep compared to NCs evidenced by a higher frequency of insomnia complaints. SCZ women also slept later in the mornings, waking 1:20h later than NCs women and about 30 minutes later than men in both groups. It is possible that additional morning sleep enabled women to stay alert during sedentary activities (TV, radio, conversations, reading). As expected, older age was associated with increased sleep disruption across groups. In SCZ, age was not associated with later wake up times as it was in NCs. This may be due to a higher occurrence of insomnia in SCZ or to differences in psychosocial variables i.e. sleeping later following retirement, since the majority of patients across ages were unemployed. Objective studies examining the effects of age and gender on sleep quality in schizophrenia are needed. Further research should also examine plausibility and appropriateness of treatment of sleep complaints in schizophrenia patients.

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**368.Q**

**SELF-REPORTED SLEEP DISTURBANCE AND MOOD STATES IN EARLY ABSTINENT OPIATE ADDICTS**

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**Introduction:** Poor sleep in the general population has many detrimental health outcomes, yet early reports suggest that the outcomes in the addicted population contribute to the relapse process, as well as continued health and psychiatric problems. While many researchers have investigated sleep disturbance in other populations, few have researched this phenomenon among drug-abusers. The primary purpose of this longitudinal descriptive study was to characterize sleep/wake patterns in early abstinence (10-90 drug-free days) of opiate-addicted men and women in a therapeutic community treatment setting. **Methods:** A longitudinal design was employed to obtain baseline and repeated measures from a convenience sample of 22 recently abstinent opiate-addicted men and women over a two-week period. Self-report of sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) and the General Sleep Disturbance Scale (GSDS). The Beck Depression Inventory (BDI) was scored on each Monday as well as a 37-item Profile of Mood States (POMS) for four consecutive evenings. Visual Analogue Scales (VAS), with one item related to sleep quality were completed for each night for the entire two-week period. A wrist actigraph was worn continuously for the complete study period of 14 days.

**Table 1**

Self-Report Data		
	Mean	SD
PSQI Global score (n = 22)	12.1	3.58
GSDS score (n = 22)	62.3	16.0
VAS (n = 19)	Week 1- 5.3	2.3
	Week 2- 5.4	1.9
BDI (n = 19)	Time 1-17.6	7.2
	Time 2-14.7	9.4
POMS (n = 20)	Week 1	
POMS fatigue-inertia subscale (T1-T4)	7.33	5.69
POMS vigor-activity subscale (T1-T4)	7.94	4.93

**Results:** The results to date are presented for 13 men and 9 women. The average age was 40.8 years (SD = 9.0) and education level ranged from eleventh grade to two years of college. The length of sobriety averaged 49.7 (SD = 23.4). The attrition rate was 14%. Cronbach's alpha for the PSQI sleep disturbance subscale was .71. The GSDS alpha coefficient was .70. The BDI's alpha coefficient for time one and time two was .82 and .87 respectively. Preliminary findings in PSQI global scores suggest opiate addicts in early abstinence period have a high degree of sleep disturbance (> 5) in this sample. GSDS

total scores ranged from 59.0 to 92.0, (scores > 60 indicate sleep disturbance). Women had a higher presence and severity of depression than men on the BDI initially, yet dropped at time 2 to a similar level to men. Sleep quality was rated on a 100mm VAS anchored at 0 = "very poor" and 100 = "very good". The VAS results (Monday thru Friday) were highly correlated (r = .78) and not statically different from week one to week two. The POMS fatigue-inertia correlated during week 1 (r = .69 to .85). The vigor-activity subscale from time 1 to time 4 was also correlated (r = .31 to .61).

**Conclusions:** These data suggest a preponderance of disturbed sleep and depression as well as labile mood states throughout the early abstinence period by subjective measures. Moreover, analysis of individual subscales may provide evidence to target specific interventions. Further analysis of objective measures of sleep/wake will provide a more detailed description of their sleep disturbance and its effect on daytime mood state.

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**369.Q**

**A QUESTIONNAIRE-BASED STUDY OF SLEEP PROBLEMS IN CHILDREN WITH AUTISM SPECTRUM DISORDERS.**

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**Introduction:** General high rates of sleep disturbances have been estimated for approximately 34 to 89% of children with Autism Spectrum Disorders (ASD). The majority of studies have been carried out on heterogeneous groups and mostly of them on school-aged children. In order to making a longitudinal analysis of sleep behavior possible, we decided to investigate sleep on a sample of young children with ASD. As a part of longitudinal study on sleep problems in children with ASD and the long- term effect of behavioral and pharmacological treatment, we reported here preliminary baseline data.

**Methods:** A sample of 25 children, (22 males, 3 females), aged 3.6-10.4 (mean age 4,3) with ASD was included in the study. Diagnosis was based on DSM IV criteria. Assessment included: neurological and cognitive evaluation, Childhood Autism Rating Scale (CARS) and Vineland Adaptive Behavior Scale. To assess sleep problems, we used the Children's Sleep Habits Questionnaire (CSHQ, Owens, 2000) completed by parents. It yields both total and 8 subscales scores, reflecting key sleep domains. Higher score are indicative of more disturbed sleep. Furthermore, a clinical interview inquiring previous child's sleep problems and current sleep patterns, including detailed information on bedtime routines and nighttime behavior, was carried out. Moreover, parents were asked to complete a diary of child's sleep. Baseline sleep variables, CSHQ scores were compared with sex- and age-matched controls.

**Results:** Clinical interview confirmed a high prevalence of

sleep problems with ASD, including bedtime difficulties (56%), nightwakings lasting more than 45 min (30%) or both (30%). No significant irregularity of sleep/wake pattern was found. Cosleeping, the practice of parents and children sleeping together in body contact for the whole night, was reported by 42% of children with ASD compared to 8.3% of controls (chi square <.001). Parents of 67% of children with ASD reported sleep disturbances in the first two year of life compared to 17% of controls (chi square <.001). While in controls onset of sleep disorders was in the first six months of life, in children with ASD a problematic sleep started usually from the second year, after a period of regular sleep/wake cycle. Children with ASD reported significant higher CSHQ scores (total 57 vs 37; bedtime resistance 12 vs 6; night wakings 11 vs 8; parasomnias 5 vs 3,  $p < .001$ ). A significant negative correlation was found only between sleep duration and CARS score ( $r = -.54$ ;  $p < .01$ ).

**Conclusions:** Consistent with other studies our children exhibit more dysomnias and parasomnias. Therefore, assessment of sleep in children with ASD need particular attention, not only because of the high prevalence, persistence and severity of the problem, but also for the additional distress that it may place upon caretakers, and for the contribution that a disturbed sleep might be making to daytime difficulties and behavior.

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### 370.R

#### THE USE OF WRIST ACTIGRAPHY TO INCREASE COMPLIANCE TO SLEEP HYGIENE INSTRUCTIONS IN UNDERGRADUATES

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**Introduction:** Compliance is a term referring to adherence to medical/treatment advice (Spilker, 1991). The interpretation of experiments involving human behavior can be confounded when research participants fail to comply with a study's instructions. The use of wrist actigraphy has become a widely used and inexpensive method of objective activity monitoring over 24-hour periods. Although applications to the field of sleep disorders medicine are numerous (Ancoli-Israel, 2000), it is unclear if instructions regarding the actigraphy procedure can significantly affect adherence. The present study compared compliance with sleep hygiene rules in subjects who were told that compliance would be verified with actigraphy, to subjects who were not told the actigraph would be used to assess compliance.

**Methods:** Sixty-eight undergraduate psychology students at Louisiana State University, age 18-30 years old, were given course credit for their participation. Participants were screened for (1) DSM-IV Axis I Disorders known to affect sleep architecture and/or sleep quality/quantity (e.g., anxiety, depression,

substance abuse/dependence); (2) self-reported signs of sleep disorders using a Sleep Disorders Inventory, and; (3) extremes in circadian tendency using the Morningness/Eveningness Questionnaire. There were 30 participants in the "instruction" group (IG) and 38 in the "no instruction" group (NIG). The IG were given instructions that stressed that the actigraph would verify reported sleep diary data, while the NIG was told that the unit would simply monitor their activity.

**Results:** A repeated measures MANOVA confirmed a main effect of group (Wilks' Lambda=.780,  $F[6,60]=2.82$ ,  $p=.017$ ), and follow-up ANOVAs confirmed a between group difference on Actigraphy bedtime ( $F=14.181$ ,  $p=.001$ ) and Actigraphy wake time ( $F=11.179$ ,  $p=.001$ ). Those in the NIG had later bedtimes and later waketimes, relative to the IG, and relative to the bedtime specified in the sleep hygiene instructions.

**Conclusions:** Although both groups were instructed to go to bed at a specified time (e.g., between 9 PM and 11 PM) and awaken 8 hours later (e.g., between 6 AM and 8 AM), the subjects who was told the actigraph would be used to verify whether they went to bed and woke at the specified times were more compliant than those who were not told their compliance would be verified. This has implications for studies requiring participants to follow sleep hygiene instructions, or in sleep disorder treatment to help ensure compliance with therapeutic recommendations.

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### 371.R

#### RECORDING MSLT IN THE HOME

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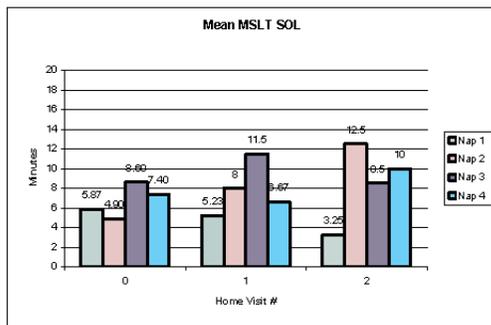
**Introduction:** Multiple sleep latency tests (MSLT) are always conducted in the laboratory to determine sleep onset latency thereby estimating the level of daytime sleepiness. Standard MSLTs are conducted the morning after an all-night polysomnogram (PSG). However, there are some situations where it may not be possible to have the patient come into the laboratory. For this reason, many research and clinical laboratories now conduct PSGs in the home. As part of a larger study on sleep in dementia, we have been conducting both PSGs and MSLTs in the home.

**Methods:** Subjects to date include 4 men and 1 woman (mean age [equiv 71.4 years; range: 54 to 82 years. All had a diagnosis of possible or probable Alzheimer's disease (AD). Each subject had a home MSLT and two had two additional home MSLTs, each three weeks apart. The first and third MSLT followed a home PSG. The second MSLT was done with no previous night's PSG. Embla recording system (Flaga Medical Devices, Iceland) and the Somnologica scoring program were used for all PSGs and a Dell Latitude laptop computer was added for the MSLT recordings. The recordings were done according to published criteria.(1) The subjects were instructed to lie down and try to sleep. The sleep recording was mon-

itored by the technician via the laptop computer. If the subject did not fall asleep within twenty minutes, or if three epochs of stage 1 sleep or an epoch of any other stage of sleep was seen, the subject was awakened and allowed to go about his or her normal daily activities. The technician periodically checked the subjects to be sure they had not fallen asleep during the interval between the recorded naps. Oft times the subject required encouragement to continue the study as they would sometimes forget about the full day commitment. Electrodes had to be replaced about 45% of the time when the subjects removed them.

**Results:** Environmental aspects could not be controlled as well in the home as in the laboratory. The subject's bedrooms were darkened as much as possible, using curtains and blinds. All windows and doors were shut. A sign was hung outside the bedroom door reminding other household members that a study was in progress and requesting quiet and reminding them not to enter. The figure shows the mean sleep onset latency (SOL) of the group.

Figure 1



**Conclusions:** Although home MSLTs do not fully conform to the published criteria for the laboratory, we have shown that it is possible to gather information about daytime sleepiness in home-bound populations, particularly in patients with dementia.

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**372.R**

**SLEEP STAGE SHIFT INDEX AS AN INDICATOR FOR THE LEVEL OF DAYTIME SLEEPINESS AND ALERTNESS**

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**Introduction:** Several sleep parameters have been identified as predictors for the level of daytime sleepiness and alertness.

Most robust indicators are sleep efficiency, sleep duration and arousal index. Our interest was to investigate the potency of the sleep stage shift index as such indicator.

**Methods:** A retrospective study was carried out utilising large database of eight hundred patients who underwent a sleep assessment in a tertiary unit during the 18-month period. This cohort served as a primary pool that provided the study sample. A subject was included if following criteria was met: a successful overnight sleep study, Multiple Sleep Latency Test (MSLT) or Maintenance of Wakefulness Test (MWT), and either of two – sleep stage shift index (SSSI) of >30 and arousal index (AI) of <15, or SSSI <20 and AI of <15. The cut-off SSSI of 30 and AI of 15 were set arbitrarily, having in mind commonly used normal values (&#61619;15 for SSSI, and &#61619;5 for AI). Four subgroups were formed with subject matched for sleep efficiency, age and AI, as tabulated below (Group I- High SSSI (MSLT); Group II -Normal SSSI (MSLT); Group III- High SSSI (MWT); Group IV - Normal SSSI (MWT):

**Results:** The subgroup selection and matching provided that the only major variable distinguishing respective subgroups was the SSSI. The most obvious finding during the matching was that there were very few subjects who had relatively normal AI and high SSSI at the same time. This dramatically reduced the numbers in all matched subgroups. The Independent samples' Mann-Whitney U-test with Bonferroni correction for p-values was used for statistical analysis of the results. This analysis suggests that the number of sleep stage shifts is an independent predictor of daytime sleepiness, but not of impaired daytime alertness. We were not able to explain this discrepancy aside from the possibility that the subject matching was less effective in the later group.

Table 1

	Age	SE	SSSI	AI	MSLT/MWT
I	49.1±19.7	80.6±8.6	35.2±3.2	9.3±3.2	9.1±5.4
II	43.3±10.4	81.3±6.7	17.2±1.8	9.1±4.3	14.9±5.9
	n/s	n/s	.00000	n/s	0.03
III	47.8±19.2	88.2±5.4	35.4±7.4	8.7±3.7	24.5±3.7
IV	39.1±8.0	94.1±3.8	16.5±2.9	8.2±2.0	24.8±4.8
	0.242961	n/s	.000000	n/s	n/s

**Conclusions:** We are aware of the critical reduction of the sample size that came as a result the multi-variable matching. Nevertheless, we were able to show that the SSSI could be used as one of the predictors of excessive daytime sleepiness, as the observed trends indicate. This may prove to be helpful in understanding the arousal mechanisms and their relation with different (sub)cortical EEG generators. The analysis of a larger sample is merited to confirm the observed trend, and should also help in understanding the absence of such trend in the MWT group, as well as relative absence of REM periods during daytests. The results also confirm that MSLT and MWT measure different neuro-physiological domains.

**373.R****CAN IMPAIRED ALERTNESS BE DETECTED MORE SENSITIVELY USING A COMPUTERIZED DRIVING SIMULATOR?**

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**Introduction:** Use of a computerized driving simulator has been validated<sup>1, 2</sup> as an effective and naturalistic research tool to measure psychomotor performance relevant to driving an actual vehicle. While the Maintenance of Wakefulness Test (MWT) is the most widely used objective test of impaired daytime alertness, we were interested whether performance in the 'virtual environment' of our driving simulator (York Computer Technologies, Kingston, Ontario, Canada)<sup>2</sup> might be a more sensitive and ecologically valid screening tool for impairment of alertness.

**Methods:** This was a naturalistic prospective study of 10 consecutive patients (aged 53.6±15.3) referred to our tertiary sleep research center for clinical investigation of excessive daytime sleepiness (EDS). Informed consent was obtained from all patients. Comorbid conditions included insomnia, mood disorders, and sleep apnea; use of psychotropic medications was allowed. Exclusion criteria were neurological or psychotic illness, substance dependence and lack of a valid driver's license. On the evening prior to testing, to control for learning effects, all subjects did one 30-minute 'trial-run' on the simulator. Subject then retired to bed at 23:00. We assessed various polysomnographic (PSG) parameters overnight, including total sleep time (TST), sleep efficiency (SE), arousal index (AI), and percent of stage 1 and slow-wave sleep (SWS). Upon being woken at 07:00 following standard overnight PSG testing, subjects were tested in four separate 30-minute MWT trials (at 09:00, 11:00, 13:00 and 15:00), each followed by four separate 30-minute computerized driving performance assessments, designed to simulate monotonous highway driving. Driving simulator outcome variables included: (i) mean reaction time to simulated 'wind gusts' (intended to provoke corrective steering maneuvers), (ii) mean time outside "safe zone" (a composite measure of driving accuracy, defined as tracking within 0.914m of the center of the right-hand lane together with a speed deviation within 20 km/h of the posted speed limit), and (iii) mean number of "crashes" off the designated lane.

**Results:** Patients displayed relatively normal sleep on the preceding night, with all measured PSG variables falling within normal range. Furthermore, mean MWT scores did not reveal impairment of alertness in our group. However, in psychomotor performance testing using the driving simulator, subjects showed significant impairment of driving ability, with respect to mean reaction times and total number of crashes and time outside the "safe zone". There was a significant correlation ( $r=0.70$ ,  $p<.05$ ) between mean reaction time and number of crashes; however, MWT did not correlate significantly with any of the three driving performance measures.

**Table 1**

Polysomnographic Measure	Mean
Total Sleep Time (min)	372.1 ± 44.0
Sleep Efficiency (%)	84.0 ± 0.7
Arousal Index (events/hr.)	11.1 ± 3.7
Stage 1 (%)	9.1 ± 3.8
Slow-wave sleep (%)	20.1 ± 6.1
Mean MWT (min)	24.5 ± 8.0

**Table 2**

Driving Measure	Mean
Reaction Time (sec)	1.26 ± 0.20
Time Outside Safe Zone (%)	28.2 ± 4.7
Number of "Crashes"	2.1 ± 1.9

**Conclusions:** In our naturalistic cohort, individuals with a relatively normal PSG sleep structure appeared normal on the MWT with respect to objective assessment of alertness. Yet, performance on a computerized driving simulator showed evidence of impairment. The driving simulator paradigm may be a standardized performance task with greater specificity than the MWT with respect to a patient's actual driving performance. In this study, we suggest that it may also be a more sensitive and specific instrument in detecting impairment in driving capacity in patients presenting with excessive daytime sleepiness, and could be clinically useful as an adjunct daytime measure with ecological validity.

**References:**

- Hack M, Choi S, Vijayapalan P, Davies R, Stradling J. Comparison of the effects of sleep deprivation, alcohol and obstructive sleep apnoea (OSA) on simulated steering performance. *Respiratory Medicine* 2001; 95:594-601.
- Arnedt J, Acebo C, Seifer R, Carskadon M. Assessment of a simulated driving task for sleep research. *Sleep* 2001; 24S:A413.

**374.R****THE FIS-10, A SHORT FORM OF THE FATIGUE IMPACT SCALE**

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**Introduction:** There is disagreement concerning the relationship between sleepiness and fatigue. Carskadon<sup>1</sup> pointed out that although these terms are often confused, a sleepy person will readily fall asleep while persons who are fatigued may not be sleepy even though they may be unable to function effectively because of their fatigue. In contrast to this view, others have implied that items that assess sleepiness should be incorporated into fatigue scales. Recently, Aaronson and her colleagues<sup>2</sup> noted that the measurement of fatigue remains a problem that needs to be addressed. We have attempted to

meet this need by developing and standardizing a short form of the Fatigue Impact Scale: The FIS-10.

**Methods:** First, we sought to gain an understanding of the components of fatigue. To do this, we identified five fatigue scales that had been published in peer-reviewed journals, i.e., the Fatigue Scale, the Fatigue Impact Scale, the Fatigue Severity Scale. All of these scales used a response format which assessed a range of degrees of fatigue to each item. Next, the 110 items that made-up these scales were entered into a larger questionnaire which was administered to approximately 1500 university students. Finally, we selected 150 male students and 150 female students who had responded to all of the questions for the analyses. These groups were matched for age and ethnicity. Finally, we computed intercorrelation matrices using the scores for each of the 110 fatigue items. These were analyzed using principal components analysis followed by varimax rotation with the following results.

**Results:** We found no difference between the factor structures of fatigue for men and women and discarded sex as a variable. We found no evidence that these items were organized into factors of fatigue as some have suggested, but rather, we observed that almost all of the 110 items loaded into a single primary factor. Next, to select the items for a fatigue scale, we identified the items in this factor with loadings  $\geq .650$  (15 items met this criterion). Finally, since 10 of these items were from the Fatigue Impact Scale, we decided to use only these items and thus, the FIS-10 is a short-form of the Fatigue Impact Scale. This 10-item scale is reliable ( $r = .88$ ) and highly correlated with the original 40-item version of the Fatigue Impact Scale ( $r = .96$ ).

**Table 1**

FIS-10 Items*
Because of my fatigue...
1. I feel that I cannot think clearly.
2. I find it hard to concentrate.
3. I have trouble maintaining physical effort for long periods.
4. My muscles feel much weaker than they should.
5. My physical discomfort is increased.
6. I require more frequent and longer periods of rest.
7. I have reduced my workload or responsibilities.
8. I am more irritable and more easily angered.
9. I am less able to deal with major emotional issues.
10. Minor difficulties seem like major difficulties.

\*Norms and scoring information will be sent on request.

**Conclusions:** See Results

**References:**

- (1) Carskadon MA (ed); Encyclopedia of sleep and dreaming. New York, Macmillan, 1993.
- (2) Aaronson LS, Teel CS, Cassmeyer V, Neuberger GB, Palikkathayil L, Pierce J, Press AN, Williams PD, Wingate A: Defining and measuring fatigue. *Image J Nurs Sch* 1999; 31: 45-50.

**Requests for information should be sent to Robert A. Hicks, Department of Psychology; San Jose State University; San Jose, CA 95192-0120. In part this research was**

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**375.R**

**COMPARING ESTIMATES OF ADOLESCENT SLEEP AND WAKE FROM TWO ACTIVITY MONITORING SYSTEMS**

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**Introduction:** The lure of obtaining estimates of behavioral sleep and wake outside of the laboratory has given rise to a variety of activity monitors (actigraphs) and associated software for estimating sleep and wake using activity patterns. Each system has its own strengths and weaknesses with respect to device reliability, recording modes, software, and documented measure validity. No single system, however, has been validated for all ages or types of patients, and reports comparing systems are rare (1). This analysis compared two actigraph systems that have fundamentally different recording methods and scoring algorithms: the Actiwatch-64 [Minimitter, Inc. (MM)] and the Basic mini-motionlogger [Ambulatory Monitoring, Inc. (AMI)]. We examined whether measures from the systems were comparable for adolescents.

**Methods:** Data for this analysis included 101,026 one-minute epochs of activity counts (4-7 nights and days per subject) from actigraphs worn on one wristband on the nondominant wrists of 7 healthy adolescents (3 girls; 12.3-14.9 y) during a forced desynchrony (FD) protocol (2). The FD protocol was chosen to provide data including higher than normal amounts of wake during 11.66-hour FD nights and brief nap opportunities during 16.33-hour FD days, thus enhancing our ability to assess differences between the 2 systems. Actigraph data were matched minute-by-minute. Inter-device reliability was assessed within each individual in two ways: (1) computing epoch scoring reliability [ $2 * \text{agreements} / (2 * \text{agreements} + \text{disagreements})$ ], and (2) computing kappa coefficients. Nights were also scored using standard lab procedures and an algorithm validated for adolescents (3) for AMI actigraphs with Action-W2 software, and using Minimitter algorithms (low sensitivity) and software for MM devices. Variables assessed from night scoring included Sleep Minutes, Wake Minutes, and Sleep Period (minutes between sleep onset and sleep offset).

**Results:** Epoch-by-epoch reliability when either system scored sleep was  $\geq .90$  across individuals during nights and  $< .39$  during days. Reliability of epochs when either system scored wake ranged from .36-.68 during nights and  $\geq .89$  during days. Kappa coefficients were generally quite low (range=.04-.65; Table 1). Summary sleep/wake variables for each system were averaged across available nights within participants (Table 2). Mean scores between systems were significantly different ( $p < .05$ ) for minutes of sleep, wake, and sleep period. Correlations of the summary scores for the two systems were low for sleep and wake minutes ( $< .54$ ) but .96 for

sleep period.

**Table 1**

Epoch-by-epoch reliability coefficients for sleep/wake scoring for nights and days for individual participants					
Participant		Inter-Rater Reliability			Kappa Coefficient
		Sleep	Wake	Sleep & Wake	
1	Nights	.97	.68	.97	.65
	Days	.39	.92	.92	.34
2	Nights	.96	.59	.96	.55
	Days	.05	.95	.95	.04
3	Nights	.90	.49	.91	.42
	Days	.06	.91	.92	.05
4	Nights	.95	.58	.95	.54
	Days	.07	.91	.91	.06
5	Nights	.94	.50	.94	.44
	Days	.23	.92	.93	.20
6	Nights	.92	.52	.86	.44
	Days	.05	.89	.89	.04
7	Nights	.94	.36	.94	.31
	Days	.11	.89	.80	.09

**Table 2**

Means (standard deviations) for scored sleep parameters in individual participants						
Participant	Total Sleep Minutes		Total Wake Minutes		Sleep Period	
	AMI	MM	AMI	MM	AMI	AMI
1	514.8 (12.6)	522.8 (5.3)	30.8 (12.5)	28.5 (5.8)	545.5 (4.6)	551.3 (4.6)
2	510.8 (46.0)	514.8 (20.2)	36.0 (46.0)	35.2 (20.4)	546.8 (5.8)	550.0 (6.5)
3	438.0 (83.6)	514.8 (14.6)	104.5 (88.0)	36.25 (17.8)	542.5 (8.3)	551.0 (4.3)
4	482.0 (24.7)	517.0 (15.7)	62.0 (17.8)	30.3 (10.0)	544.0 (8.6)	547.3 (8.1)
5	484.9 (36.9)	505.0 (30.2)	42.3 (13.6)	28.6 (8.8)	527.1 (38.2)	533.6 (30.5)
6	469.3 (81.5)	495.6 (27.7)	74.9 (87.1)	52.9 (30.2)	544.1 (18.5)	548.4 (19.3)
7	511.0 (40.1)	517.7 (17.6)	31.2 (28.8)	28.2 (8.5)	542.2 (12.7)	545.8 (11.4)

AMI = Ambulatory Monitoring; MM = Minimitter

**Conclusions:** These data indicate that the two systems do not yield equivalent sleep/wake measures for adolescents. Thus, the systems cannot be used interchangeably within studies, and caution is required when comparing across studies that use different systems. We plan to examine whether one system more accurately follows scores from polysomnographic records for these participants.

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- (1) Sadeh A, Acebo C: The role of actigraphy in sleep medicine. *Sleep Medicine Reviews*, in press.
- (2) Carskadon MA, Acebo C, Labyak SE, Seifer R: Intrinsic circadian period of adolescent humans measured in conditions of forced desynchrony. *Neuroscience Letters* 1999; 260: 129-132.

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**376.R**

**ENHANCEMENT OF ACTIGRAPHIC ASSESSMENT FOR PERIODIC LIMB MOVEMENTS USING TOE ACTIVITY**

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**Introduction:** Actigraphy is often used to assess periodic limb movements (PLMs) outside the sleep lab setting. Activity monitors are traditionally placed on the ankle to measure activity associated with limb movement. In addition to leg and ankle movement, toe extensions have also been observed in PLMs (Nozawa, Wantanbe, et. al). Actigraphs, which are usually about the size of a wristwatch, are too large for placement on the big toe. Therefore, toe activity has not been fully assessed as a measure of PLM activity. The MicroPAM (IM Systems, Baltimore, MD), a dime-sized activity monitor, can be comfortably attached to a patient's big toe. This study evaluated the utility of measuring toe activity, as compared to ankle activity, for PLM assessment.

**Methods:** 12 PLM patients (each  $\geq 10$  PLMs/hr) and 6 controls were admitted for a standard overnight polysomnographic (PSG) evaluation; additionally, measurements were taken for posterior tibialis EMGs, and a MicroPAM monitor was placed on each the ankle and big toe of one leg. PSG data was scored for PLM activity by a trained technician. PLMs per hour were compared to total activity for that period as measured by the MicroPAM units.

**Results:** Data from the ankle-worn MicroPAM were not significantly correlated with the PSG ( $r=0.11$ ,  $p > 0.05$ ). Comparison of activity data from the toe-worn MicroPAM to the PSG data yielded a higher level of agreement ( $r=0.64$ ,  $p < 0.05$ ). Combination of both toe and ankle data did not improve upon use of toe data only ( $r=0.63$ ,  $p < 0.05$ ).

**Conclusions:** The results of the current study indicate recording activity from the big toe, rather than the ankle, might improve PLM assessment. The pilot data here makes a strong case for further exploration of this new methodology. Further work should include point-by-point comparisons of activity and tibialis data to determine if individual events can be detected by this method.

**References:**

- (1) Nozawa, T: Periodic limb movement disorder. *Nippon Rinsho* 1998 Feb; 56(2):389-95
- (2) Wantabe S, Ono A, Naito H: Periodic leg movements during either epidural or spinal anesthesia in an elderly man without sleep-related (nocturnal myoclonus). *Sleep* 1990 Jun; 13(3):262-66

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**377.R****PILOT EVALUATION OF AN AMBULATORY AIRFLOW PRESSURE MONITOR FOR IMMEDIATE IDENTIFICATION OF SLEEP DISORDERED BREATHING EVENTS**Spiro JR,<sup>1</sup> Gorny SW,<sup>1</sup> Allen RP,<sup>1</sup> Krausman DT<sup>2</sup>

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**Introduction:** There are several systems available for at-home recording of Sleep Disordered Breathing Events (SDBEs). One type typically consists of a small tabletop recorder, with an array of tethered sensors, from which data must be downloaded to a computer for analysis. A second type is self-contained, disposable unit that provides an on-line indication of SDBE severity at the end of a sleep period, but can only be used for a single night. These are features not fully efficient for use in a clinical setting. A new version of the ApneaCheck (IM Systems, Baltimore, MD) was designed to quantify SDBEs for multiple nights, in real-time, with no off-line analysis required; a cumulative count of detected SDBEs is displayed on an LCD display. The current pilot study evaluated the efficacy and accuracy of this new ApneaCheck model.

**Methods:** 6 participants with a range of SDBE severity, were admitted for a standard, overnight, polysomnographic (PSG) evaluation. Participants were also outfitted with the ApneaCheck monitor, which is comprised of a small, self-contained recording unit that is clipped to the wearer's shirt and attached to a disposable airflow pressure cannula. To facilitate comparison with standard PSG measure, the ApneaCheck monitor used in the current study was specially modified by the manufacturer to allow two channels of information to be sent from the monitor to the PSG: the air pressure signal and a marker (a pen deflection on the PSG tracing when the ApneaCheck's algorithm detected a SDBE). The PSG data was scored by a trained technician for the identification of SDBEs, defined as a reduction of 50% or greater in air pressure, lasting for a minimum of 10 seconds. A point-by-point comparison of the PSG and ApneaCheck estimations of SDBEs was conducted. Each participant then wore the device at home for two consecutive nights to evaluate comfort and ease of self application.

**Results:** Point-by-point comparison of the PSG and ApneaCheck data indicated a high level of agreement. Of the 315 apnea events identified from the PSG data across all patients, the ApneaCheck yielded an 82.3% sensitivity and 89.9% specificity. Further analysis indicated that discrepancies between the two measures typically occurred when a potential SDBE had borderline characteristics for acceptance/rejection as a candidate event, either in terms of duration percentage or airflow pressure decrease. In the at-home trials, all subjects reported that the ApneaCheck monitor was easy to use and caused no significant sleep disturbance. The observation of expected data for all subjects during the at-home trials indicated that the monitors were properly self-applied.

**Conclusions:** The results of this pilot study indicate that the latest version of the ApneaCheck device provides a new and

unique means of identifying and recording SDBEs without the use of traditional, multi-channel PSG recording. A larger scale study is now necessary to assess the technology more fully and to suggest possible enhancements to the overall accuracy of the system. The stand-alone, non-downloadable design of the system represents a significant technological advance in the development of ambulatory devices for measurement of SDBEs.

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**378.S****USE OF AN OBJECTIVE STANDARDIZED CLINICAL EXAMINATION (OSCE) IN SLEEP MEDICINE TRAINING**Ware J,<sup>1</sup> Vorona RD,<sup>1</sup> Matson CC,<sup>1</sup> Ullian JA,<sup>1</sup> Winn MP<sup>1</sup>

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**Introduction:** We used an Objective Standardized Clinical Examination (OSCE) case to investigate whether a lecture to third year medicine clerks could improve students' physical exams when obstructive sleep apnea syndrome (OSAS) was suspected. For the case, a standardized patient presents with morning headaches, and reveals on careful history symptoms of OSAS. Students have 20 minutes for a history and focused physical examination (PE). For the class graduating in 2001, most students correctly diagnosed the patient. However, the focused PE often did not match their diagnosis, lacking inspection of the oral cavity and nose despite a diagnosis of OSAS. Therefore, we studied whether a lecture to third year students on the PE of suspected OSAS patients would improve subsequent performance.

**Methods:** One of the authors [RV] provided 45-minute lecture on the PE for apnea to 41 students taking Internal Medicine clerkships in the last half of their third year. Those taking the clerkship in the first half did not receive the lecture, and served as the control group. The lecture covered the definition and epidemiology of OSAS, pertinent physical findings including vital signs (specifically blood pressure), and body habitus. It stressed the importance of the examination of the nose, oropharynx and facial features, including the modified Mallampati classification of oropharyngeal anatomy as well as dental and jaw findings. Discussion of cardiopulmonary stigmata of pulmonary hypertension and the overlap syndrome followed, as did ocular findings such as floppy eyelid syndrome, endocrine abnormalities including acromegaly and hypothyroidism, findings of end-stage renal disease, and Marfan's syndrome. At the beginning of their fourth year, 100 students completed a nine-station OSCE. Student scores for the OSA case were based on a 78-item checklist (including PE items) completed by the standardized patient and ten multiple-choice questions answered by the student. Those who administered and scored the OSCE were blind to which students had received the lecture.

**Results:** We examined the PE scores on the eight non-apnea cases and the OSAS case. Because of skewed PE data, we used a log transformation. The mean score for the lecture and control groups on the non-OSA cases was 1.79 (t = 0.286; p = 0.78, ns). For the OSA case, the mean score for the lecture

group was 1.45 versus 1.37 for the control group ( $t = 1.97$ ;  $p = 0.051$ ).

**Conclusions:** The development and use of an OSCE OSAS case 1) resulted in an additional sleep medicine teaching opportunity, 2) revealed a deficiency in the PE performance, and 3) gave us information on the effectiveness of a lecture addressing that deficiency. Although the probability that this one lecture would affect OSCE performance several months later may be unlikely, we believe that students' poor performance on the previous year's OSCE increased the likelihood for improvement. However, coordination with sleep medicine and ward attendings for subsequent demonstration of PE techniques with patients is probably necessary for long-term improvement in students' performance.

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### 379.S

#### SLEEP APNEA, INSOMNIA AND DEPRESSION IN THE PRIMARY CARE SETTING

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**Introduction:** Sleep disorders are routinely under-diagnosed by primary care physicians. Education sessions aimed at these physicians are attempting to improve this problem but small-town primary care physicians are often not able to attend sessions, which are held in large urban centres. The aim of this pilot study was to examine if sleep disorders constitute an important part of small-town primary practice by investigating what proportion of small-town primary care patients screen positive for sleep apnea, insomnia and depression.

**Methods:** Waiting room patients for five primary care physicians in two small towns (Beamsville and Fort Erie) in Southern Ontario, Canada, were administered questionnaires to screen for sleep apnea (the Berlin Questionnaire), insomnia (the Athens Insomnia Scale) and depression (the CES-D scale). Physicians were contacted in advance and permission to approach their patients was obtained. The patients were asked to complete the questionnaire battery before going in to see their physician. The outcome variables were the scores on the three questionnaires.

**Results:** In total, 141 patients across the five practices agreed to be interviewed. Of those patients, 33% screened positive for sleep apnea, 38% screened positive for insomnia and 28% screened positive for depression. On further analysis of the total population, 8% screened positive for both insomnia and sleep apnea, 1% for sleep apnea and depression, 14% for insomnia and depression and 6% screened positive for all three disorders. None of these patients were currently diagnosed with or were undergoing treatment for any of the three disorders. As one purpose of this exercise was to help inform physicians an outline of our findings in these patients was given to their physician.

**Conclusions:** A very high proportion of small-town primary care patients screen positive for sleep apnea, insomnia and depression, as assessed by self-report questionnaires. The percentages are well above the population norms. This study sup-

ports earlier findings that patients with sleep disorders are not diagnosed as such and emphasizes that a substantial number of small-town primary care patients may have undetected sleep apnea, insomnia and depression. The high frequency of depression could be in part secondary to the untreated sleep apnea and insomnia. The reason for the failed diagnosis of the sleep disorders cannot be attributed to an absence of facilities to which to refer patients since a sleep clinic is located in the immediate area. A likely reason for the inability of primary care physicians to identify these patients is a lack of knowledge about sleep disorders. The findings of this study support our previous findings of a lack of primary care physicians' knowledge about sleep apnea and underscore the need for making post-graduate education in sleep medicine available to primary care physicians in non-urban areas.

### 380.U

#### WORK SCHEDULES, STRESSFUL LIFE EVENTS, AND SLEEP QUALITY IN WOMEN

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**Introduction:** Over 25% of the US workforce is engaged in some form of shift work; nearly half are women. Monk<sup>1</sup> has suggested that the quality of sleep for women shift workers may be of special concern because of life stress. The major questions addressed in this study were: (1) Are women whose work schedules involve day shifts only significantly different regarding life stress and sleep quality from women whose work schedules involve other shifts? (2) Is life stress related to sleep quality? (3) Are background characteristics (age, hormone replacement therapy, and employment in a health-care profession) related to reports of stressful life events or sleep quality?

**Methods:** The subjects for this project were 476 employed women aged 18-74 years old ( $M=43.3$ ,  $SD=10.6$ ). Other sample characteristics are shown on Table 1. Sixty-four percent ( $n=303$ ) of subjects worked day shifts only. Those who worked days only were compared with all other shifts combined. Table 2 shows the frequency with which other shifts or combinations of shifts were worked. Life stress was measured by the Holms and Raye Life Events Checklist (LEC)<sup>2</sup> using unit scoring. Sleep quality was measured by the Global Score on the Pittsburgh Sleep Quality Index (PSQI)<sup>3</sup>. Non-parametric statistics were used whenever variables were not normally distributed in the population. Alpha was set at .05.

**Results:** The number of stressful life events ranged from 0-14 ( $M=2.3$ ,  $SD=2.3$ ). The median was 2.0; the mode was 1.0. The Global PSQI Score ranged from 0-16 ( $M=6.1$ ,  $SD=3.1$ ). For the total sample poor sleep quality was related to the number of stressful life events, Kendall's  $\tau_b = .14$ ,  $p = .000$  but unrelated to age. Work schedules were not related to the number of reported stressful life events, but dayshift-only workers had better sleep quality ( $M=5.9$ ,  $SD=3.0$ ) than those with other work schedules ( $M=6.5$ ,  $SD=3.4$ ),  $t(428) = 1.76$ ,  $p = .039$ . Older subjects reported fewer stressful life events than younger subjects, Kendall's  $\tau_b = .10$ ,  $p = .007$ . Neither hormone replacement therapy nor employment in a health-care

profession was related to life stress or sleep quality.

**Table 1**

**Sample Characteristics**

Demographic Characteristics	Frequency	Percent
<b>Race</b>		
Caucasian	386	81.1
African-American	31	6.5
Others	19	4.0
Missing data	40	8.4
<b>Employment in a health-care profession</b>		
Yes	235	49.4
No	225	47.3
Missing data	16	3.4
<b>Working hour/week</b>		
< 40 hrs	135	28.4
≥ 40 hrs	327	68.7
Missing data	14	2.9
<b>Hormone replacement therapy</b>		
Yes	85	17.9
No	391	82.1

**Table 2**

**Frequency and Percentage of Work Schedules**

Work Schedules	Frequency	Percent
1. Day shift only	303	63.7
2. Shift worker		
2.1 Afternoon	20	4.2
2.2 Night	23	4.8
2.3 Day and afternoon	89	18.7
2.4 Day and night	18	3.8
2.5 Afternoon and night	5	1.1
2.6 All rotating shifts	13	2.7
3. Missing data	5	1.1
<b>Totals:</b>	<b>476</b>	<b>100.0</b>

**Conclusions:** The results of this study of women shift workers support previous research findings that shift workers have lower sleep quality than day workers. Although this sample of women workers had relatively poor sleep quality and stressful life events were correlated with poor sleep quality, the differences in sleep quality in women shift workers was not accounted for by differences in stressful life events or other background variables explored in this study. We recommend further studies of women shift-workers that include other explanatory variables.

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**381.U**

**WOMEN'S SLEEP HYGIENE KNOWLEDGE, SLEEP HYGIENE PRACTICES, AND SLEEP QUALITY**

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**Introduction:** Few studies have been published that focus on sleep hygiene knowledge and sleep hygiene practices in the general population. However, there is some evidence that general population women may have less knowledge of sleep promotion practices and use them less than women diagnosed with insomnia<sup>1</sup>. Thus, having diagnosed insomnia may lead to learning about and using sleep hygiene practices. Does the same pattern hold in the general population? Do women with lower sleep quality know more about sleep hygiene and use more sleep hygiene practices?

**Methods:** Subjects (N=591) were women aged 18 to 90 years (M=46, SD=14) who responded to public notices inviting them to participate in a survey focused on many aspects of sleep. Subjects were predominantly Caucasian (81%, n=478) and employed (80%, n=476). Approximately 40 percent (n=236) were employed as healthcare professionals (nurses, physicians, psychologists, and social workers). Seventeen percent (n=103) indicated they were on hormone replacement therapy (HRT). Sleep hygiene knowledge and sleep hygiene practices were measured by the Lacks Sleep Hygiene Awareness and Practice Scale<sup>2</sup>. The global score on the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality<sup>3</sup>.

**Results:** Descriptive statistics for sleep hygiene knowledge (SHK), sleep hygiene practices (SHP), and sleep quality are shown on Table 1. SHK was positively correlated with use of SHP (r = .22, p=.000), but was uncorrelated with sleep quality. SHP was highly correlated with PSQI scores (r = -.51, p=.000). Age was negatively correlated with SHK (r = -.19, p=.000), positively correlated with SHP (r=.28, p=.000), but uncorrelated with sleep quality. Women employed in a health care profession reported more SHK (M=9.0, SD=2.6) than other subjects (M=7.9, SD=3.27), t(450) = -4.15, p=.000. They also reported more SHP (M=112.7, SD=9.14) than those employed outside the healthcare professions (M=110.3, SD=10.33), t(387) = -2.39, p=.017. Women on HRT were not different from others regarding SHK, but did report more SHP (M=114.9, SD=7.74) than other women (M=111.1, SD=10.00), t(160) = -3.97, p=.000.

**Table 1**

**Descriptive Statistics for Sleep Hygiene Knowledge, Sleep Hygiene Practices, and Sleep Quality**

Variable	Min	Max	Mean	Median	Mode	SD
1. SHK	0	13	8.2	9.0	9.0	3.2
2. SHP	73	133	111.8	113.0	112.0	9.7
3. PSQI	0	16	6.1	6	6	3.1

**Conclusions:** Unlike comparisons between insomniacs and normal controls—where insomniacs report more knowledge and sometimes more adoption of practices than controls—in this sample of women from the general population, there was no evidence that poorer sleep quality led to learning more about sleep hygiene or using more sleep hygiene practices. Rather, knowledge was not related to sleep quality and more use of sleep hygiene practices was associated with higher rather than lower sleep quality. Women’s adoption of good sleep hygiene practices and avoidance of poor ones was only partially accounted for by accurate knowledge of the effects of practices on sleep. Additional research is needed to identify factors affecting adoption of positive sleep hygiene practices.

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**Research supported by Funding from Summer Grants from the Center for Health Research at Wayne State University College of Nursing.**

**382.U**

**SLEEP, EXERCISE, AND WORK-RELATED CORRELATES OF CHRONIC FATIGUE IN CRITICAL CARE NURSES**

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**Introduction:** The national sleep debt in the U.S. population is growing, particularly in shiftworkers, with dangerous consequences in terms of fatigue (Bonnet & Arand, 1995). Little is known about the relationships between sleep, fatigue, health promoting behaviors, and work-related issues among nurses. The purpose of this study was to explore the relationships among sleep quality, chronic shiftworker fatigue, exercise habits, job satisfaction, mental workload, and emotional stress in a representative sample of critical care nurses.

**Methods:** The random, nationwide sample included 142 female registered nurses who were full-time providers (8, 10, or 12 hour shifts) of direct patient care in critical care units (M age = 45 years; SD = 8.31). Of this sample, 67 nurses worked permanent day shifts without night rotation, and 75 worked permanent night shifts. Participants completed the Pittsburgh Sleep Quality Index (PSQI), the Standard Shiftwork Index Chronic Fatigue and General Job Satisfaction Scales, one-item ratings of mental workload and emotional stress at work, and indicated the number of days per week that they engaged in exercise and napping behavior.

**Results:** Means, standard deviations, and Pearson’s correla-

tions for the major study variables are shown on the table. Sixty-eight percent of the participants (n = 96) were poor sleepers (Global PSQI > 5) (Buysse et al., 1989). Global PSQI and sleep quality were moderately and positively correlated with chronic fatigue. Exercise had a small, negative relationship with sleep quality, disturbance, daytime dysfunction, and napping behavior. Lower job satisfaction was associated with lower sleep efficiency and more sleep disturbance. Napping had a moderate, positive relationship with chronic fatigue and a small, negative relationship with exercise. PSQI sleep duration, latency, and the use of sleep medication were not significantly correlated with chronic fatigue, exercise, or job satisfaction. Additional findings indicated that poor sleep quality was positively correlated with perceptions of increased mental workload (r = .20; p < .05) and emotional stress at work (r = .20; p < .05).

**Table 1**

Descriptive Statistics and Correlations between Sleep, Chronic Fatigue, Exercise, and Job Satisfaction

Sleep Quality Dimensions (PSQI)	Chronic Shiftworker Fatigue	Exercise (days/week) (0-7)	General Job Satisfaction
Nap item+ M 1.1+ .77	M 26.7+9.2	M 2.4+2.1	M 22.5+5.8
Sleep Quality	.50**	-.19*	-.14
Sleep Efficiency	.20*	-.07	-.17*
Daytime Dysfunction	.64**	-.21*	-.15
Sleep Disturbance	.47**	-.22*	-.24**
Global Disturbance	.49**	-.16	-.10
Naps (0 - >3 days/week)	.33**	-.19*	-.14

\*p<.05; \*\*p<.001; +number of days per week when naps are taken

**Conclusions:** Poor sleep quality is common in critical care nurses and is impacted by chronic fatigue, exercise, mental workload, and stress. Decreased job satisfaction is associated with increased sleep disturbance and lower sleep efficiency. Future studies should examine the critical care work environment and job satisfaction, and test interventions to improve the sleep quality of critical care nurses and encourage increased exercise.

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383.U

MIDDLE SCHOOL SLEEP-SMART PROGRAM: A PILOT EVALUATION

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**Introduction:** School-based health education is considered a critical step in helping adolescents develop lifelong healthy behaviors. One health behavior, sleep, has received little attention from health educators, despite the knowledge that sleep plays a critical role in daytime functioning (1). The aim of this study is to examine the effectiveness of a prevention program to teach young adolescents healthy sleep habits.

**Methods:** Participants were 27 seventh graders (M = 12.85 yr) recruited from health classes at a middle school in a New England city. One class was recruited for the 7-week Adolescent Sleep-Smart Program (prevention, N = 11) that met 1/week as a part of the students' health class. A similar health class was recruited to participate in a study of middle schoolers' sleep patterns (control, N = 16). The 2 groups had no contact with each other as they were in different randomly assigned 7th grade clusters in their school. 75% of the participants were from a minority background, and 35% came from families with incomes below \$30,000. Students completed an 8-day daily sleep diary at baseline (Time 1) and 7 weeks later, after the prevention group completed the program (Time 2). The cognitive-behavioral oriented program was lead by a clinical psychologist and 2 assistants. We compared the two groups on 5 sleep variables (averaged over school/weekend nights): bedtime (BT), rise time (RT), total sleep time (TST), delay (weekend - school BT), oversleep (weekend - school TST), and daytime sleepiness both pre and post-intervention. Difference scores were calculated to assess change from Time 1 to Time 2 for both groups.

**Results:** At Time 1 there were no significant differences in diary reported school or weekend-night sleep habits between the prevention and control groups (Table 1). Overall, 7th graders were obtaining an inadequate amount of sleep. Average school-night sleep habits for both groups at Time 1 were: TST = 475 min., BT = 22:10, and RT = 6:04. Following the Sleep-Smart Program (Time 2), there were no significant differences between the groups on school-night sleep habits; however, the prevention group reported earlier weekend bedtimes and rise times, and shorter weekend delays than the control group (p's < .05). Sleep-smart students also reported less daytime sleepiness on weekends (p = .016). Also, on average, individual sleep-smart group students improved their sleep habits more than the control group over the 7 weeks. They increased their school-night TST, advanced their weekend night bedtime, and reported less weekend daytime sleepiness

(p's < .05) in comparison to the control group.

Table 1

	Group	TIME 1		TIME 2		TIME 1-2 DIFF	
		M	SD	M	SD	M	SD
Sc TST	Prev	471	34	501	48	30*	38
	Cont	478	64	499	34	4	26
Sc BT	Prev	22:02	1:08	21:38	1:00	-25	:50
	Cont	22:17	:59	22:00	:50	-10	:32
Sc RT	Prev	5:57	:22	6:04	:32	:07	:27
	Cont	6:11	:37	6:20	:42	:00	:34
Wk TST	Prev	499	66	511	52	.44	.44
	Cont	539	100	556	87	-10	.42
Wk BT	Prev	22:37	1:15	21:49*	1:17	-53**	1:17
	Cont	22:54	1:40	22:53	1:13	:20	:44
Wk RT	Prev	7:20	1:39	6:49	1:33	-43	:54
	Cont	8:13	1:42	8:05	1:46	-10	1:14

\*p < .05

\*\*p < .01

**Conclusions:** The Adolescent Sleep-Smart Program aimed to improve sleep habits and, specifically, to increase total sleep and obtain greater sleep schedule regularity between school/weekend-nights. Trends seen in the prevention group reflect a positive effect of this pilot program on sleep patterns, particularly on weekends. Across time, sleep-smart 7th graders reported increased school-night total sleep, earlier weekend bedtimes, greater school-weekend night bedtime regularity, and decreased weekend daytime sleepiness.

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384.U

THE ROLE OF SLEEP SPINDLES IN SIMPLE MOTOR PROCEDURAL LEARNING

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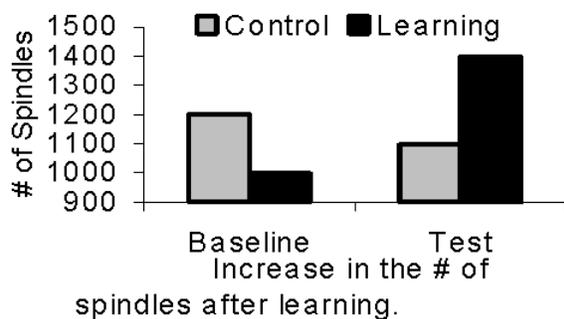
**Introduction:** The present study investigated the effect of new simple motor procedural learning on Stage 2 sleep EEG. It has been recently discovered that deficits in simple motor procedural memory but not more cognitively complex motor procedural memory occur after Stage 2 sleep deprivation (1, 2). A related line of research has found that the native number of spindles is related to overall intelligence and Performance IQ, but not Verbal IQ (3).

**Methods:** All participant's (N=8) IQ scores were collected, followed by three consecutive nights in the sleep lab including acclimatization, baseline and test nights. The experimental group (N=6) was exposed to two hours of simple motor procedural learning immediately before sleep on their final night in the lab. Two of the memory tasks involved learning fine motor movements and dexterity (simple tracing task and the operation game) and two required more gross motor coordination (the pursuit rotor and the ball and cup game). These par-

Participants were retested one week later to assess any improvements in task performance.

**Results:** A 42% increase in the number of sleep spindles was observed (Fig. 1) after simple motor procedural learning ( $F=8.22$ ,  $p<.05$ ). There was no corresponding increase in Stage 2 sleep following learning, or any other stages of sleep. The native number of spindles was found to be positively correlated with Performance IQ ( $r=.72$ ,  $p<.05$ ) but not Verbal IQ or Full Scale IQ. The spatial subscale of Performance IQ was found to be positively correlated with baseline spindle density ( $r=.78$ ,  $p<.05$ ). None of the Verbal IQ subscales were related to spindles. It was also found that Performance IQ was positively correlated with the increase in Sigma power from the baseline to the test night ( $r=.88$ ,  $p<.05$ ).

Figure 1



**Conclusions:** The results indicate that one of the roles of sleep spindles is the consolidation of simple motor procedural memory. Spindles originate from the oscillatory firing of thalamocortical loops throughout the cortex. The findings implicate thalamocortical loops in the consolidation of simple motor procedural memory. The IQ data suggest that spindles may serve as a biological marker for Performance IQ, and that this relationship may involve spatial abilities. Furthermore, knowing an individual's Performance IQ can be predictive of the magnitude of the increase in spindle activity after motor learning.

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**385.U**

**THE TIMING OF ANAESTHETIC INCIDENTS: EXAMINATION OF TIME-OF-DAY EFFECTS**

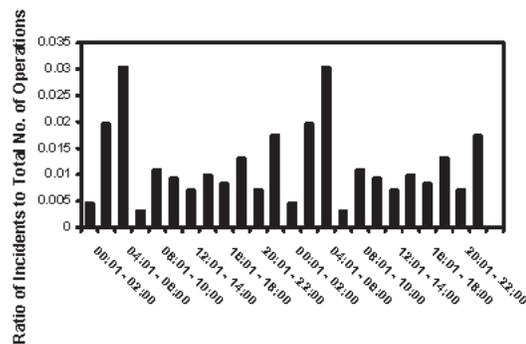
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**Introduction:** Circadian patterns in relative road traffic accident rates mirror the changing levels in sleep propensity across the 24-h day [1]. Similar time-of-day effects have been found in association with "real job" performance across continuous shift systems in different occupational settings [2], such that worst performance was evident during the night with a secondary, minor decline around 1400 h. This study examines whether comparable circadian patterns are evident in the rate of reported anaesthesia incidents.

**Methods:** The Australasian Incident Monitoring Study (AIMS) is an anonymous and voluntary incident reporting system that is used by anaesthetists in various Australian and New Zealand hospitals. Anaesthetists are asked to complete a report form whenever an event resulted in, or may have resulted in, harm to anyone, or which could result in a complaint. Data associated with 389 incidents collected in a large New Zealand hospital across 2.5 years were analysed. To examine when incidents occurred during the 24-h day, the frequency of incidents relative to the total number of theatre cases (i.e. all medical and surgical procedures undertaken in operating theatres) were calculated in two hour blocks.

Figure 1



**Results:** The 389 reported incidents represented approximately 1% of all theatre cases occurring during the period of data collection ( $N = 35,157$ ). Figure 1 presents the circadian pattern in the timing of reported incidents. The relative frequency of reported incidents was highest between 0200 - 0600 h. A second block of relatively high numbers of incidents occurred between 2201 - 2400 h, a time when trainee anaesthetists were completing a 14 h day shift or commencing a night shift.

**Conclusions:** The increased rate of reported incidents which occurred between 0200 - 0600 h identifies this time as an "at risk" period for anaesthesia-related incidents and parallels findings of other studies examining workplace performance across the 24 h day. Although only trainee anaesthetists

worked rostered night shifts, while specialists were on call, both groups reported similar numbers of incidents overall. Thus, the increased rates of incidents occurring during the night are not due to trainees being more frequent incident reporters. While under-reporting of medical errors is expected [3], the temporal pattern of under-reporting is unknown, and the obvious time-of-day effects found are perhaps surprising given that during the night, sleepy anaesthetists could reasonably be expected to be less inclined to complete incident forms.

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**386.U**

**ESTIMATING THE CONTRIBUTION OF FATIGUE TO REPORTED ANAESTHESIA INCIDENTS**

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**Introduction:** The Australasian Incident Monitoring Study (AIMS) is an anonymous, voluntary incident reporting system used by anaesthetists in various Australian and New Zealand hospitals. Recent analysis of 5,600 AIMS forms found that fatigue was identified as a contributing factor by the reporting anaesthetist in only 2.7% of cases [1]. This estimate differs widely from findings in a national survey of New Zealand anaesthetists, when 32% of respondents reported making a fatigue-related error in the previous 6 months [2]. Based on methodology developed in an aircraft accident investigation [3], this study trialled a more objective means of assessing the likely contribution of fatigue to anaesthesia incidences reported in the AIMS system.

**Methods:** Supplementary questions related to circadian phase, and sleep and duty times at the time of the incident were added to AIMS forms used in a New Zealand hospital. Rates of self-reported fatigue-related incidents were calculated in relation to other incidents across ranges of sleep loss, prior time awake, and time-on-duty to investigate cut-off points when risk increased for these factors. A "fatigue risk grid" was developed which allowed incidents to be systematically ranked according to their likely association with fatigue.

**Results:** Across 2.5 years, 3% of the total number of incidents (12/389) were reported as fatigue-related. Fatigue-related incidents were 7.4 times more likely to be reported by an anaesthetist two or more hours in sleep debt (O.R. = 7.39, 95% C.I.

= 2.07 - 26.33), and 6.5 times more likely to be reported by an anaesthetist working for 10 hours or more (O.R. = 6.52, 95% C.I. = 1.87 - 22.73). Among incidents where fatigue was not reported as a contributing factor, no other contributing factors displayed a similar "fatigue pattern". The fatigue risk factors of 10+ h at work, 2+ h of sleep loss and time of day between 0200 - 0600 h were used to construct the "fatigue risk grid" (Table 1). All reported incidents providing complete risk factor data sets (N = 251) were ranked according to their levels of risk. Using this process, 205 incidents (85%) were unlikely to be fatigue-related (levels 1 - 3). Eleven (5%) were moderately likely to be fatigue-related (levels 4 and 5), and 24 (10%) were highly likely to be fatigue-related.

**Table 1**

**Number of incidents associated with combinations of time-of-day, sleep and duty time categories ranked according to expected fatigue-related performance effects.**

Level of risk of fatigue effects	Risk Categories			No. of reported incidents (N = 240)
	10+ h at work	2+ h sleep loss	Time of day 0200 – 0600	
(Low) 1				167
2	✓			1
3		✓		37
(Moderate) 4			✓	1
5	✓	✓		10
(High) 6	✓		✓	21
7		✓	✓	3
(Very High) 8	✓	✓	✓	0

**Conclusions:** The 10% rate of highly likely fatigue-related incidents plus the 5% of moderately likely fatigue-related incidents is considerably greater than the 3% rate based on self-assessment. While not all of the "at risk" incidents would be fatigue-related, a more accurate assessment of the "true" rate of fatigue-related incidents amongst this group of incident reports is likely to lie somewhere between the 3% and 15%.

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387.U

**STRAIN DIFFERENCES IN SLEEP, LOCOMOTOR ACTIVITY AND BEHAVIORAL TESTS IN INBRED MICE**

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**Introduction:** Strain differences exist among inbred mice in total sleep, sleep diurnal ratio, locomotor activity and behavioral responses to environmental stimuli (1,2,3). Sleep and activity, as well as emotional reactivity, may be correlated within a given strain. More active animals could have less sleep, and the level of activity could influence the outcome of behavioral tests, which often rely on some measure of motor performance. This raises the possibility that examining the interrelationship among sleep, activity and emotional behavior could provide a clearer picture of phenotypic variation in sleep, than would reliance on sleep recordings alone.

**Methods:** Three inbred strains of mice (C57BL/6J (B6), BALB/cJ (C) and DBA/2J (D2)) were studied. Home cage activity was determined by photobeam interruption over three consecutive days. The mice were then assessed in behavioral tests (open field, emergence, elevated zero maze) relevant for anxiety. Afterwards, the mice were implanted with transmitters (DataSciences ETA10-F20) for recording sleep via telemetry. Behavioral state (wakefulness, NREM and REM) was visually scored (10 sec epochs) based on EEG and activity.

**Results:** Table 1 presents sleep parameters and activity measures for all strains. B6 mice had the most sleep, D2 mice were intermediate and C mice displayed the least sleep. There were no differences in total REM. The diurnal ratio of total sleep (light/dark), was greatest in D2 mice, intermediate in B6 mice and least in the C mice. Home cage activity was greatest in the C mice, intermediate in the B6 mice and least in the D2 mice. Table 2 presents performance on three behavioral tests for all strains. In the open field, the B6 mice exhibited the least anxiety-like behavior, with no difference between the more reactive C and D2 strains. On the emergence and elevated zero maze tests, the D2 mice exhibited less anxiety-like behavior than did the C mice.

**Table 1**

Sleep and home cage activity in inbred strains over 72-hours of recording. Values are mean and SEM.

	B6 (n=25)	C (n=20)	D2 (n=16)
<b>Sleep Parameters</b>			
Total Sleep	687.2 ±10.2 a	631.0 ±11.6 b	642.8 ±13.4 ab
Sleep %	47.73 ±0.71 a	43.82 ±0.81 b	44.64 ±0.93 ab
Total NREM	623.3 ±9.91 a	570.1 ±11.22 b	577.1 ±12.0 b
Total REM	63.89 ±2.03	60.89 ±1.99	65.71 ±2.70
REM %	4.44 ±0.14	4.23 ±0.14	4.56 ±0.19
Diurnal Ratio	1.53 ±0.06 b	1.20 ±0.06 c	2.21 ±0.14 a
<b>Home Cage Activity</b>			
Ambulation	15486 ±1177 bc	24967 ±2055 a	13168 ±1163 c
H/Activity	3094 ±122 b	4371 ±197 a	2431 ±114 c
V/Activity	489 ±40 bc	1357 ±76 a	353 ±35 c

1) Different letters indicate significant differences within rows (p < .05).

2) H: Horizontal; V: Vertical.

**Table 2**

Performance in behavioral tests across inbred strains. Values are mean and SEM.

	B6 (n=25)	C (n=24)	D2 (n=28)
<b>Open Field Test</b>			
H/Activity	1828 ± 67 a	1405 ±46 b	1223 ±68 b
V/Activity	85.2 ±8.7 a	27.4 ±5.8 b	48.9 ±7.3 ab
T/Center	42.6 ±4.4 a	22.5 ±2.7 b	21.0 ±2.7 b
T/Margin	257.4 ±4.4 b	277.5 ±2.7 a	279 ±2.7 a
<b>Emergence Test</b>			
H/Activity	1606 ±52 a	838 ±125 b	1354 ±89 a
V/Activity	88.8 ±11.4 a	10.6 ±4.3 b	62.9 ±5.2 a
T/Center	76.8 ±5.8 a	51.6 ±8.3 b	44.8 ±5.4 ab
T/Margin	223.2 ±5.8 b	248.4 ±8.3 a	255 ±5.4 a
<b>Zero Maze Test</b>			
T/Open	35.8 ±3.8 a	9.9 ±3.4 b	18.8 ±3.2 b
N/Transition	11.1 ±2.1 a	2.1 ±0.8 b	6.0 ±1.4 ab
N/Head Dip	16.5 ±1.9 a	6.4 ±1.7 b	5.0 ±1.9 b
N/Stretch	3.4 ±0.6 b	7.1 ±1.0 a	0.9 ±0.3 b

1) Different letters indicate significant differences within rows (p < .05).

2) H: Horizontal, V: Vertical, T: Time Spent, N: Number.

**Conclusions:** Significant differences were observed among the inbred strains in sleep, home cage activity and performance on behavioral tests related to emotion. The C mice exhibited the greatest level of activity and showed the most behaviors indicative of anxiety and, at the same time, had the least total sleep. The D2 mice were the least active, had the most inactive/non-sleep time and were intermediate on tests of anxiety. The B6 mice had the least anxiety-like behavior and had intermediate levels of home cage activity and total sleep. These findings suggest that strain differences in EEG-defined sleep alone may not be sufficient to fully characterize differences in sleep phenotypes.

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388.U

**SLEEP ALTERATIONS AFTER DIFFERENT LEVELS OF CONDITIONED FEAR TRAINING**

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**Introduction:** In fear conditioning, associations formed over the course of 4 days of tone-shock pairings imbues the tone with ability to affect sleep in much the same manner as shock itself (1). However, the effects of fewer training trials on sleep are not known. Therefore, we evaluated the effects of single day training with either one or fifteen tone-shock pairings in BALB/cJ (C) mice, which are highly reactive in putative anx-

xiety provoking situations (1).

**Methods:** Sixteen C mice were intraperitoneally implanted with transmitters (DataSciences ETA10-F20) for sleep recording via telemetry. Behavioral state was visually scored based on EEG and activity. After baseline sleep recording sessions, the mice were trained to associate a cue (tone) with footshock. One group (n=8) received a single cue-shock pairing and the second group (n=8) received 15 cue-shock pairings on a single day. All training was conducted between 0800 to 0900 h. For testing, the mice were presented 15 cues alone in their home cage between 1045 and 1100 h on day 5, 12, 19, 26, 33, 40 (cue 1 to 6) following shock training. Sleep was recorded from 0900 (following shock) or 1100 (following cue) to 0700 in the next day.

**Results:** Single shock-training trials (SST) produced REM suppression in the 4 h immediately after training whereas following multiple (15) shock-training trials (MST) both total NREM and REM were decreased (Table 1). On the day following training, REM had returned to baseline levels in the SST mice, but was still suppressed in the MST mice. NREM was increased in SST mice and at baseline levels in MST mice. In MST mice, cue presentations continued to produce significant suppressions of REM for up to 26 days after training, whereas in SST mice, presentations of the cue did not significantly alter REM (Figure 1). Cue presentation did not significantly alter NREM in either MST or SST mice.

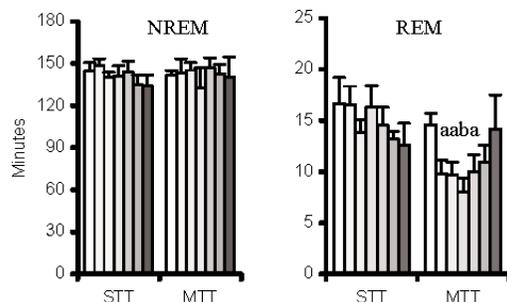
**Table 1**

Total NREM and REM (min) during 4 h following SST, MST and circadian matched h on baseline and post-training day.

	Baseline		Training		Post Training	
	M	SEM	M	SEM	M	SEM
<b>SST</b>						
NREM	145.3	±6.7	126.0	±12.4	159.4	±4.6 *
REM	13.8	±2.0	7.9	±1.4 *	15.2	±0.9
<b>MST</b>						
NREM	132.8	±6.3	70.9	±12.1 **	130.4	±10.8
REM	12.6	±1.5	4.5	±1.2 ***	8.1	±1.2 *

\* P < .05, \*\* P < .01, \*\*\* P < .001, compared to baseline.

**Figure 1**



Total NREM and REM during 4 h following cue presentation in SST and MST mice. The bars (means ± SEM) from left to right are baseline (blank) and cue 1 - cue 6. a, p < .05; b, p < .01 compared to baseline.

**Conclusions:** These data demonstrate that a single shock can alter sleep in reactive mice, and that the impact of shock on REM is greater and longer lasting suppression after MST. The relative absence of effects on sleep with repeated presentations of cues after SST compared to after MST demonstrate that the alterations in sleep are produced by the psychological value of the tones as reminders of the shock, and not by the sound alone. Differences in sleep after SST and MST suggest that it may be possible to examine graded sleep responses to different levels of foot shock stress and shock-associated cues.

**References:**

(1) Sanford LD, Tang X, Ross RJ, Morrison AR. Influence of anticipatory anxiety on sleep in “anxious” and “non-anxious” mice. Sleep 2001; 24: 53.

Research supported by NIH grant MH61716.

**389.U**

**STRAIN DIFFERENCES IN SLEEP ARCHITECTURE OF MICE AFTER REPEATED PRESENTATIONS OF FEAR CONDITIONED CUES**

Liu X,<sup>1</sup> Tang X,<sup>1</sup> Sanford LD<sup>1</sup>

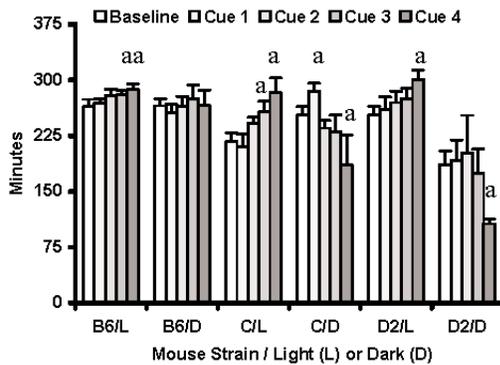
(1) Sleep Research Laboratory, Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA.,

**Introduction:** Shock training and the presentation of auditory cues associated with shock produce alterations in sleep that can be long-lasting and can vary with mouse strain (1). Effects on sleep, particularly reduced REM, could last for up to six hours in mice that were more reactive on behavioral tests of anxiety (BALBc/J (C) and DBA/2J (D2)). Reductions in REM were of shorter duration in less reactive mice (C57BL/6J (B6)). This raised the question of whether mice strains would differentially respond to repeated presentations of “reminders” associated with shock.

**Methods:** Three inbred strains (B6, n=10; C, n=10; D2, n=8) were used in this study. The mice were intraperitoneally implanted with transmitters (DataSciences ETA10-F20) for recording sleep via telemetry. Behavioral state was visually scored based on EEG and activity. After baseline sleep recording sessions, the mice were trained to associate a cue (tone) with footshock (15 tone - shock pairing on 4 consecutive days, conducted between 0800 - 0900 h). The mice were presented with the cue alone in their home cage between 1045 to 1100 h on day 5, 12, 19 and 26 (cue 1 to 4) after the last shock-training day. Sleep was recorded from 1100 following cue presentation to 0700 in the next day.

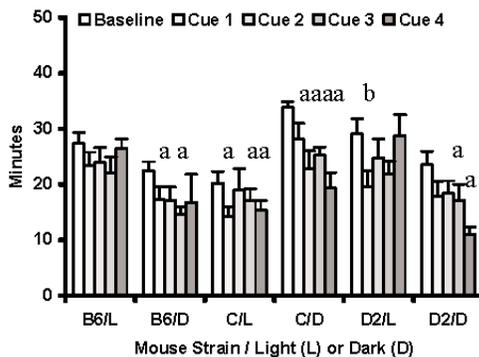
**Results:** All mice showed an increase in total NREM during the light period, especially on later cue presentation days (Figure 1). During the dark period total NREM was decreased in C and D2 mice, whereas there was no change in the B6 mice. The effects on total REM varied among strains (Figure 2). During the light period, REM was suppressed in both C and D2 mice, with the suppression in C mice persisting through the final cue presentation. Light period REM was not significantly altered in the B6 mice. During the dark period, REM was suppressed in all strains, though the effect lasted longer and was greater in the C and D2 mice.

Figure 1



Total NREM during light (8 h) and dark (12 h) periods after fear-conditioned cues. Bars indicate mean (SEM). a,  $p < .05$ , compared to baseline.

Figure 2



Total REM during light (8 h) and dark (12 h) periods after fear-conditioned cue. Bars indicate mean (SEM). a,  $p < .05$ ; b,  $p < .01$ , compared to baseline.

**Conclusions:** Changes in sleep-wakefulness patterns could be induced by fear-conditioned cues for at least 26 days after training. Greater alterations were observed in strains that were more reactive on behavioral tests of anxiety. These results indicate that reminders of an aversive event can impact sleep for prolonged periods after the initial experience, and that the degree of the effect varies with strain. Understanding the genetic and physiological variables responsible for the differential levels of changes in sleep may have importance for understanding the impact of emotion on sleep.

**References:**

(1) Sanford LD, Tang X, Ross RJ, Morrison AR. Influence of anticipatory anxiety on sleep in behaviorally “anxious” and “non-anxious” mice. *Sleep* 2001; 24: A53-54

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**390.U**

**SHORT SLEEPERS ARE NOT AT HIGHER RISK FOR DRIVING ACCIDENTS OR OTHER VIOLATIONS**

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**Introduction:** The 2001 “Sleep in America” Poll indicated that although over half of the respondents reported they had driven a car or other vehicle while feeling drowsy, only 1% reported that they had an accident while driving because they were too tired to drive or because they fell asleep while driving<sup>1</sup>. Representative data with objective sleep recording and verified driving records may expand this inquiry.

**Methods:** A randomly selected population sample studied by Kripke et al between 1990 and 1995 consisted of 190 women and 165 men between the ages of 40 and 64 years and 65 women between the ages of 20 and 39. Each subject had 3 nights of Actillum recording (AMI, Ardsley, NY) and up to 3 nights of oximetry data in addition to completing several questionnaires regarding physical health, drug use, sleep habits and mood<sup>2</sup>. California Department of Motor Vehicle (DMV) records were obtained from subjects who offered accurate and complete drivers’ license numbers.

**Results:** Of the 303 subjects for whom records were obtained, 51 contained violation data of any kind (accidents, moving violations, etc.). These data were compared with 24 variables from questionnaires, objective sleep recordings and oximetry. As reported elsewhere<sup>3</sup>, presence of sleep apnea (as measured by desaturation index) was not a contributing factor to DMV-reported incidents. Although many variables, including objectively measured total sleep time, age, use of caffeine, alcohol, tranquilizers or stimulants, trouble staying awake or waking in the morning, unintentional napping, oxygen desaturation index, etc. were compared to DMV-reported incidents, only one variable was significantly related to DMV record at the  $p < 0.05$  level. Seeking medical help for daytime sleepiness predicted absence of DMV violations ( $p < 0.001$ ). Total sleep time was not related to the DMV record.

**Conclusions:** These data further confirm that even very short sleepers and those who have other troubles with wakefulness do not have a seriously greater likelihood of being involved in accidents or DMV-reported violations than do other adults. The significance of the relationship between those seeking medical help for daytime sleepiness and a clean DMV record may be reflective of a desire to avoid accidents or other violations. These analyses differ from other reports in employing objective prospective recording of both sleep and driving behaviors and in use of a sample representative of the population. The data do not support the hypothesis that those who seek medical attention for daytime sleepiness have a seriously-increased accident rate.

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391.U

THE SLEEP BEHAVIOUR OF LOCOMOTIVE DRIVERS DURING RELAY OPERATIONS

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**Introduction:** Relay operations for the return trip from Adelaide to Perth involve the use of two locomotive crews, one driving and the other resting in a relay van, each working alternating eight hour shifts. To date, there is no published data concerning the quality and quantity of rest attained by train crew during relay operations, nor about the degree of work-related fatigue experienced by relay workers. This study sought to investigate the sleep behaviour of train drivers working relay operations, and the impact that sleeping in relay vans has on sleep quality and quantity.

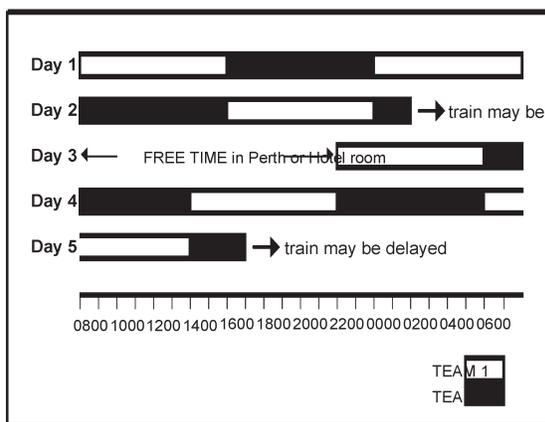
**Methods:** Twelve locomotive drivers volunteered for the study. A schematic representation of the relay work is displayed in Figure 1. During each trip, drivers were asked to (1) provide detailed information about their sleep/work patterns, (2) wear a wrist actigraph, (3) provide saliva sample every 2-hours during periods of wakefulness, and (4) complete a 10-minute psychomotor vigilance task (PVT) at the beginning and end of each 8-hour work shift. Each driver participated in three separate Adelaide-Perth relay trips (drivers typically have a minimum of five days off between each relay trip), resulting in 36 data sets.

ing each sleep period (including the time spent in Perth), drivers obtained an average of only 3.86 (SD=1.8) hours sleep. Sleep periods that were initiated at night and early in the morning (2100 to 0600 hr) were significantly ( $p<0.0001$ ) longer than sleep initiated during the day or the evening (0600 to 2100 hr). Specifically, sleep periods initiated at night and during the early morning hours were 4.8 (SD= 1.7) and 4.6 (SD=1.5) hours in length, respectively, while periods initiated during the day and evening were only 2.9 (SD=1.4) and 3.0 (SD=1.6) hours, respectively.

**Conclusions:** Although analysis of the data is still in progress, the findings thus far suggest that locomotive drivers do not obtain sufficient sleep during relay operations. However, it should be noted that during the initial phase of data collection training of drivers for accreditation was still in progress, resulting in unusual disruption in the usual roster. Furthermore, new crew vans that are better equipped have recently been introduced, which is expected to significantly impact on the quality and quantity of sleep obtained.

Research supported by the Australian Rail Consortium: Shiftwork and Workload Study Phase II

Figure 1



Work and rest periods for the two locomotive crews during relay operations from Adelaide to Perth.

**Results:** Preliminary analysis of the data indicates that drivers averaged 3.8 (SD=1.98) sleep periods on each 5-day trip. Dur-



Tuesday, June 11

## 392.A

SAPORIN LESIONS OF THE DORSOLATERAL PONS INCREASE NIGHTTIME SLEEP WHEREAS  $\alpha$ -DBH-SAP LESIONS DO NOTBlanco-Centurion CA,<sup>1</sup> Gerashchenko D,<sup>1</sup> Murillo-Rodriguez E,<sup>1</sup> Shiromani PJ<sup>1</sup>

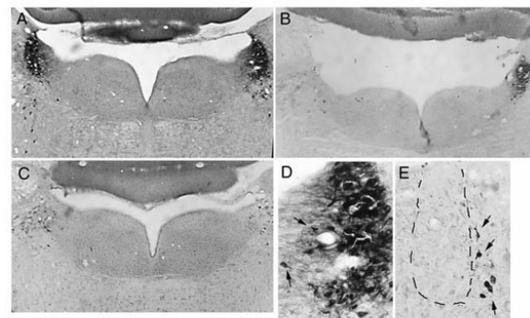
(1) Veterans Affairs Boston Healthcare System, Harvard Medical School, West Roxbury, MA, USA.,

**Introduction:** Loss of hypocretin (HCRT) neurons has been linked to narcolepsy. These neurons project widely throughout brain, but it is not known which projection to which target site produces what symptom. We showed that HCRT receptors are present in brainstem areas implicated in REM sleep. Since abnormal REM sleep triggering characterizes narcolepsy, we used HCRT2-saporin (HCRT2-SAP), a toxin that selectively lesions HCRT receptor bearing cells, to assess the effects of such lesions on sleep. We also used  $\alpha$ -DBH-sap to specifically destroy NA-LC neurons, which are the major brainstem targets of HCRT neurons.

**Methods:** Twenty-three male Sprague-Dawley rats (350-620 g) instrumented for sleep recordings were given a single bilateral microinjection of either saline (n=11), or  $\alpha$ -DBH-sap (n=5; 100 ng), or HCRT2-SAP (n=6; 46 ng). All injections were stereotaxically aimed to dorsolateral pons (A=-0.7; L=±1.4-1.6; V=±3.0). Then 24 h sleep recordings were done on 3rd, 6th, 9th, 12th and 18th days post-injections (12:12h lights on/off). Scoring was made visually on a computer (Icelus software) in 12s epochs for waking, slow wave sleep (SWS) and REM sleep (REMS) by one technician blind to treatment. ANOVA and t-test were used to compare changes in sleep parameters. Then brain were fixed, removed and sectioned for immunohistochemistry against DBH (1:50K;Chemicon) TH (1:12K; Chemicon) and NeuN (1:1K;Chemicon) proteins. Histochemistry for NADPH was made as well. A technician blind to treatment counted DBH-ir and NADPH+ cells in a 1:5 sections across the mesopontine tegmentum.

**Results:**  $\alpha$ -DBH-sap lesioned DBH-ir cells in the locus coeruleus (LC) region but did not affect the number of NADPH+ cells (cholinergic) in the LDTg (Fig 1). In addition  $\alpha$ -DBH-sap produced a major loss in DBH fibers-ir among several LC-projection sites. TH and NeuN-ir neurons were not evident in the LC after  $\alpha$ -DBH-sap either. Despite all these major degenerative signs observed in the LC after  $\alpha$ -DBH-sap, sleep parameters over the long-term were not different from saline-injected rats. In contrast rats lesioned with HCRT2-SAP showed a significant increase in nighttime sleep time across three weeks after injections (Table 1). Nighttime SWS+REMS time percent increased by 44% in HCRT2-SAP lesioned rats (P<0.01). The nighttime increase in sleep was associated with a significant increase in SWS and REMS bouts (P<0.05) but not with any change in bout duration. Daytime sleep was not affected by HCRT2-SAP. This toxin lesioned NADPH+ neurons in LDTg as well as NeuN-ir neurons in the parabrachial nucleus although DBH-ir cells were spared in the LC.

Figure 1



1.DBH-SAP lesioned NA-LC neurons but spared cholinergic cells. A=saline, B=unilateral lesion, C=bilateral lesions, D and E=magnifications of LC region in saline and DBH-SAP rats. Arrows point NADPH+ cells.

Table 1

Light period	W		SWS		REMS	
	On	Off	On	Off	On	Off
Saline	30.45 (±1.32)	75.03 (±2.38)	55.52 (±1.16)	19.67 (±1.50)	14.25 (±0.93)	5.29 (±0.92)
HCRT2-SAP	31.37 (±1.43)	63.92♦♦ (±1.92)	56.02 (±1.32)	27.85** (±1.14)	12.71 (±0.36)	8.07* (±0.91)

Percent of wake (W), SWS and REM sleep during 12h light on and light off periods. HCRT2-SAP lesions increased SWS and REM sleep at night compared to saline rats. ♦♦ p=0.003; t=3.911; DF=5, \*\* p=0.001; t=-4.350; DF=10, \*p=-2.476; DF=10

**Conclusions:** The present study does not support the hypothesis that LC neurons play a key role in wakefulness since their complete lesion was not followed by increase in sleep. In contrast other HCRT bearing receptor cells in the pons inhibit SWS and REM sleep since when they are lost after HCRT2-SAP lesions both SWS and REM sleep are increased. We hypothesize that these neurons have the HCRT-2 receptor. Additional sites in the pons are being investigated to determine where dysfunction of HCRT receptor bearing neurons produces narcoleptic-like behavior.

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**Research supported by NIH grants NS30140, AG09975, AG15853, MH55772, and Medical Research Service of the Department of Veterans Affairs.**

**393.A****HYPOCRETIN1/OREXIN-A RELEASE ACROSS THE SLEEP-WAKEFULNESS CYCLE**

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**Introduction:** Hypocretinergic cells project to structures involved in sleep generation but the pattern of hypocretin (Hcrt) release in the CNS across the sleep-wake (S-W) cycle is unknown. The current study employed in vivo microdialysis to determine the pattern of Hcrt1 release across the S-W cycle in the perifornical hypothalamic region (PFHR), the lateral preoptic area (LPO) and the locus coeruleus (LC), areas with dense Hcrt innervation and an important role in S-W cycle regulation.

**Methods:** Four freely moving cats were used for simultaneous sleep recording and collection of microdialysis samples. Temporally adjacent 10-minute samples from active waking (AW), quiet waking (QW), rapid eye movement (REM) sleep and nonREM (NREM) sleep were collected into a 20 µl Manual Sample Injector using a Micro Syringe Pump connected with a dialysis probe (type NDP-35-015, Eicom, Kyoto, 100 KDa) and analyzed by radioimmunoassay.

**Results:** In the PFHR Hcrt1 release was maximal in AW ( $91.5 \pm 11.4$  fmol/ml) and REM sleep ( $89.5 \pm 12.5$  fmol/ml) and decreased to  $75.1 \pm 11.0$  fmol/ml in QW and to  $69.7 \pm 10.5$  fmol/ml in NREM sleep ( $F=8.36$ ,  $p<0.0001$ ,  $df=3, 204$ ). Significant differences in Hcrt release were seen between AW and QW ( $t=3.15$ ,  $p<0.005$ ,  $df=51$ ), between AW and NREM sleep ( $t=3.98$ ,  $p<0.0005$ ,  $df=51$ ), QW and REM sleep ( $t=2.54$ ,  $p<0.05$ ,  $df=51$ ) and between NREM sleep and REM sleep ( $t=4.31$ ,  $p<0.0001$ ,  $df=51$ ). In the LPO Hcrt1 release also was maximal in AW ( $63.7 \pm 8.2$  fmol/ml) and REM sleep ( $71.8 \pm 6.9$  fmol/ml) and decreased to  $48.9 \pm 6.1$  fmol/ml in QW and to  $47.7 \pm 4.8$  fmol/ml in NREM sleep ( $F=10.63$ ,  $p<0.0001$ ,  $df=3, 160$ ). In the LPO significant differences in Hcrt1 release were found between AW and QW ( $t=3.61$ ,  $p<0.001$ ,  $df=40$ ), AW and NREM sleep ( $t=3.01$ ,  $p<0.005$ ,  $df=40$ ), QW and REM sleep ( $t=4.15$ ,  $p<0.0005$ ,  $df=40$ ) and between NREM and REM sleep ( $t=5.26$ ,  $p<0.0001$ ,  $df=40$ ). In the LC highest Hcrt1 level ( $48.1 \pm 4.1$  fmol/ml) was detected during AW ( $F=8.37$ ,  $p<0.0001$ ,  $df=3, 160$ ) and significant differences were found between AW and QW ( $t=4.02$ ,  $p<0.005$ ,  $df=40$ ), AW and NREM sleep ( $t=4.77$ ,  $p<0.0001$ ,  $df=40$ ), AW and REM sleep ( $t=2.73$ ,  $p<0.01$ ,  $df=40$ ). Hcrt levels during QW, NREM sleep and REM sleep ranged from  $31.8 \pm 3.0$  fmol/ml to  $35.5 \pm 3.5$  fmol/ml and were not significantly different. The cerebellum (CB) which does not have substantial Hcrt innervation was used as a control. In the CB measured Hcrt1 levels across S-W cycle ranged from  $17.3 \pm 3.8$  fmol/ml to  $20.0 \pm 2.3$  fmol/ml and did not significantly differ across all stages ( $F=0.48$ ,  $p>0.5$ ,  $df=3, 88$ ).

**Conclusions:** The elevated Hcrt release during AW is consistent with a role for this peptide in facilitation of motor output. Enhanced Hcrt release during REM sleep may be related to the activation of central motor systems and the excitation of ascending activating systems and may have role in the regulation of this state. Moreover, the elevated release of Hcrt during REM sleep suggests that the loss of this release may be related to the dissociated REM sleep phenomena that characterize narcolepsy.

**Research supported by NIH grants R01 MH64109, NS14610 and the Medical Research Service of the VA.**

**394.A****NGF-INDUCED EFFECTS ON THE ELECTRICAL ACTIVITY OF NEURONS OF THE NUCLEUS PONTIS ORALIS IN THE ADULT DECEREBRATE CAT**

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**Introduction:** The nucleus pontis oralis (NPO) contains neurons that are involved in the generation of REM sleep (Baghdoyan et al., 1987). The microinjection of the neurotrophins nerve growth factor (NGF) and neurotrophin-3 (NT-3) into the NPO rapidly induces a state that is indistinguishable from REM sleep (Yamuy et al., 1995). In addition, we have recently reported that neurons in the NPO exhibit both high- and low-affinity neurotrophin receptors (Yamuy et al. 2000). Based upon these data, the present study was designed to test the hypothesis that neurotrophins are capable of acting as neuromodulators to directly affect the electrical activity of neurons in the NPO.

**Methods:** Recordings from NPO neurons were carried out in three decerebrate cats. A partial cerebellectomy was performed to expose the floor of the fourth ventricle and directly visualize the level of the electrode descent into the pons. Multibarreled pipette electrodes were used for the juxtacellular pressure ejection of NGF (0.1-0.5 µg/µl in PBS with 0.1% BSA, using a PLL-100 picoinjector, Medical Systems, NJ) and intracellular as well as extracellular recording from pontine neurons. The tips of the recording pipettes (filled with 3M KCl, 40-80 MO tip resistance), which protruded approximately 50-120 µm from the tips of the ejection pipettes, were directed to an area of the NPO ventral and medial to the locus coeruleus (P -3, L 2, H -3.5, according to Berman's atlas) where neurotrophin application induces the REM sleep-like state.

**Results:** Following NGF pressure application, it was found that a subpopulation of NPO neurons (11 out of 18 cells) exhibited an increase in their frequency of discharge. No changes were detected in their spike configuration. These effects occurred approximately 1-5 seconds after NGF application and lasted for several minutes. Because the recorded NPO neurons were discharging spontaneously, changes in cell input resistance and rheobase were not assessed. The electrical activity of another portion of NPO neurons was not altered by the ejection of NGF.

**Conclusions:** These data suggest that NGF is capable of

inducing rapid, long-lasting changes in the electrical activity of neurons in the NPO. This finding is consistent with the concept that neurotrophins induce REM sleep by modulating the activity of NPO neurons that are involved in the generation and/or maintenance of REM sleep.

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### 395.A

#### OREXIN INNERVATION OF SPINAL NEURONS CONTROLLING SYMPATHETIC OUTFLOW

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**Introduction:** The neuropeptide orexin (ORX) plays a major role in regulating arousal and also affects autonomic functions, such as blood pressure and feeding. ORX-immunoreactive (IR) neurons are located in the lateral hypothalamus, and their axons innervate much of the brain and spinal cord. This study was designed to determine whether ORX neurons might influence diurnal variations in sympathetic function via a direct input to spinal sympathetic preganglionic neurons (SPN), the final central neurons involved in controlling sympathetic outflow.

**Methods:** Sections of perfused spinal cord were immunostained to reveal simultaneously ORX-IR nerve fibers and SPN. SPN were identified in thoracic and upper lumbar cord either by immunoreactivity for choline acetyltransferase (ChAT) or by immunoreactivity for cholera toxin B subunit (CTB) that had been retrogradely transported to SPN cell bodies from an injection into the superior cervical ganglion. Immunocytochemically-stained tissue was examined by light and electron microscopy.

**Results:** Light microscopy showed that the intermediolateral cell column (IML) and dorsolateral funiculus (DLF) of spinal cord segments T1 and T2 were heavily supplied by ORX-IR nerve fibers, which formed many close appositions on ChAT-IR or CTB-IR SPN. The density of ORX fibers dropped precipitously in more caudal segments so that only rare SPN in the IML of segments T4-L2 received close appositions. ORX-IR fibers also formed some appositions on ChAT-IR SPN in

the intercalated nucleus and the central autonomic area at all thoracic and upper lumbar levels. At the electron microscope level, SPN that projected to the superior cervical ganglion and had cell bodies in the IML and DLF were confirmed to receive synapses from ORX-IR nerve fibers.

**Conclusions:** Since cardiovascular SPN are concentrated in the IML of spinal cord segments caudal to T2, these findings suggest that ORX probably affects the cardiovascular system mainly through its action on supraspinal neurons. However, visceral function may be regulated by the ORX inputs to SPN in the central autonomic area throughout the thoracic and upper lumbar cord.

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### 396.A

#### GENERATION OF OREXIN-A DEFICIENT MICE

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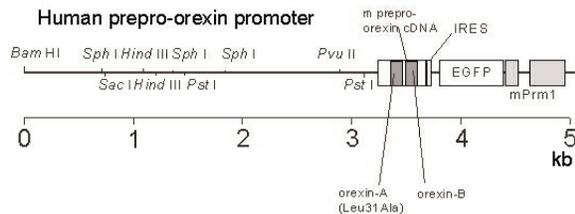
**Introduction:** Orexins (hypocretins) are two recently identified neuropeptides that are derived from a common precursor peptide1. Prepro-orexin knockout mice have a phenotype remarkably similar to human narcolepsy, implicating these peptides in arousal control2. However, differential roles of each orexin peptide, orexin-A and orexin-B, have remained unclear. We have generated mouse strains that produce only orexin-B but no functional orexin-A. Here we describe the initial immunohistochemical and biochemical characterization of orexin-A deficient mice.

**Methods:** The transgene consisted of a 3.2-kb fragment of the 5'-upstream region of the human prepro-orexin gene as promoter3, which was ligated to a mutated mouse prepro-orexin cDNA. We substituted Leu31 to Ala31 iL31A jin the mature orexin-A by introducing a point mutation into the cDNA (Figure 1). This mutation almost totally abolishes the biological activity of orexin-A. We introduced an internal ribosomal entrant site fused to enhanced green fluorescent protein (EGFP) into the 3' non-translated region of the cDNA for histological examination. In total, we established 8 lines of transgenic mice, and additionally generated transgenic lines with an identical construct except for the L31A mutation as positive control. These transgene-positive mouse lines expressed the transgenes eutropically in orexin neurons as determined by expression of EGFP. They were then crossed with prepro-orexin knockout mice to obtain prepro-orexin (-/-), transgene-positive lines, termed "orexin (-/-);orexin-A-mut E

**Results:** transgenes are exclusively transcribed and expressed only in orexin neurons. To confirm that receptor-activating capability of the mature orexin-A derived from orexin (-/-);orexin-A-mut mice is eliminated, we applied high-perform-

ance liquid chromatography fractions from brain extracts of these mice to cell lines expressing rat orexin 2-receptor, and assayed intracellular calcium transients. We could readily detect both orexin-A and orexin-B activities in brain extracts from wildtype mouse. However, we detected no orexin-A activity in the orexin(-/-);orexin-A-mut brains.

**Figure 1**



**Conclusions:** We have generated mouse lines that produce only orexin-B, but no functional orexin-A. These mice will be useful in examining the physiological roles of orexin-A versus orexin-B in vivo.

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**397.A**

**IDENTIFICATION OF WAKE-ACTIVE DOPAMINERGIC NEURONS IN THE VENTRAL PERIAQUEDUCTAL GRAY (PAG)**

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**Introduction:** Although evidence from basic and clinical research indicates that dopamine (DA) plays a key role in arousal and reward, the cell group responsible for regulation of arousal is not known. The ventral tegmental area DA neurons (VTA A10) that project to the prefrontal cortex, thalamus and ventral striatum are often assumed to regulate arousal state; however, these DA neurons do not show increased firing activity during waking in freely behaving rats. We therefore set out to find whether the activity pattern of DA neurons in the CNS correlated with wakefulness.

**Methods:** (1) We examined the expression of the immediate gene product Fos in the central DA system in rats that were either naturally awake (n=5, ZT 14 or 21:00) or asleep (n=5, ZT 03 or 10:00). The total amounts of sleep and wakefulness were determined by EEG/EMG recording. The rats were perfused and brains were sectioned. We used tyrosine hydroxylase (TH, an enzyme is involved in synthesize DA) to label DA containing cells in the midbrain. We counted the percent-

age of TH cells in the midbrain DA cell groups that expressed Fos during wakefulness and sleep. (2) To assess the role of ventral periaqueductal gray (vPAG) DA neurons in wakefulness, we ablated vPAG DA cells by injecting 0.6% 100 nl 6-hydroxydopamine into the vPAG region in six rats and examined the effects of DA cell loss on sleep three weeks after the lesion surgery. Animals (n=4) received saline injection into the vPAG region. (3) To understand the mechanisms of DA control of wakefulness, we injected the anterograde tracer biotin-dextran (BD) into the vPAG in two rats and injected the retrograde tracer Fluorogold (FG) into BD labeled terminal regions (n=6) and combined this with TH immunocytochemistry to verify that the projections from the vPAG originate from DA cells. (4) To examine the inputs to the DA cells in the PAG from the sleep-active cells in the ventrolateral preoptic nucleus (VLPO), we injected Phaseolus vulgaris-leucoagglutinin (PHA-L) into the VLPO and examined the relationship of PHA-L terminals in the PAG with TH immunoreactive neurons in the midbrain. We also injected the retrograde tracer cholera toxin subunit (CTB) into the ventrolateral PAG in rats and perfused them while they were asleep (ZT03), and then examined cells that were double-labeled with Fos and CTB in the VLPO.

**Results:** (1) We found significantly higher Fos expression in the TH labeled DA cells (50-60 %, p < 0.01) in the vPAG in awake rats than in sleeping control rats which had virtually no double (Fos-TH)-labeled cells. Almost no Fos was seen in the DA neurons in the VTA (A10) and substantia nigra (SN, A9) in either wakefulness or sleep. (2) We found that a 50-60 % loss of wake-active DA cells increased total sleep by 20% over 24 hour compared to the controls (p < 0.05). (3) BD injections in the ventrolateral PAG showed the BD-labeled terminals in the midline thalamus, intralaminar thalamus and prefrontal cortex. That was verified by double labeling of FG and TH (CY3) in the vPAG in rats with FG injections into the midline thalamus, intralaminar thalamus or prefrontal cortex. (4) After VLPO injections, we found many PHA-L labeled terminal boutons apposing the TH-labeled cell bodies and dendrites in the vPAG. This projection was confirmed by the presence of double-labeled cells in the VLPO containing Fos (sleep-active) and CTB (retrogradely labeled from the vPAG).

**Conclusions:** The DA neurons in the vPAG constitute the endogenous dopamine source that is involved in regulating wakefulness perhaps by activating the thalamus and prefrontal cortex. The wake-active DA cells in the vPAG are under the influence of the sleep-promoting cells in the VLPO.

**Research supported by NS 33987, MH55772**

**398.A****ALTERATIONS IN ANATOMY AND FUNCTION OF SLEEP AND CIRCADIAN CENTERS IN DARK-REARED RATS**

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**Introduction:** Postnatal exposure to atypical lighting conditions such as continuous dark causes anatomical and functional deficits in the image forming visual system.<sup>1</sup> Little is known about how light may affect the non image-forming visual system, a collection of subcortical retinorecipient nuclei that are involved in a variety of light-mediated behaviors, including sleep-wakefulness.<sup>2,3</sup> We analyzed the distribution of retinofugal projections to the non-image forming visual system and characterized the sleep-wakefulness patterns in varying light-dark cycles in light-dark (LD) and dark-dark (DD)-reared rats.

**Methods:** The anterograde tracer cholera toxin-beta (CT $\beta$ ) was injected into the vitreous of rats (F344) reared in LD or DD from before birth until adulthood (p56). Five days following injection, rats were anesthetized and perfused with 4% paraformaldehyde. Brains were sectioned and immunoreacted for the presence of CT $\beta$  (1:20K; visualized with DAB). Images from at least six sections that included the hypothalamus, lateral geniculate complex, pretectum, and superior colliculus were analyzed with an automated image analysis system (Image Pro Plus, Version 3). The automatic intensity range feature extracted the CT $\beta$ -labeled fibers from the background tissue. Sleep architecture and the sleep-wakefulness responses to acute light-dark shifts were evaluated in rats reared in LD- and DD environments. At postnatal week 8, four rats from each condition were implanted with EEG and EMG electrodes, and baseline sleep patterns were recorded in a 12:12 LD cycle. Sleep-wakefulness responses to acute lighting changes were also assessed using short LD cycles. An automated scoring system calculated mean rectified amplitudes for EEG, EMG, and midline ("theta") EEG recording electrodes. Each 30 second epoch was classified using the PASS algorithm as waking, REM, or non-REM sleep.

**Results:** Dark-rearing was associated with a decreased density of retinofugal fibers in the pretectum, lateral geniculate complex, and superior colliculus and an altered distribution of fibers in intermediate layers of the superior colliculus and select pretectal nuclei, as compared with LD-reared rats. Electrophysiological recordings from LD- and DD-reared rats suggested that dark-rearing increased the magnitude of the REM-sleep triggering response following lights off. However, dark-rearing was not associated with any significant changes in basic sleep architecture or in daily percentages in wake, sleep, and non-REM sleep.

**Conclusions:** These data demonstrate that dark-rearing reduced retinofugal projections to the all subcortical visual nuclei, including structures that modulate sleep-wakefulness responses to light. Preliminary analysis suggests that sleep-

wakefulness responses to light differed in dark-reared versus control rats. A greater understanding of how early exposure to light affects the developing non image forming visual system may provide insight into etiology of sleep and circadian disorders.

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**399.A****EFFECTS OF ELECTROMAGNETIC FIELDS OF MOBILE PHONES ON THE HUMAN SLEEP EEG**

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**Introduction:** In two previous studies (1,2) we demonstrated that electromagnetic fields (EMF) emitted by mobile phones affect the human sleep EEG. Healthy young subjects were exposed to EMF either during nocturnal sleep or during the waking period preceding a daytime sleep episode. In both experiments spectral power in the 9-14 Hz frequency range in non-REM sleep (NREMS) was initially increased compared to sham exposure. No asymmetrical EEG effect was observed after unilateral EMF exposure. The current study aimed at clarifying whether one of the modulation frequencies (2, 8, 217, 1736 Hz) or the carrier frequency alone (900 MHz) may be responsible for the observed changes in the NREMS power spectrum.

**Methods:** In the first experiment subjects were exposed intermittently during an 8-h nighttime sleep episode (bilateral exposure; 1) while in the second experiment unilateral exposure was performed for 30 min prior to a 3-h daytime sleep episode (2). In the current experiment the subjects' left cortical hemisphere was exposed unilaterally to EMF for 30 min prior to a nighttime sleep episode. Two active (EMF) conditions were applied: continuous wave (CW, no modulation) and pulse modulation (PM, 1/8 duty cycle, in contrast to 7/8 in the first two studies). All experiments were performed according to a double-blind sham controlled cross-over design. The spatial peak specific absorption rate (SAR) was set to 1 W/kg (international exposure limits 2 W/kg). Polysomnographic recordings were performed. For both exposure setups (bilateral and unilateral) the distribution of the SAR within the brain

was simulated. In addition, for both hemispheres the mean SAR was estimated for cortex and thalamus.

**Results:** Preliminary analyses revealed that PM EMF exposure increased EEG power in the spindle frequency range in stage 2. This increase was limited to the PM condition. In both setups maximal exposure occurred in the cortex. However, a second focus was observed in subcortical regions. The simulated SAR distribution revealed a similar exposure of left and right cortex and thalamus when EMF exposure was bilateral (during sleep). Unilateral exposure (prior to sleep) resulted in an asymmetrical exposure of the cortex. However, left and right thalamus were similarly exposed (Table 1).

Table 1

Specific absorption rate

	left (W/kg)	right (W/kg)
bilateral exposure:		
- cortex	0.16 (0.08)	0.17 (0.08)
- thalamus	0.08 (0.04)	0.11 (0.07)
unilateral exposure:		
- cortex	0.24 (0.18)	0.03 (0.02)
- thalamus	0.13 (0.02)	0.10 (0.03)
mean (standard deviation)		

**Conclusions:** The two previous studies (1,2) and the current study demonstrate that pulse modulated EMF affect the sleep EEG in the spindle frequency range. Here we present the first indication of a differential effect of CW and PM EMF on the human sleep EEG. Simulations of the SAR distribution suggest that both bilateral and unilateral exposure affected the thalamus symmetrically. This supports the hypothesis that deeper brain structures are mainly responsible for the observed EEG effect.

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## 400.A

### IDENTIFICATION OF POTENTIAL TARGET GENES FOR CAMP RESPONSE - ELEMENT BINDING PROTEIN (CREB); A BIOINFORMATICS APPROACH

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**Introduction:** The cyclic AMP (cAMP) response-element binding protein (CREB) belongs to a family of transcriptional factors that mediate cell responses to external stimuli. The cAMP-responsive element (CRE; 5'-TGACGTCA-3') is critical for cAMP-induced transcriptional activation. Correlative studies indicate that CREB plays a role in sleep/wakefulness regulation in mammals. It has been demonstrated that: (1) CRE-mediated transcription oscillates in the SCN; (2) the activated form of CREB increases in the brain during wakefulness and following sleep deprivation; (3) mice lacking  $\alpha$  and  $\delta$  isoforms of CREB show differences in sleep and the homeostatic response to sleep deprivation; (4) activity and rest is disturbed in CREB mutants in *Drosophila*. We sought to perform a comprehensive search of the human genome for genes containing CRE sites. Discovery of CREB target genes is the first step toward better understanding of CREB involvement in the regulation of sleep and wakefulness.

**Methods:** Searches for CREB-binding sites were performed using promoters of genes that were: (1) previously identified to increase their mRNA level in the rat brain following spontaneous wakefulness or sleep deprivation (27 genes, [1]); (2) randomly selected (350 genes) from different gene ontology groups (<http://www.informatics.jax.org/go/>). The search for CRE sites is an ongoing effort; we plan to analyze all human genes available from the RefSeq database (<http://www.ncbi.nlm.nih.gov/LocusLink/refseq.html>) for which promoter sequences are obtainable through the UCSC Genome Browser (<http://genome.ucsc.edu>). Promoter sequences (-1000 bp) were acquired using the Genome Browser following searches of the RefSeq database with the accession number of the relevant gene. The Transcription Element Search System (<http://www.cbil.upenn.edu/tess/>), along with TRANSFAC, IMD and CBIL matrices, were used to identify CREB-binding sites. The minimum log-likelihood ratio (13.0) applied to all analyses was based on the test searches of known genes containing the CRE sites. The CREB-binding site was considered "present" when the CRE consensus sequence (5'-TGACGTCA-3') was identified; all asymmetric CRE sites were marked as a "potential" binding site.

**Results:** In genes that have been identified as being up-regulated in the rat brain after spontaneous wakefulness or sleep deprivation [1], four promoters contained the CRE site, i.e., STAT3 (NM\_003150), MAPK8 (NM\_002750), LMO4 (NM\_006967), and NGF-inducible protein (VGF/NM\_003378); the first three belong to a group of transcription regulators. VGF has an unknown function, but is strongly implicated in energy balance [2]. Our searches also identified CREB-binding sites in a number of other genes. Examples of such genes along with the abbreviation and accession number are: ADCY8/NM\_001115,

CAMK1/NM\_003656, PPM1A/AF070670, PPIR2/NM\_006241, STK15/NM\_003600.

**Conclusions:** Preliminary data indicates that CREB target genes code a diverse group of key regulatory proteins. Although a majority are involved in signal transduction, other processes such as energy metabolism can be influenced through CREB-mediated gene activation.

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#### 401.A

##### EFFECTS OF BIBN-99, A SELECTIVE MUSCARINIC-2 RECEPTOR BLOCKER, ON SLEEP IN AGED RATS

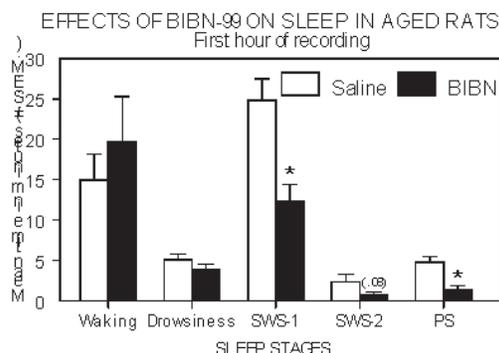
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**Introduction:** Aged rats show fragmented sleep, decreased slow-wave sleep (SWS) and moderately decreased paradoxical sleep (PS). BIBN-99 is a selective muscarinic-2 receptor antagonist shown to increase acetylcholine (ACh) release and improve performance in aged rats (1). Given the relationships between ACh, sleep and performance, the aim of the present work was to evaluate the effects of BIBN-99 on sleep in aged rats.

**Methods:** Sixteen Long-Evans rats aged 26-27 months were implanted for EEG and EMG recordings. After at least 7 days of recovery, rats were distributed in either one of two treatment groups: saline (0.5 cc NaCl 0.9%, s.c., n=7) or BIBN-99 (0.5 mg/kg, s.c., n=9). Rats were injected at the onset of the light period and sleep recording was started immediately, for four hours. Sleep stages were determined visually in 10 sec. epochs as wakefulness (W), drowsiness, SWS-1, SWS-2 and PS. Results for each 1-hour periods were compared using t-tests for independent groups.

Figure 1



**Results:** BIBN-99 significantly increased latencies to sleep onset ( $7.8 \pm 1.3$  vs  $25.3 \pm 6.4$ ;  $p < .03$ ) and PS ( $13.9 \pm 2.6$  vs  $29.6 \pm 6.1$ ;  $p < .04$ ) and non significantly to SWS-2 ( $15.9 \pm 4.6$  vs  $33.5 \pm 9.0$ ;  $p < .10$ ). Only the first hour of recording showed group differences on sleep architecture whereas wake time after sleep onset (WASO) was not affected (see Figure). Decreases in sleep stages duration was found to be compensated by increased sleep latency, not by WASO. No rebound was observed upon the following three hours of recording.

**Conclusions:** Sleep organization following BIBN-99 s.c. in aged rats is similar to the effects of intracerebral injections of other M2 antagonists in young rats, including PS and SWS suppression (2). In a previous study with drug-naive young rats and scopolamine-treated young rats (an experimental model of aging) we found that BIBN-99 rather increased SWS-2 (3). This suggests that the scopolamine model do not reproduce all sleep features of natural aging in the rat. It is possible that BIBN-99 cannot increase EEG slow-wave activity in aged subjects, an issue that should be resolved by quantified EEG analysis.

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#### 402.A

##### HYPOCRETIN (OREXIN)-LIKE IMMUNOREACTIVITY IN THE CENTRAL NERVOUS SYSTEM OF THE GUINEA PIG

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**Introduction:** Two recently discovered hypothalamic neuropeptides: hypocretin-1 (hcrt-1) and hypocretin-2 (hcrt-2) (also known as orexin-A and orexin-B, respectively) are involved in the control of food intake and the regulation of normal sleep behavior (1,2). Both hcrt-1 and hcrt-2 are derived from the same 130-amino acid residue (rodent) or 131-amino acid residue (human) polypeptide (prepro-hypocretin) by proteolytic processing (1). The distribution of hypocretin in the brainstem has been studied in several species, including the mouse, rat, cat and monkey (2). However, in the guinea pig, there are no detailed descriptions regarding the localization of hypocretin. Accordingly, the present experiments were undertaken to

examine hypocretin-like immunoreactivity in the central nervous system of the guinea pig.

**Methods:** Four adult guinea pigs were employed in the present study. The animals were deeply anesthetized with pentobarbital sodium (35 mg/kg, i.v.) and perfused transcardially with a fixative containing 4% paraformaldehyde, 15% saturated picric acid and 0.25% glutaraldehyde in 0.1 M phosphate buffer (PBS) (pH 7.4). The brain was then removed and post-fixed overnight at 4°C, frozen sections (15 µm in thickness) were cut with a cryostat. The immunohistochemical staining was similar to previously published procedures. Two goat antibodies were used to identify hcr1-1 and hcr1-2 (Diagnostic Systems Laboratories, Inc. Texas), respectively.

**Results:** Hcr1-ir somata were found exclusively in the hypothalamus, principally in the lateral hypothalamic area (LHA) at the level of the tuberal cinereum; a small number of positive somata were located in the dorsal and posterior hypothalamus. In the LHA, the majority of the neurons were located dorsal and lateral to the fornix. Hcr1-ir fibers with varicose terminals were widely distributed throughout the central nervous system. In the hypothalamus, hcr1-ir fibers were highly concentrated in the infundibular nucleus (INF), the supra- and pre-mammillary nuclei, the suprachiasmatic nucleus, and the tuberomammillary nucleus (TM). In the brainstem, high densities of fiber were present in the nucleus raphe dorsalis, the laterodorsal tegmental nucleus and the locus coeruleus. Fibers were also observed in the nucleus pontis oralis (NPO) and in brainstem motor pools.

**Conclusions:** (1) Both hcr1-1 and hcr1-2 neuropeptides are widely expressed throughout the central nervous system of the guinea pig. (2) High densities of hcr1-1 and hcr1-2 positive fibers are present in structures that are believed to participate in the control of sleep and wakefulness, suggesting an important role for hypocretin peptides in the modulation of these behaviors in this species.

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### 403.B

#### EFFECTS OF ACOUSTIC STIMULATION ON HEART RATE AND PERIPHERAL ARTERIAL TONOMETRY (PAT) DURING SLEEP

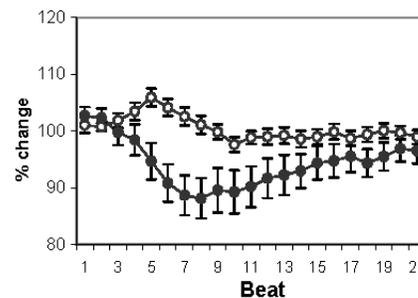
Lavie P,<sup>1</sup> Iani C,<sup>1</sup> Pillar G,<sup>2</sup> Lavie P<sup>1</sup>

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**Introduction:** Sleep fragmentation in the form of recurrent brief arousals due to respiratory disturbance events or periodic leg movements is a prevalent finding in clinical sleep laboratories patients' population. Although the definition of brief arousal requires the occurrence of alpha EEG activity for at least 3 seconds, it has been suggested that even autonomic arousals in the form of brief transient elevation in heart rate (HR) and blood pressure without accompanying signs of EEG activation may have daytime consequences. In order to better understand the dynamics of the arousal response during sleep, and its effects on daytime behavior, several studies have employed controlled acoustic stimulation. It is well documented that acoustic stimulation during sleep results in a biphasic cardiac response of tachycardia, that reaches a peak on the 4th beat after stimulation, followed toward the 7th beat by a bradycardia. HR then returns to prestimulus levels by the 10th beat. Peripheral vasoconstriction in response to acoustic stimulation on the other hand has been found to reach its maximum value 8 seconds after stimulation and return to its prestimulation levels by the 22nd second. In the present study we compared the cardiac and vasomotor responses induced by multiple acoustic stimulation during daytime sleep.

**Methods:** We used a recently developed technique that allows for the non-invasive long-term monitoring of peripheral arterial tone (PAT). EEG, HR and PAT recordings were collected from 10 young healthy males and females during daytime sleep. After the first 20 minutes of sleep, subjects were administered acoustic stimulation in the form of pure tones, at increasing intensities. EEG recordings were scored to determine if ASDA-defined EEG arousals occurred following stimulus onset. HR and PAT responses to stimulation were defined as the percentage of change from a prestimulus baseline (15 sec.) for 21 beats following each stimulation.

**Figure 1**



The general response pattern of the PAT (closed circles) and HR (open circles) after acoustic stimulation during sleep. Signals are expressed as percent of a 15-sec pre-stimulus baseline. Error bars indicate SEM.

**Results:** Both PAT and HR responded to acoustic stimulation during sleep. PAT response was unimodal and longer lasting than the HR response (Figure 1). While HR accelerated 4 seconds after stimulus onset and decelerated to return to baseline levels 10-11 beats after stimulation, PAT attenuated 8 seconds after stimulus onset. Both measures discriminated between "arousal" and "non arousal" responses in stage 2 and REM, while only PAT showed a borderline difference between the two response types in stage 3-4.

**Conclusions:** Our results suggest that the vasomotor system shows a more profound and sustained response to arousal than the cardiac system.

#### 404.B

##### SLEEP AND BODY TEMPERATURE IN MICE LACKING A FUNCTIONAL GHRH RECEPTOR

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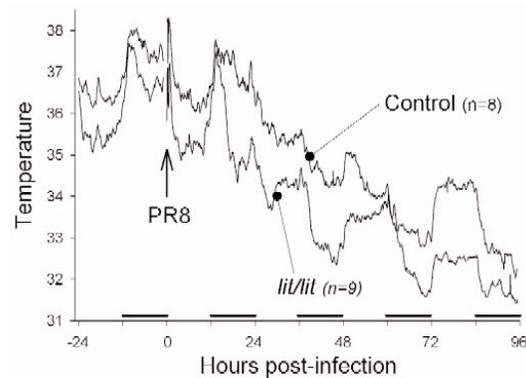
**Introduction:** A role for growth hormone-releasing hormone (GHRH) in the regulation of sleep is established (1), although the mechanisms involved are relatively undefined. In addition, Toth *et al.* have proposed the GHRH receptor as a candidate gene responsible for viral-induced NREMS responses. We previously demonstrated that mice lacking a functional GHRH receptor, *lit/lit* mice, have significantly less NREMS and REMS under basal conditions compared to control mice (3). Furthermore, *lit/lit* mice showed a surprising decrease in the amount of NREMS sleep during influenza infection compared to control mice, which demonstrated the expected increase in NREMS during infection (3). The objective of this study was to compare the severity of infection in control and *lit/lit* mice by measuring body temperature ( $T_{sb}$ ), motor activity, and lung viral titers.

**Methods:** Mice (control C57BL/6; dwarf *lit/lit*) were implanted with intraperitoneal Minimitters for recording activity and  $T_{sb}$ s. Animals were caged individually on a 12:12-h L/D cycle at an ambient temperature of 29 °C in sound-attenuated chambers. After 5 days of habituation, spontaneous activity and  $T_{sb}$ s were recorded for 48 h. Data from these two days were averaged and used as baseline values. Mice were then intranasally infected with A/PR/8/34 (H1N1) influenza virus ( $2.5 \times 10^6$  TCID<sub>50</sub>s) at light onset and subsequent changes in activity and  $T_{sb}$ s were recorded. Viral lung titers (TCID<sub>50</sub>s in MDCK cells) were determined at 2 days post-infection.

**Results:** The  $T_{sb}$ s of *lit/lit* mice was reduced under basal conditions ( $35.51 \pm 0.02$  °C versus  $36.45 \pm 0.01$  °C during light phase, and  $36.84 \pm 0.03$  °C versus  $37.54 \pm 0.02$  °C during dark phase for *lit/lit* and control mice, respectively). Following influenza infection, both strains of mice demonstrated typical hypothalamic responses (2) beginning 24h after challenge (Fig. 1). By 48h post-infection, the normal L/D variations in  $T_{sb}$ s were reversed in both strains such that  $T_{sb}$ s decreased, rather than increased, during the dark period. Spontaneous activity was not different between the two groups of mice under basal conditions, and both groups showed similar decreases in activity during infection. There were no differences in the viral lung

titers of *lit/lit* and control mice at 2 days post infection and virus was not detected in the brains of either strain.

**Figure 1**



Body Temperature in control and *lit/lit* mice following influenza (PR8) infection

**Conclusions:** 1) The low  $T_{sb}$ s of *lit/lit* mice under basal conditions may be attributed to the larger surface area to body mass ratio that makes maintenance of normal temperature more difficult in the dwarfs. 2) Theoretically, low body temperature may contribute to a reduction of NREMS. The control mice, however, spent significantly more time in NREMS post-infection when their  $T_{sb}$ s decreased to the same level as seen in *lit/lit* mice (3). 3) Although the thermoregulation deficiency in itself cannot explain decreased sleep in *lit/lit* mice it may contribute to their higher death rate (3).

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#### 405.B

##### INCREASE IN BARORECEPTOR SENSITIVITY IN CHILDREN DURING SLEEP

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**Introduction:** The arterial baroreflex provides a powerful moment by moment regulation of the circulation, that minimizes excessive blood pressure (BP) fluctuations. We hypothesized that the sleep-associated decline in BP is accompanied by an increase in baroreflex sensitivity (BRS).

**Methods:** Seven children, mean age  $11.9 \pm 3.6$  years, underwent overnight polysomnography study together with continuous BP recording with a portapres monitor. Sleep patterns

were normal and without obstructive sleep apnea. BRS was measured by non-invasive techniques based on computer analysis of heart rate and BP using the sequence and the spectral techniques. The sequence method measures the slope of the changes in BP to changes in RR interval. Different slopes were derived for rising systolic BP sequences (Slope +) and for decreasing systolic BP sequences (Slope-). The spectral technique provides a frequency domain measure of baroreflex control of heart rate. The alpha coefficient was derived by dividing the square root of RR interval variability by the square root of BP variability in the low frequency (LF) and high frequency (HF) ranges. Variability in the HF range is a marker of vagal modulation. BRS and BP results are expressed as mean  $\pm$  standard deviation in ms / mmHg and mmHg respectively. The duration of the recording was divided into four equal sequential periods (I to IV). While period I includes quiet wakefulness and early sleep, periods II, III and IV reflect only the progressively later parts of sleep without wakefulness. Periods were analyzed regardless of sleep stage. Analysis of variance was used to compare mean BRS and mean BP among the different time points.

**Results:** 1) There was a significant increase in BRS for rising and decreasing sequences of systolic BP. 2) By the spectral technique there was a significant increase in the alpha coefficient in the HF range but not in the LF range. 3) There was a parallel decrease in mean BP during sleep.

**Table 1**

	Period I	Period II	Period III	Period IV	P
Slope +	15.3 $\pm$ 6	20 $\pm$ 8.5	20 $\pm$ 7.8	25.5 $\pm$ 8.7	<0.0001
Slope -	16.3 $\pm$ 7.9	20.9 $\pm$ 9.1	19.8 $\pm$ 9.1	25.3 $\pm$ 9.6	<0.0001
HF alpha	19.2 $\pm$ 10.8	24.2 $\pm$ 12.7	23.8 $\pm$ 11.7	30.9 $\pm$ 11.3	<0.0001
LF alpha	7.9 $\pm$ 1.5	7.9 $\pm$ 1.3	8.3 $\pm$ 1.5	8.2 $\pm$ 1.3	0.13
Mean BP	78 $\pm$ 9	71 $\pm$ 10.1	72 $\pm$ 7	73 $\pm$ 6	0.0001

**Conclusions:** Arterial baroreflex gain increases during sleep compared to measurements obtained during wakefulness and the early stages of sleep (period I). This increased gain is evident even when measurements are obtained independent of sleep stage. Modulation of baroreflex gain may be an important mechanism in maintaining the lower BP and slower heart rate during sleep.

**Research supported by Children's Hospital Medical Center Research Foundation and American Heart Association**

## 406.B

### EXTRACELLULAR HYPOCRETIN-1 (OREXIN A) LEVELS IN RATS IN RELATION TO SLEEP/WAKE ACTIVITIES

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**Introduction:** Impaired Hypocretin (orexin) neurotransmission is involved in the pathophysiology of narcolepsy (1,2,3). Taken together with the fact that the central administration of hypocretin-1 induces wakefulness, the hypocretin system plays a key role in control of vigilance. Although recent data suggest that the hypocretin system may control vigilance by modulating monoaminergic, cholinergic and histaminergic tone, little is known about the physiological changes in hypocretin neurotransmission in freely-moving animals. In order to examine how hypocretin activity fluctuates with respect to the sleep-wake cycle, we measured changes in extracellular hypocretin-1 immunoreactivity (IR) levels in the lateral hypothalamus (LH) and medial thalamus (mTA) of freely-moving rats by using microdialysis with simultaneous sleep recordings.

**Methods:** Sprague-Dawley rats were used. Electrodes for recording electroencephalograms, electro-oculograms, electromyograms and a thermistor probe were implanted under pentobarbital anesthesia. One or two guide cannula(e) were also implanted into the target regions: LH; [AP] = -3.2, [L] = 1.6, [D] = 9.2, mTA; [AP] = 3.0, [L] = 1.4, [D] = 7.9 with an angle of 10° from the midsagittal plane. Microdialysis probes (C-I-8, EiCOM, Kyoto, Japan, membrane length, 3 mm; cutoff value, 50 KDa.) were inserted into the guide cannula(e). After a recovery and acclimation period in the recording cages, perfusion of artificial cerebrospinal fluid was started (perfusion rate: 0.4  $\mu$ l/min). Microdialysis sampling with simultaneous sleep recording was performed during 1) a 12-h light: 12-h dark cycle, 2) a 4-h lights-on shift, 3) a 6-h sleep deprivation and 4) a 72-h food deprivation paradigm. Hypocretin-1 IR was measured with commercially available 125I RIA kits (Phoenix Pharmaceuticals, CA, USA). In vitro recovery of hypocretins was 0.8%.

**Results:** Hypocretin-1 IR levels exhibited a robust diurnal fluctuation; levels slowly increased during the dark (active) period, and decreased during the light (rest) period in both the LH and mTA. However, levels were not correlated with the amount of wakefulness or sleep in either the dark or light period. Although an acute 4-h light shift did not alter hypocretin levels, 6-h of sleep deprivation significantly increased hypocretin release.

**Conclusions:** Hypocretin activity is likely to build up during spontaneous and forced wakefulness and decline with the occurrence of sleep, and the levels were not affected by the acute light shift. These findings, together with the fact that a difficulty in maintaining wakefulness during the daytime and forced wakefulness are primary symptoms of hypocretin-deficient narcolepsy, suggest that the build up of hypocretin activity may be critical to counteract sleep propensity during pro-

longed wakefulness. In contrast, decline of these levels may help to free the sleep propensity accumulated during wakefulness and resulting in consolidated sleep. The lack of this regulation may result in the observed fragmented sleep patterns in hypocretin-deficient narcoleptic subjects. Influence of the food deprivation on the hypocretin-mediated vigilance control system will be further discussed.

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Research supported by MH01600, NS23724

### 407.B

#### DIFFERENTIAL CHANGES IN SLEEP ONSET LATENCY, PERIPHERAL AND CORE BODY TEMPERATURES FOLLOWING CAFFEINE AND TEMAZEPAM ADMINISTRATION

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**Introduction:** Sleep onset latency has been linked with a rapid reduction in core body temperature (TC) through increased peripheral heat loss 1. However, as the analysis of peripheral temperature physiology has been limited to single temperature thermistors attached to discrete body areas, it has not been possible to observe sleep onset-related changes in peripheral temperature in an integrated or cohesive manner. Recently, however, low cost high resolution thermal imaging systems have become available enabling the measurement of real-time changes in peripheral temperature across the whole body simultaneously 2. By using thermal imaging as well as standard thermistors and employing both an alerting agent (caffeine) and hypnotic agent (temazepam) to manipulate sleep propensity, we aimed to determine whether the capacity to dissipate heat at both proximal and peripheral skin sites may affect sleep onset in young adults.

**Methods:** Preliminary results from four male subjects (18–23y) have been obtained thus far and only the thermistor data have been analysed. For these subjects, the thermoregulatory and soporific effects of temazepam (20mg) were compared. with caffeine (100mg), both given orally at 1400h. The study was placebo-controlled and counter balanced. From 0900-1830h, subjects lay quietly in bed during which time, skin and rectal temperatures were recorded continuously. Sleep propensity was measured using 30 minute multiple sleep latency tests (MSLT) performed hourly from 1100-1800h. Subjects were scored as being asleep after 3 consecutive epochs in stage 1 sleep (SOL1). Infra-red thermal images of the upper body (torso, head, arms and hands) were also taken

during the MSLT protocols. Repeated measures ANOVAS were used for statistical analyses.

**Results:** Following temazepam administration, significant reductions in both TC (-0.23°C) and SOL1 (-11.6min) as well as a significant increase in foot temperature (0.86°C) were observed relative to placebo. Following caffeine administration, a significant increase in SOL1 (11.8min) and significant decrease in foot temperature (-2.05°C) were observed relative to placebo while TC did not differ significantly from placebo. For both caffeine and temazepam, a significant ( $p < 0.05$ ) Pearson's correlation coefficient of -0.49 was obtained between changes in SOL1 and foot temperature.

**Conclusions:** From these results it could be argued that a decrease as well as an increase in peripheral heat loss may be involved in the regulation of sleep propensity.

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### 408.C

#### A CYCLOOXYGENASE-2 INHIBITOR ATTENUATES NON-RAPID EYE MOVEMENT SLEEP IN RABBITS

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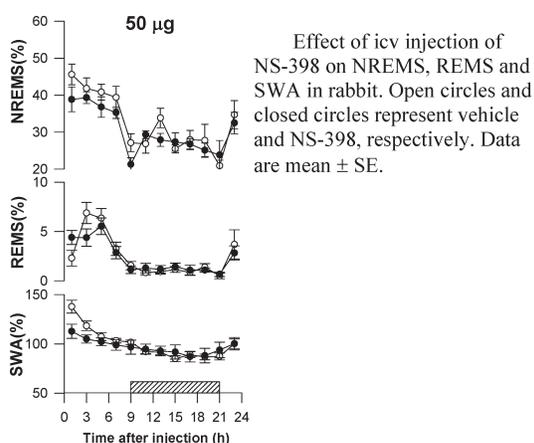
**Introduction:** Sleep is regulated in part by the brain cytokine network including interleukin-1b (IL1b) and tumor necrosis factor alpha (TNF $\alpha$ ). IL1b and TNF $\alpha$  activate the transcription factor nuclear factor kappa B (NF $\kappa$ B) which in turn promotes transcription of many genes including cyclooxygenase-2 (COX-2). COX-2 is in the brain and is one of the enzymes responsible for the production of prostaglandin D2 (PGD2). A separate literature describes the involvement of PGD2 and PGE2 in sleep regulation. It was reported that in rats the systemic injection of a COX-2 inhibitor attenuates the sleep responses induced by IL1 or TNF, although at the doses used, the COX-2 inhibitor failed to alter spontaneous sleep. It is hypothesized, however, that it is central COX-2 that might play a role in the regulation of spontaneous sleep. To test this idea, we injected a highly selective COX-2 inhibitor, NS-398, into the cerebroventricular system, and investigated its effect on spontaneous sleep in rabbits.

**Methods:** Male New Zealand White Pasteurella-free rabbits weighing 3.5-4.5 kg were surgically implanted with electroencephalogram (EEG) electrodes and brain thermistor following ketamine-xylazine anesthesia. A lateral intracerebroventricular (icv) cannula was also placed in the left lateral ventricle, 2.7-mm lateral of the bregma. After at least 2 wk of recovery, the animals were placed in experimental chambers. They were kept on a 12:12-h light-dark cycle (0600 light on) at  $21 \pm 1^\circ\text{C}$  ambient temperature. Water and food were provided ad libi-

tum throughout the experiment. Three doses of NS-398 (0.5, 5 and 50 mg) were used. The animals were injected icv with vehicle (40% dimethyl sulfoxide) and one dose of NS-398 on 2 separate days. All analysis were performed with two-way analysis of variance for repeated measures followed by the Student-Newman-Keuls test. A significant level of  $P < 0.05$  was accepted.

**Results:** The lower two doses tested failed to affect significantly any of the parameters measured, non-rapid eye movement sleep (NREMS), REMS, EEG slow-wave activity (SWA) and brain temperature (Tbr). The highest dose, however, significantly decreased duration of NREMS and EEG SWA (Fig). The reductions were greatest during the first 3 hours post injection.

Figure 1



**Conclusions:** Our results suggest that COX-2 is related to the regulation of spontaneous sleep in rabbits.

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**409.C**

**SUBSTANCE USE FOR INSOMNIA: DAYTIME SYMPTOMS AND DISABILITY**

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**Introduction:** People with insomnia typically are not treated medically for their insomnia. Several epidemiological studies have now shown that 10-30% of people with insomnia self-medicate with alcohol or over-the-counter medications.

This study was done to determine the associated daytime symptoms and disability in persons reporting self-treatment versus those reporting medical treatment.

**Methods:** A random-digit-dial, computer assisted survey of a representative sample of adults aged 18-65 yrs is being conducted. The survey response rate is 70%. A sample of all respondents over an eighteen-month period was collected (n=1324). Exclusive past-year use of alcohol (ALC) for sleep was reported by 10% (n=132), over-the-counter medication (OTC) use by 10% (n=135) and prescription medication (RX) use by 8% (n=108). Five percent used both alcohol and sleep medications. The exclusive substance users formed the three comparison groups of the study.

**Results:** RX users had more severe insomnia than the other groups, reporting more frequent episodes of difficulty sleeping lasting more than a month ( $X^2=16.0, p<.05$ ), more difficulty falling asleep ( $X^2=19.4, p<.02$ ), and more difficulty returning to sleep ( $X^2=18.5, p<.01$ ). RX users were more likely to report daytime fatigue ( $X^2=19.2, p<.01$ ) than the others, while ALC users reported more daytime sleepiness, more often falling asleep in conversation ( $X^2=22.6, p<.001$ ), and falling asleep in < 5 min ( $X^2=24.3, p<.001$ ). The RX users compared to the others had higher Eysenck Neuroticism scores ( $F=10.98, p<.001$ ). The RX users reported over the last three months more lost days from work ( $F=4.17, p<.02$ ) and from social activities ( $F=5.07, p<.01$ ) than the other two groups.

Table 1

	Associated Daytime Symptoms		
	ALC	RX	OTC
N	132	108	135
Fatigue <sup>1</sup> *	16%	40%*	21%
Asleep in Con <sup>1</sup> *	14%*	9%	1%
Drowsy Driving <sup>1</sup>	26%	25%	25%
Asleep <5 min <sup>1</sup> *	62%*	38%	45%
Eysenck Neurot *	4.16 (3.16)	5.39 (3.33)*	3.40 (3.26)

<sup>1</sup>Percentages of the group responding Yes; analyses were done on frequencies (Chi-square)  
ALC=alcohol use, RX=prescription drug use, OTC=over-the-counter drug use  
Asleep in Con=falling asleep in conversations;  
Asleep <5 min=falling asleep in <5 min during the day;  
Eysenck Neurot=Eysenck Neuroticism Scale scores (means  $\pm$  standard deviations)  
\* differs from the other two groups;  $p < .01$

Table 2

	Three-Month Days of Insomnia and Disability		
	ALCRXOTCp<		
N	132	108	135
Insomnia *	21.4 (28.6)	37.9 (37.5)*	23.8 (30.1)
Work/school *	0.97 (2.79)	1.63 (9.16)*	0.29 (1.12)
Housework	6.65 (14.5)	9.21 (18.2)	6.02 (12.2)
Social Activities *	2.14 (8.59)	5.05 (15.6)*	1.02 (2.48)

Data are means ( $\pm$ standard deviations)  
ALC=alcohol use, RX=prescription drug use  
OTC=over-the-counter drug use  
\* differs from the other two groups;  $p < .01$

**Conclusions:** In the US population, insomniacs receiving medical treatment have more severe insomnia and greater disability than those self-treating. But, while the insomnia of those self-treating is less severe, it is still associated with some risks and disability.

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#### 410.C

##### CEP-11124, A NOVEL NON-DOPAMINERGIC WAKE PROMOTING AGENT, ENHANCES MOTIVATION IN THE ABSENCE OF OVERT SLEEPINESS

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**Introduction:** We describe CEP-11124, a prototype for a series of novel, non-dopaminergic wake promoting agents unrelated to traditional CNS stimulants. CEP-11124 produced wakefulness in rats lasting greater than three hrs ( $p < 0.0001$  vs. vehicle). Additionally, using immunohistochemical expression of cFos as an indicator of neuronal activation, we have demonstrated that CEP-11124 increased activity of neurons in discrete brain regions, including posterior hypothalamus, frontal association and cingulate cortex (see accompanying abstract). Modafinil, another wakefulness promoting agent (1), also activates posterior hypothalamus, frontal association and cingulate cortex (2). Activation of cingulate cortex by CEP-11124 and modafinil has led to the hypothesis that these novel wake promoting compounds may also enhance motivation. This hypothesis was tested in a preclinical model of behavioral despair.

**Methods:** Sprague-Dawley rats were evaluated in a forced swim behavioral despair model following administration of single doses of CEP-11124 (3-100mg/kg, ip) or modafinil (3-100 mg/kg, ip), or repeat doses of the reference compound imipramine (3-30 mg/kg, ip). Duration of active efforts to escape from an escape-proof water tank was quantified in a blinded manner. Potential effects of CEP-11124 and modafinil on motor activity were assessed in an automated open field chamber.

**Results:** In awake animals, single doses of CEP-11124 or modafinil produced dose-related increases in duration of active escape behavior (ED<sub>50</sub>=35 mg/kg, ip, CEP-11124; ED<sub>50</sub>=21 mg/kg, ip, modafinil). A maximal increase in escape activity was achieved with 100mg/kg CEP-11124 (212% of vehicle control,  $p < 0.01$ ). The potency and efficacy of CEP-11124 and modafinil were similar to that for the traditional antidepressant imipramine dosed repeatedly. Neither CEP-11124 nor modafinil increased wake-associated motor activity.

**Conclusions:** The results show that even single dose administration of the wakefulness promoting agents, CEP-11124 and modafinil, can potentiate motivation and goal oriented behavior in awake animals. These effects are independent of enhanced motor activity, but are associated with activation of frontal cortex. These data further suggest that wakefulness is a complex state in which discrete behavioral components can be

individually pharmacologically modified. Modafinil and novel wake promoting agents, typified by CEP-11124, may have utility in enhancing motivation and other components of waking behavior even in the absence of overt sleepiness.

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#### 411.D

##### DEFINITIONS OF DREAMING: A COMPARISON OF DEFINITIONS OF DREAMING UTILIZED BY DIFFERENT STUDY POPULATIONS (COLLEGE PSYCHOLOGY STUDENTS, SLEEP LAB PATIENTS, AND MEDICAL PROFESSIONALS)

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**Introduction:** The researchers and therapists involved in the study of the dream state often (> 85% of published articles in the Journal "Dreaming" [1]) allude to dreaming in their published papers without defining what is meant by "dream" to either their readers or their research subject populations. Field specific definitions of dream are the norm rather than the exception. Commonly used definitions of dream for one field (i.e. bizarre, hallucinatory mental activity occurring in REM sleep) may be mutually exclusive of definitions used by another field of study (illogical, bizarre thoughts occurring in either wake or sleep). Because of the diversity and spectrum of individuals involved in this field of study, a general accepted structural definition of dreaming has not been possible, and an inclusive paradigm has been developed for comparing definitions used in studies of dreaming across epistemologically diverse fields (2). The authors postulate that significant differences in definitions of the dream state may also exist for the study populations commonly used for research in this area.

**Methods:** A questionnaire was designed that offered a selection of alternative definitions of dreaming derived from the analysis of differing definitions used in different fields of dream study (Table 1). Respondents were asked to select one response. This questionnaire was presented to three different study populations: (1) under-graduate psychology students at two different Colleges (N=158), (2) sleep laboratory patients referred for polysomnography at an accredited sleep disorders center (N=189), and (3) medical professionals attending conferences in which the topic of presentation was dreaming (N=108).

**Results:** There was no generally accepted definition for "dreaming" found in these study populations. Significant differences in definition were found between groups. Overall, the most commonly selected definition was "a report of mental activity occurring during sleep (30.3%)". 17.9% of respondents

selected “any non-conscious thought feeling or emotion” (the highest response for college psychology students (33.5%) and one of the lowest for medical professionals (4.6%)). The commonly utilized research definition - bizarre hallucinatory mentation occurring during sleep – was selected overall by 9.1% of respondents, however, this definition was the second most likely to be utilized by medical professionals.

**Table 1**

Comparison of Definitions of Dreaming Reported by College Psychology Students (N=158) to Definitions Used by Sleep Lab Patients (N=189) and Medical Professionals (N=108)

Dream Definition	Psy. Stud %	Lab Pts. %	Med Prof %
Sleep Mental activity	30.4	34.4	47.2
Illogical thoughts in sleep or waking	6.3	10.1	4.6
Non-conscious thought feeling or emotion	33.5	20.6	4.6
Bizarre REMS mentation	10.1	8.5	15.7
Wish fulfillment	3.2	1.1	1.9
Other	6.3	6.9	14.8

**Conclusions:** There is no generally accepted definition for “dreaming” found in these study populations that are commonly utilized in research studies of “dreaming.” Significant differences in definition exist between groups. This finding may have methodological considerations for dream research. Conceptual differences in dream definition are likely to affect what an individual or group describe as reports of “dreaming.”

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**412.D**

**ALPHA POWER AND SLEEP MENTATION: A PILOT STUDY.**

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**Introduction:** Much evidence supports the possibility that alpha and theta oscillations reflect cognitive and memory performance during wakefulness (1). Klimesh (2) suggests that during REM sleep an alpha reduction could be interpreted as an event-related suppression. In others words, an alpha decrease could be viewed as analogous to the alpha desynchronization observed when an awake, alert subject performs a task. To the extent that dreaming involves mechanisms sim-

ilar to task performance, alpha reduction during sleep could be explained in similar terms. Some authors have reported a relation between suppression of alpha power (8-12 Hz) over EEG sites corresponding to Broca’s and Wernicke’s areas and the degree of language content in dream reports (3). We hypothesized that alpha power may be a predictor of mentation recall from different sleep stages.

**Methods:** To determine if changes in EEG alpha power are associated with recall of mentation following awakenings from REM and NREM sleep we used a within subjects design. We assessed 3 minutes of EEG immediately preceding a subject’s awakening from REM sleep (8 subjects who had at least two awakenings in REM sleep, one with and the other without, mentation recall), or Stage 2 sleep (8 subjects who had at least two awakenings in Stage 2 sleep, one with and the other without, mentation recall). Artifact- and microarousal-free epochs were selected for analysis by Fast Fourier Transform (FFT). Frequency bandwidths were defined as: Alpha (8.00-12.00 Hz), slow Alpha (7.50-9.50Hz), middle Alpha (9.50-11.50 Hz), and fast Alpha (11.50-13.50 Hz). Paired t-tests were used to compare EEG variables between Recall and No Recall Conditions for both sleep stages.

**Results:** EEG preceding Stage 2 awakenings followed by No Recall, compared with EEG preceding Stage 2 awakenings followed by Recall, had a significantly higher mean Alpha Absolute Power in all frequency bandwidths considered (Table 1). Similar differences were observed for REM sleep (Table 2).

**Table 1**

Channel	12.00-14.00 Hz	7.50-9.50 Hz	9.50-11.50 Hz	11.50-13.50 Hz
FP1-ref	0.0311*	0.0462*	0.0517	0.2497
FP2-ref	0.0166*	0.0684	0.0149*	0.1855
F3-ref	0.0333*	0.2369	0.0575	0.0836
F4-ref	0.0019*	0.0227*	0.0092*	0.1032
F7-ref	0.0538	0.1116	0.0938	0.0629
F8-ref	0.0010*	0.0441*	0.0026*	0.1359
C3-ref	0.0579	0.3877	0.0298*	0.0788
C4-ref	0.0194*	0.2067	0.0234*	0.0681
P3-ref	0.0143*	0.0472*	0.0107*	0.0590
P4-ref	0.0162*	0.0500	0.0143*	0.0677
O1-ref	0.0784	0.1943	0.0756	0.0823
O2-ref	0.1653	0.4283	0.0433*	0.1188
T3-ref	0.0105*	0.0099*	0.0318*	0.0221*
T4-ref	0.0049*	0.0253*	0.0058*	0.0628
T5-ref	0.0044*	0.0037*	0.0398*	0.0277*
T6-ref	0.0885	0.4463	0.0215*	0.0652
FZ-ref	0.0219*	0.0146*	0.0759	0.2249
CZ-ref	0.0765	0.0851	0.0791	0.1450
PZ-ref	0.0049*	0.0024*	0.0088*	0.0680

p-values for t-test comparisons between Recall and No Recall conditions in Stage 2 sleep  
 \*meaningful difference at p < .05, St2 No Recall has a mean Absolute Power higher than St2 Recall.

Table 2

Channel	12.00-14.00Hz	7.50-9.50 Hz	9.50-11.50 Hz	11.50-13.50 Hz
FP1-ref	0.0701	0.1490	0.1421	0.5324
FP2-ref	0.0371*	0.1203	0.0908	0.5152
F3-ref	0.0226*	0.0869	0.0341*	0.1293
F4-ref	0.0451*	0.1351	0.1577	0.2761
F7-ref	0.0306*	0.0546	0.0457*	0.1371
F8-ref	0.0284*	0.0787	0.1279	0.5336
C3-ref	0.0356*	0.0722	0.0252*	0.1721
C4-ref	0.0617	0.0845	0.0541	0.3855
P3-ref	0.0182*	0.0697	0.0049*	0.1400
P4-ref	0.0818	0.1960	0.0594	0.1764
O1-ref	0.0305*	0.1032	0.0224*	0.1751
O2-ref	0.0455*	0.1471	0.0573	0.1468
T3-ref	0.0769	0.1089	0.1316	0.2226
T4-ref	0.2528*	0.3573	0.1917	0.1270
T5-ref	0.0243*	0.0985	0.0040*	0.2173
T6-ref	0.0850	0.1126	0.0434*	0.0871
FZ-ref	0.0675	0.1757	0.0678	0.0846
CZ-ref	0.3632	0.2306	0.3160	0.5880
PZ-ref	0.2374	0.1080	0.1626	0.3362

p-values for t-test comparisons between Recall and No Recall conditions in REM sleep  
 \*meaningful difference at  $p < .05$ , REM No Recall has a mean Absolute Power higher than REM Recall.

**Concluions:** Alpha activity behaves similarly in St2 and REM Sleep relative to success or failure of recall of previous mentation. In both sleep conditions, a lower alpha power was related to successful dream recall. Our hypothesis concerning alpha power as a predictor of mentation recall in different sleep stages is thus supported by these results. The lower levels of alpha activity may mean that alpha is reflecting some aspect of information processing, e.g., event-related alpha suppression, rather the physiological states per se underlying REM and NREM sleep. Replication of these pilot findings is needed to determine whether they generalize to all sleep states.

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**413.D**

**DREAM CHARACTERISTICS IN MIDDLE-AGED, NON HOSPITALIZED PATIENTS WITH CHRONIC SCHIZOPHRENIA**

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**Introduction:** Most studies on dream in schizophrenia have been performed in small samples and most often lacked con-

rol participants (1). The aim of this study was to evaluate dreams characteristics in a large group of patients with schizophrenia and control participants using a questionnaire.

**Methods:** The study included 80 patients with schizophrenia (51 men, 29 women, aged  $44.05 \pm 5.9$  years) and 36 healthy individuals (16 men, 20 women, aged  $45.11 \pm 6.35$  years) free from sleep disorders and from personal or familial (first degree) history of psychiatric or neurologic disorders. All participants were asked to fill a questionnaire on dream habits.

**Results:** See Table 1): Patients with schizophrenia reported to dream more regularly than controls, but they reported the same amount of dreams as controls. On the other hand, patients with schizophrenia reported an impairment for the actual recall of dream content. Still, patients with schizophrenia reported to experience bad dreams and nightmares more frequently than controls. The frequency of 11 emotions in dream was also evaluated: joy, fear, sadness, relaxation, confusion, satisfaction, sexual arousal, anger, frustration, apprehension and embarrassment. Patients with schizophrenia were different from controls only on decreased presence of sexual arousal.

Table 1

Dream variables in patients with schizophrenia and healthy individuals. (mean± SEM)

Variables	Sz	Ctl	P
Regularity of dream recall <sup>b</sup>	1.5±0.1	1.2±0.1	0.02*
Number of dream per night <sup>a</sup>	0.9±0.1	0.9±0.2	0.90
Recall of a content <sup>a</sup>	3.2±0.1	3.8±0.2	0.003*
Recall next evening <sup>b</sup>	0.4±0.1	0.7±0.1	0.03*
Bad dream <sup>b</sup>	1.8±0.1	1.3±0.2	0.01*
Nightmare <sup>b</sup>	1.6±0.1	1.0±0.0	0.001*
Dream repetition <sup>b</sup>	0.6±0.1	0.7±0.1	0.10
Dream reality <sup>b</sup>	0.7±0.1	0.5±0.1	0.29
Dream control <sup>b</sup>	0.3±0.1	0.3±0.1	0.85
Vividness <sup>a</sup>	2.9±0.2	2.8±0.2	0.90
Pain sensation <sup>b</sup>	0.2±0.0	0.1±0.1	0.56

Notes : \*=significant; <sup>a</sup>= Mann-Whitney test, <sup>b</sup>= Chi<sup>2</sup> test.

**Conclusions:** Patients with schizophrenia reported more regularity in dream recall than controls. This could be related to increased awakenings from REM sleep in schizophrenia (2), a process that could facilitate the recall of the dream experience. However, patients with schizophrenia also have difficulties to recall the actual content of their dreams; the memory deficits in schizophrenia (3) may explain in part this problem of recall. Emotion frequencies in dreams of patients with schizophrenia did not differ from controls except for sexual arousal. This is in line with sexual dysfunction observed in schizophrenia. Whether these observations are present in younger patients and/or in neuroleptic-naive patients still needs to be determined.

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#### 414.D

##### EYE MOVEMENT INDEXES NETWORK STATE IN SLEEP

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**Introduction:** Eye movement often correlates with hallucinatory experience at sleep onset and in Stage REM. The properties of eye movement vary distinctively during the sleep onset period<sup>1</sup> and within and between periods of Stage REM sleep. How do these variations map onto neural network state in sleep? To address this question, eye movement in sleep may be compared to a model of network state alternation in sleep.

**Methods:** In a related study, the architecture of neural network state in sleep was modeled as a composite function of (1) a biochemically determined threshold for sleep onset<sup>2</sup> and (2) classically described “REM-on” and “REM-off” patterns of discharge in 5-HT and NE neurons of the brainstem.<sup>3</sup> This model defines network state in terms of sinusoidal variation in ‘primary inhibition’—membrane voltage oscillation secondary to hyperpolarization—or, reciprocally, in terms of ‘primary excitation’;• applies to real networks, such as the thalamic reticular-thalamocortical network;•specifies thresholds for spindling, slow waves, and eye movement;•responds to sleep deprivation.We are (1) quantifying the architecture of eye movement across the sleep period in five human sleep records and (2) mapping it onto the network model. Early data are available for two records.

**Results:** Preliminary results for eye movement during sleep onset and during the first REM period (REMP) are reported. Given the small n, only qualitative data are described.Sleep Onset:• Distinctive “nystagmoid” eye movement, prominent in one record, corresponds to the commencement of network inhibition, where levels of neuromodulation remain high.• Sleep onset eye movement maps onto the first third of the ascending slope of network primary inhibition.• Well-formed slow eye movement occurs only below the (inhibitory) threshold of EEG spindling.• Very slow EOG excursions, degraded in form and susceptible to EEG artifact, surpass the spindling threshold.First REMP:• The first REMP corresponds to threshold diminution in network primary inhibition (thus, to threshold increase in primary excitation). That diminution, simultaneous with the first nadir of neuromodulation by 5-HT and NE, produces a network state that• is not present at sleep onset, and that• varies quantitatively within the REMP, corresponding to within-REMP variability in eye movement velocity and morphology.One of the subjects was sleep deprived. In the first REMP of that subject, in contrast to that of the second subject, the eyes moved infrequently. Network primary inhibition—elevated in response to sleep deprivation—barely

crossed the model’s eye movement threshold. Nonetheless, whereas saccadic eye motion did not occur at sleep onset, saccades did appear even during the sleep deprived first REMP.

**Conclusions:** Eye movement in sleep may provide a sensitive, measurable index of neural network state in sleep, and thus may illumine the physiological bases of hallucinatory cognition in sleep.

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#### 415.E

##### THE SLEEP BEHAVIOUR OF COMMERCIAL AVIATION PILOTS CROSSING MULTIPLE TIME ZONES

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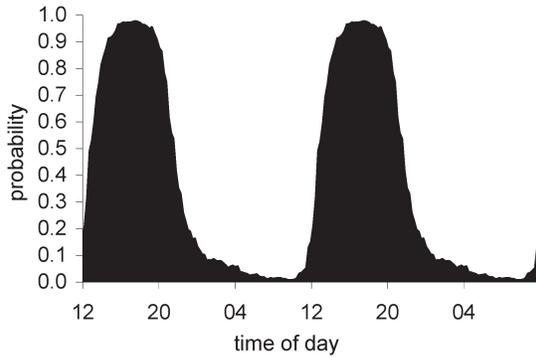
(1) Centre for Sleep Research, The University of South Australia

**Introduction:** The quantity and quality of sleep obtained by commercial aviation pilots working international flight routes has implications for the safety of crew and passengers. Providing aviation regulators and commercial operators with more detailed information about the likely sleep behaviour of pilots will better enable them to manage the work-related fatigue associated with sleep disruption in the aviation environment. This study sought to investigate the sleep behaviour of pilots crossing multiple time zones, and the impact of time zone changes on sleep quantity and quality.

**Methods:** Forty commercial aviation pilots working international flight routes volunteered to participate in the study. Data was collected from each participant over the duration of an international flight pattern. Baseline data was collected for five days prior to and post the flight pattern. The study protocol required participants to (1) provide detailed information about their sleep/wake behaviours and duty/rest schedules, (2) wear a wrist actigraph, (3) report flight details including departure and arrival times and flight destinations. All pilots lived in or near Sydney, Australia (GMT +10:00) and used Greenwich Mean Time in the reporting of time-based data.

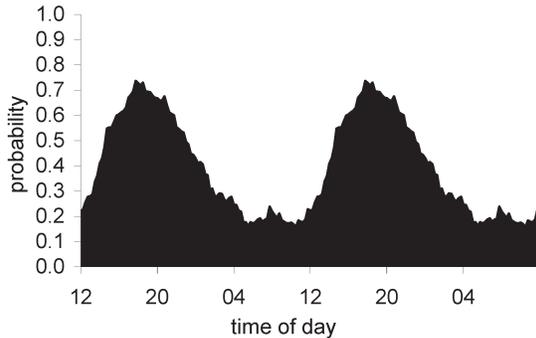
**Results:** Preliminary analysis of the data indicates that layover sleep episodes (M = 5.60, SD= 3.13) were significantly (p <0.0001) shorter in duration than baseline sleep episodes (M = 7.43, SD= 2.56) but were of similar quality as indicated by sleep efficiency scores (M = 83.05, SD = 13.88 and M = 81.49, SD = 15.34 respectively) and self-ratings (M = 2.31, SD = 1.15 and M = 2.53, SD = 1.10 respectively) on a positively coded six-point rating scale. The sleep probability curves provided in figure 1 and 2 show that sleep episodes between the hours of GMT 12 PM and GMT 24 PM were less probable in layover sleep than baseline and more probable between the hours GMT 00 AM and GMT 12PM. Nonetheless, the peak sleep probabilities in figure 1 and 2 occur within similar time periods.

Figure 1



Double plot of the probability that pilots were asleep during baseline periods across the 24-hour day.

Figure 2



Double plot of the probability that pilots were asleep during layover periods across the 24-hour day.

**Conclusions:** The findings of the study indicate that layover sleep is shorter in duration than baseline sleep at home. This result suggests that pilots would accumulate a substantial sleep debt over the duration of international flight patterns. However, these results do not take account of sleep episodes that might have occurred in-flight, such as passenger seat or cockpit sleep episodes and naps. These additional sleep periods could reduce the sleep debt substantially. The results from the sleep probability curves indicate that time zone changes alongside pilot duty/rest schedules influence the timing and duration of layover sleep but that pilots obtain a substantial proportion of their sleep during normal sleeping hours.

416.E

**BRONCHIOLAR TONE IS AFFECTED BY THE CIRCADIAN PACEMAKER**

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**Introduction:** Epidemiological studies have determined that asthma related deaths peak at approximately 4AM. It is unclear whether the chronological peak in asthma severity is a function of a sleep process and/or an intrinsic circadian process. To determine the independent contributions and interaction of sleep and circadian influences on bronchomotor tone, a 10-day *forced desynchrony* (FD) protocol was conducted in healthy and asthmatic subjects.

**Methods:** Four asthma (2 female, 2 male) and four control subjects (4 male) completed the FD protocol. The circadian and sleep/wake rhythms were disassociated by scheduling a recurring artificial day length of 28 hours with a 9.33-hour sleep opportunity. Thus, sleep occurred 4-hours later on subsequent 24-hour days such that sleep spanned all circadian phases. Experiments were conducted in time isolation, dim light (< 8 lux), controlled behavioral and environmental conditions allowing the circadian pacemaker to free run at its intrinsic period. Circadian phase was estimated from core body temperature measurements (minimum assigned 0-degrees). Airways resistance (Rint) was measured using the interrupter technique every 2-4 hours during wakefulness and immediately following scheduled awakenings from sleep. Independent effects and interaction of sleep/wake state, time into sleep or wake and circadian phase were tested with a 3-way repeated measures of ANOVA. Amplitude of the circadian rhythm was determined with cosinor analysis.

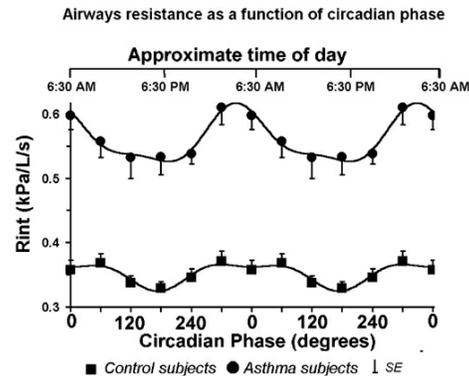
Table 1

Comparison of Rint results for asthma and control subjects.

	Mean Rint (SE)	Wake	
		Amplitude	Peak Phase°
Control	0.35 (0.02)	0.02 *	351
Asthma	0.56 (0.02)	0.04 *	335
		Sleep	
Control	0.37 (0.01)	0.02	318
Asthma	0.58 (0.07)	0.06	11

Where \* denotes P < 0.02; Units for mean and amplitude are kPa/L/s.

Figure 1



**Results:** The table illustrates that (1) the asthma and control subjects had a significant ( $P < 0.02$ ) circadian rhythm in airway resistance while measured during scheduled wake periods. (2) The asthma subjects have twice the amplitude variation in airway resistance. (3) Asthma subjects have a significantly higher average airway resistance at all circadian phases during wakefulness (see Figure). (4) Awakenings from sleep or time into scheduled sleep, did not independently affect airways resistance.

**Conclusions:** Pulmonary resistance is affected by the circadian system. Subjects with asthma have a larger amplitude circadian variation in bronchiolar tone than healthy controls. The time of the peak and larger amplitude in airways resistance in asthma subjects may explain a proportion of the 4 AM asthma related events identified in epidemiological studies. There appeared to be little impact of sleep on airway resistance. However, this is based on the assumption that measurements immediately following awaking subjects from sleep are representative of airways resistance during sleep. Determining mechanisms for the increased circadian amplitude in airways resistance may lead to appropriate chronopharmacological intervention.

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#### 417.E

##### CLOCK GENE EXPRESSION OUTSIDE THE SCN CAN MODULATE SLEEP TIME

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**Introduction:** The timing and consolidation of sleep are regulated by the circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The opponent process theory of sleep regulation states that the circadian pacemaker consolidates sleep by actively promoting wakefulness, acting in opposition to a homeostatic sleep-promoting process (1). The Clock gene is known to be a crucial component of the molecular machinery of the circadian pacemaker. Previously, we have found that mice homozygous for the Clock mutation (*Clock/Clock*) spend about 10% more time awake than their wild-type littermates(2,3). Since Clock is expressed throughout the brain and body, it has been unclear whether its influence on sleep is mediated specifically by the SCN. Thus, we wanted to determine: a) whether the SCN promotes wakefulness in mice and b) whether the *Clock* mutation influences wakefulness via the SCN or extra-SCN tissues. To answer these questions, we recorded sleep in SCN-lesioned *+/+* and *Clock/Clock* mice under baseline and recovery conditions.

**Methods:** Male *+/+* and *Clock/Clock* C57Bl/6J mice of 4-6 mo. of age received either bilateral electrolytic lesions of the SCN (n=7 and 6, respectively) or sham lesions (n=10 and 9, respectively). Mice were maintained under a 12:12 light:dark cycle. Following a 2-week recovery period, all animals were implanted with EEG and EMG electrodes for polysomnographic recording and transmitters for body temperature

recording. Animals were given another two weeks of recovery and four days of adaptation to sleep chambers prior to baseline sleep recording. Sleep was recorded for a 24 h baseline period and following a 6 h sleep deprivation procedure during the last 6 h of the light phase.

**Results:** During a 24 hour baseline period, *+/+* SCN-lesioned mice spent significantly more time asleep than sham controls ( $x = 12.70 \pm 0.26$  h vs  $10.77 \pm 0.18$  h, respectively), an effect that was not observed in *Clock/Clock* SCN-lesioned mice (genotype x lesion:  $F = 5.67$ ,  $p = 0.02$ ; post hoc tests:  $p < .05$ ). In response to sleep deprivation, only sham *+/+* mice exhibited an increase in NREM sleep time, recovering almost all the NREM sleep that they had lost (genotype x lesion:  $F = 7.65$ ,  $p = 0.009$ ). However, all groups exhibited a similar and significant increase in NREM sleep delta power in response to sleep deprivation (recovery x time:  $F = 44.28$ ,  $p < .00001$ ). In addition, no differences were detected between any of the groups in the amount of REM sleep recovered after sleep deprivation (genotype x lesion:  $F = 0.66$ ,  $p = 0.42$ ).

**Conclusions:** These data show that SCN lesions in C57Bl/6J mice result in significantly increased sleep time which supports the opponent process theory of sleep regulation. In addition, the *Clock* mutation reduces total sleep time even in SCN-lesioned animals, indicating that *Clock* influences sleep outside of the SCN. Although, the homeostatic response to sleep deprivation is largely intact in SCN-lesioned animals, the failure of both *Clock* mutant and SCN-lesioned mice to lengthen their NREM sleep times in recovery suggests that both are necessary for recovery sleep to be extended.

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#### 418.E

##### EFFECTS OF THE MSLT PROCEDURE ON ADOLESCENTS' CORE BODY TEMPERATURE DURING THE CONSTANT ROUTINE

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**Introduction:** Our inspections of raw core temperature (Tb) data from constant routines (CR) in adolescents showed striking alterations occurring in temporal association with Multiple Sleep Latency Tests (MSLT) (Figure 1). Kleitman (1) was among the first to show that postural changes associated with preparation for sleep produce decreases in Tb. Because the CR

involves minimal postural change, it provides an opportunity to assess the role of inactivity on Tb. This report summarizes factors that contributed to MSLT-related changes in Tb during CR in adolescents.

**Methods:** Participants were 8 healthy girls and 1 boy (ages 10.2-13.9). The CR began at 0800 following 12 cycles of forced desynchrony on a 28-hr LD with light  $\leq 17$  lux throughout. Participants remained seated at a 45° angle, took small meals at 2-hr intervals, and interacted with a research assistant, except during SLTs and performance batteries at 2-hr intervals. SLTs began with a 5-min calibration requiring inactivity, and then participants were told to sit back, stay still with eyes closed, and try to fall asleep. Although change in posture was minimal, activity levels were suppressed. SLTs lasted 20 minutes if no sleep occurred; otherwise, tests ended at unequivocal sleep with lights on and return of the research assistant. Rectal Tb was recorded continuously using the Mini-logger system (Mini-Mitter, Co., Sun River, OR) and aggregated in 1-min bins. Phase of temperature minimum (Tmin) was determined from Tb data excluding the first 5 hours (2). Sleep was continuously monitored and scored in 30-second epochs with standard methods. Sleep and Tb records were aligned and SLTs identified. The chief dependent variable was slope of Tb change across 25-min intervals beginning during calibrations. Circadian phase, minutes of sleep, and SLT length (sleep latency+sleep) were examined.

**Results:** Multiple regression (with subjects nested) showed that SLT Tb slope was significantly associated with circadian phase ( $F=2.8$ ,  $p=.006$ ;  $\eta^2=.18$ ) and SLT length ( $F=2.5$ ,  $p=.01$ ;  $\eta^2=.16$ ). Minutes of sleep contributed to Tb slope ( $F=2.8$ ,  $p=.006$ ;  $\eta^2=.16$ ) only when SLT length was removed from the model. Figure 2 displays these associations, showing phase-dependent slope changes for long ( $\geq 13$  minutes) and short SLTs ( $\leq 4$  min) (Fig 2). In addition, individual differences occurred; for example, participants' average Tb slopes were correlated with Body Mass Index ( $r=.686$ ,  $p<.05$ ), indicating steeper decline in Tb across SLTs for participants with lower body mass.

Figure 1

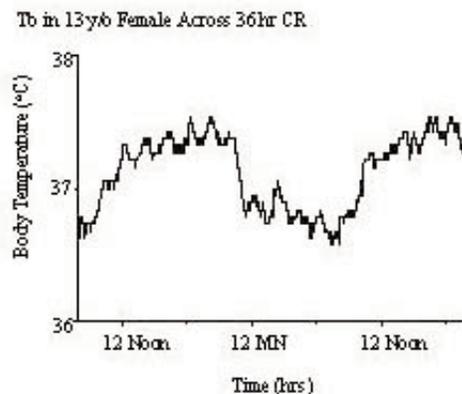
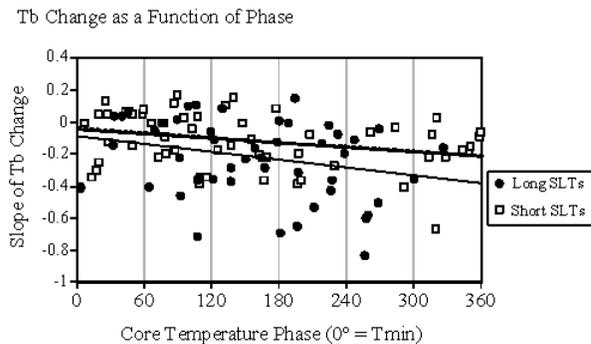


Figure 2



**Conclusions:** In summary, relaxation and inactivity associated with the MSLT procedure had greatest impact on Tb change in smaller adolescents, when quiescence was longer, and towards the falling phase of the Tb rhythm, even with minimal postural change or sleep.

**References:**

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**419.E**

**HOW LONG DOES IT TAKE SUBJECTS OF DIFFERENT AGES TO ADJUST FROM DAYLIGHT SAVING TIME TO STANDARD TIME?**

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**Introduction:** It is not known whether subjects of various ages adapt to the change from Daylight Saving Time to Standard time at different rates. A previous study done in adult subjects exclusively reported that it took around 5 days to adapt to their new schedule. Subjects typically woke up earlier than usual and without an alarm for several days following this time change.

**Methods:** 50 healthy subjects, comprising 19 males and 31 females, ranging in age from 1-55 years were asked to keep detailed sleep logs for 10 days before and following Sunday, October 28, 2001 when the clocks are set back 1 hour for the transition from Daylight Saving Time to Standard Time at 2am. Subjects (or parents in the case of toddlers and young children) were also asked to note whether they awoke spontaneously or with the help of an alarm clock and if any tiredness or sleepiness was noted and for how long after the time change.

**Results:** 26 subjects showed no delay in adapting to their new wake up time, whereas 24 subjects reported that it took between 2-4 days before they began getting up at their usual wake-up time. For the whole group, it took  $1.9 \pm 0.9$  days for this to occur and no significant differences between age groups

were noted. Eighteen subjects reported feeling tired or sleepy in the daytime, especially in the evening for an average of 2 days.

**Conclusions:** In our study which included younger children as well as adults, no significant differences in adaptation from Daylight Saving Time to Standard Time were observed. However, our subjects took an average of 2 days to adjust to their new schedule compared to 5 days that was previously reported by Monk et al.

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**420.E**

**CIRCADIAN PHASE OF SLEEP ONSET AND SENSITIVITY TO BRIGHT LIGHT IN A CASE OF HYPERNYCHTHEMERAL SYNDROME**

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**Introduction:** It has been hypothesized that the occurrence of the hypernycthemeral syndrome in sighted individuals is linked to a decreased sensitivity to environmental synchronizers (1) or to an abnormal relationship between the endogenous circadian pacemaker and the sleep-wake cycle (2). We report the pattern of melatonin secretion in a 38-year old sighted woman with a non-24 hour sleep-wake syndrome (Figure 1).

**Methods:** The patient suffered brain injury in a 1991 car accident. She subsequently developed epilepsy (treated with Valproic Acid) and a tendency to delay her sleep episodes by  $\geq 1$  hour from one day to the other. The patient was admitted to the laboratory for a 3-day observation in 2000. She was allowed to sleep *ad libitum* to avoid sleep deprivation that could trigger epileptic seizures. Upon admission to the laboratory, an indwelling catheter was inserted into her forearm and plasma melatonin was sampled at least 1/hour for ~50 hours. Sleep episodes occurred in darkness and were recorded polysomnographically. The waking episode following the first sleep episode was spent in dim light ( $\leq 10$  lux). Four hours after her second bedtime, the patient was awakened for a 90-minute melatonin suppression test under 10,000 lux after which she resumed sleep in darkness. Upon awakening, she remained in light of 2,500 lux until the final sleep episode.

**Results:** The first sleep episode in the laboratory occurred from 00:01 to 11:04. Total sleep time was 10:29 and sleep efficiency (98%) was within normal limits. REM sleep latency was short (56 minutes). She went to bed at 03:24 and 02:46 on the subsequent nights. Melatonin secretion was robust under dim light conditions but was undetectable during periods of bright light exposure (Figure 2). The patient displayed a tendency to sleep in the declining phase of her melatonin secretion curve, where the midpoint of peak melatonin concentration occurred 3.9 hours before the start of her sleep episode.

Figure 1

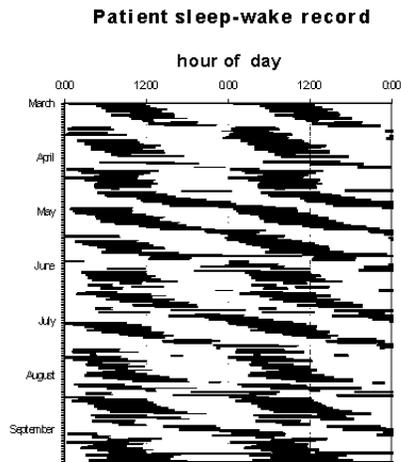
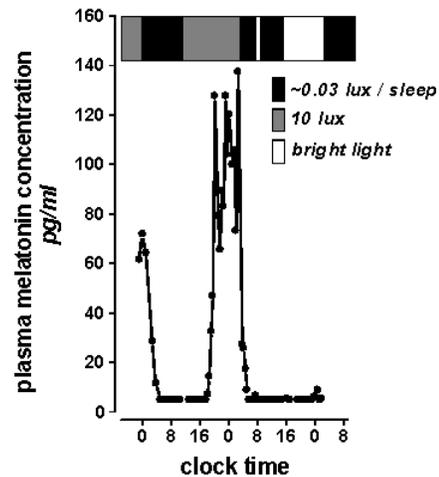


Figure 2



**Conclusions:** In healthy individuals, melatonin onset occurs 2-6 hours prior to the so-called opening of the sleep gate (3). This patient demonstrated a tendency to initiate sleep at a delayed phase for reasons that remain unclear. This situation may worsen her tendency to delay her activities by shielding the phase advance portion of her circadian cycle from light exposure. Indeed, our results suggest that bright light exposure either inhibited or delayed the rhythm of melatonin secretion.

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nary 6-sulfatoxymelatonin. *J Biol Rhythms* 1993;8:199-209.

#### 421.E

##### INFLUENCE OF WORK SCHEDULE ON INSOMNIAS AND DAYTIME SLEEPINESS.

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(1) Centre hospitalier le Vinatier, Bron, France, (2) Stanford sleep epidemiology Research Center, school of medicine, Stanford University, Stanford, CA, USA.,

**Introduction:** Background: Several conditions influence the sleep quality. Work schedule is a well documented factor related to the occurrence of sleep disorders especially for individuals working on shifts. A main consequence of the occurrence of the main sleep period at an unusual time is an excessive sleepiness during wakefulness and sleep drunkenness upon awakening (1).

**Methods:** All the staff members of the psychiatric hospital were invited to participate in the study ; 817 employees have been volunteers. Two physicians conducted the interview during the working hours. All the participants answered to a standardized computer questionnaire assessing work conditions, work schedule and their consequences on health, social and professional life. Diagnostic exploration was done with the Sleep-EVAL knowledge system (C Sleep-EVAL, MM Ohayon, 1994) (2) that used two classifications : the DSM IV (Diagnostic and Statistical Manual of Mental Disorders) and ICSD (International Classification of Sleep Disorders). Three groups were constituted according to their work schedule: 1) a group currently on rotating shifts (n=335) ; 2) a group of former shift workers (n=229) and 3) a group currently on a daytime work schedule and who never have done shift-work (n=253).

**Results:** Current shift-workers were younger ( $37.6 \pm 8.3$  y.o.) than the two other groups (Daytime schedule:  $41.8 \pm 9.0$  y.o.; former shift-workers:  $42.3 \pm 6.5$  y.o.;  $p < .001$ ) and had a higher proportion of women (78.6% vs. 68.1% in the group with a fixed daytime schedule and 59.6% in the group of shift or nighttime workers ( $p < .001$ )). When they were working on shifts, a quarter (n=58, 25.3%) of former shift-workers had insomnia problems, a third had insufficient sleep and 8.3% had difficulty staying awake at work. Insomnia problems were still present for 27 of the 58 former shift-workers who reported insomnia. Employees currently working on shifts reported more frequently having difficulty initiating sleep (19.4%) than the two other groups (13.5% and 11.5%;  $p = .02$ ). Daytime sleepiness also was more frequent in the group of shift-workers (28.4%) compared with former shift-workers (13.6%) and daytime workers (12.7%;  $p < .001$ ).

**Conclusions:** Former shift workers were comparable to daytime workers for sleep duration and sleep latency. However, irregularity of the sleep/wake schedule was more frequent in the group of former shift workers (50.2%) compared to daytime workers (38.7%;  $p = .01$ ). Sick leaves in the previous 12 months were more frequent in the shift work (62.1%) and former shift work (45.4%) groups compared with daytime work group (34.8%;  $p < .05$ ).

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#### 422.E

##### LIGHT EXPOSURE PATTERNS IN HEALTHY YOUNG AND OLDER ADULTS

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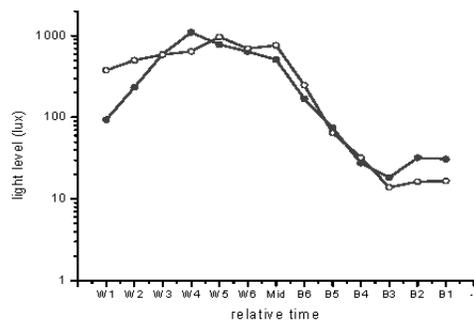
(1) Division of Sleep Medicine, Brigham and Womens Hospital, Boston, MA,

**Introduction:** Exposure to light is the major environmental influence on the mammalian circadian timing system (1). Even light of normal room intensity has been demonstrated to affect the phase of human circadian rhythms (1). The timing of circadian rhythms in older adults has a significantly different phase relationship to the sleep/wake and light/dark cycle than in younger adults (2). However, the mechanism underlying this age related change remains unknown. The present study was carried out to examine whether an age-related difference in light exposure patterns exists. Such a difference might underlie the age-related alteration in the phase relationship between circadian rhythms and the sleep-wake/light-dark cycle.

**Methods:** Healthy volunteers were recruited to wear a wrist light/activity monitor, (Actiwatch-L, Mini-Mitter Company, Bend, Oregon) for at least one week of ambulatory recording while living at home. The subjects also maintained a sleep wake diary during this time. The Actiwatch-L was programmed to record at one-minute intervals. Seven days of light data for each of eighteen older (average age 68.72 years) and seven young (average age 20.29 years) subjects were examined. Each day was reviewed, and hourly averages were created for the six hours following morning awakening and the six hours before bedtime, based on the self-reported wake/bed time from the diary. Daily averages were then compiled, for each subject across a three to seven day period. Then the average data from each subject in the group (older or young) were averaged according to time of day to create a composite waveform for each group.

**Results:** Simple averages show each subject to have similar light exposure patterns across multiple days. Comparing data between the young and older groups shows the patterns between the two age groups to be quite similar (see figure).

Figure 1



Average light exposure patterns of eighteen older (closed symbol) and seven young (open symbol) subjects from wake time to bedtime. The x-axis is divided into hourly segments for the six hours after awakening (W1 to W6), six hours before bedtime (B6 to B1) and the remaining mid day hours (Mid). The y-axis represents light exposure data in lux on a logarithmic scale.

**Conclusions:** Our preliminary analysis of light exposure patterns from healthy young and older subjects living in the community does not suggest large age-related differences. However, given our relatively small sample size, and the large reported seasonal and inter-subject variability in light exposure patterns (3), further studies will need to be carried out to explore the contribution of light exposure patterns to age-related differences in circadian phase and sleep-wake timing.

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#### 423.E

#### INDIRECT PROJECTIONS FROM THE SUPRACHIASMATIC NUCLEUS TO THE MEDIAN PREOPTIC NUCLEUS: A DUAL TRACT-TRACING STUDY IN RAT.

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**Introduction:** The suprachiasmatic nucleus (SCN) generates a circadian signal for virtually all physiological and behavioral functions in mammals, including sleep-wake cycles. However,

how the SCN is linked with the sleep-wake regulatory system is not well understood. We previously showed that the SCN may have indirect projections to the ventrolateral preoptic area (VLPO)[1], which is known to contain sleep-active neurons, and wake-related neuronal groups in the forebrain and brainstem [2], with relays in the medial preoptic area, subparaventricular zone, and dorsomedial and posterior hypothalamic nuclei. Recent evidence suggests that the median preoptic nuclei (MnPO) is yet another sleep-promoting cell group in the preoptic region<sup>3</sup>. The MnPO is also known to be involved in water balance and blood pressure control. Here we examined whether the MnPO might receive SCN output via the previously identified relay nuclei that link the SCN with the VLPO.

**Methods:** In adult male Wistar rats, biotinylated dextran amine (BDA; 10% in saline) or a mixture of BDA (10%) and cholera toxin B subunit (CTB; 0.25 %) were injected into selected hypothalamic regions known to receive SCN efferents. One set of sections was used to visualize anterograde BDA labeling in the MnPO. A second set was used, where applicable, to visualize retrograde CTB labeling in the SCN; some of these sections were also immunostained for vasopressin and neuropeptide Y to delineate the shell and core subdivisions of the SCN, respectively.

**Results:** Tracer injections into the medial preoptic area, caudal part of the dorsomedial hypothalamic nucleus or oral part of the posterior hypothalamic area resulted in moderate to dense anterograde labeling in the MnPO. Injections into the subparaventricular zone or oral part of the dorsomedial nucleus yielded light to moderate labeling. Injections into the dorsal hypothalamic nucleus gave light labeling. The labeling in the MnPO was predominantly ipsilateral. Generally, the labeling in the MnPO was comparable to that in the VLPO when examined in the same animals. Numbers of retrogradely labeled neurons in the SCN shell and core varied depending on the injection site.

**Conclusions:** We identified several possible relay nuclei for the indirect SCN projections to the MnPO. Of these nuclei, the medial preoptic area, the caudal part of the dorsomedial nucleus and the oral part of the posterior hypothalamic area stand out in terms of the number of SCN source neurons and the density of terminal labeling in the MnPO. These intermediary nuclei might mediate SCN output to sleep-active neurons in the MnPO as well as the VLPO, and these pathways may play an important role in the circadian control of sleep-wake states and other physiological functions.

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Research supported by Canadian Institutes of Health Research (MOP-42553) and Fondation Singer-Polignac.

## 424.E

## SELF-REPORTED SLEEP PROBLEMS IN SHORT AND LONG SLEEPERS

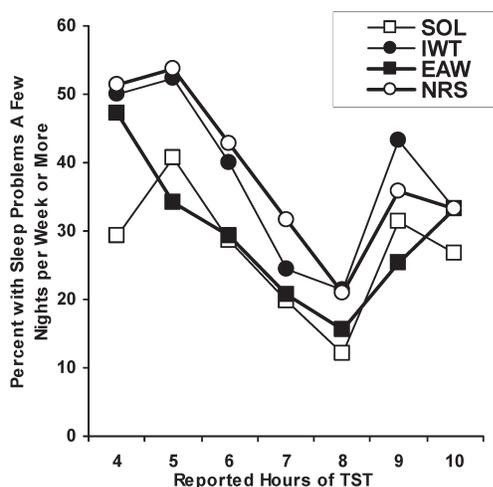
Grandner MA,<sup>1,2</sup> Kripke DF<sup>1,2</sup>

(1) San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, (2) Department of Psychiatry, University of California, San Diego 92093-0667,

**Introduction:** Past research has focused on sleep problems relating to insufficient sleep. Newer findings suggest that sleep problems may also be characteristic of long sleepers (1), indicating a U-shaped distribution of sleep disturbance. The present study evaluated this relationship in the national sample from the Sleep in America Poll conducted by the National Sleep Foundation.

**Methods:** Data were collected as part of the National Sleep Foundation's annual Sleep in America Poll for 2001 (2). The poll sample consisted of adults above age 18. Subjects were interviewed by phone and were asked a number of questions regarding sleep-related habits, ideas and behavior. Among these questions, they were asked for an estimate of total amount of hours slept on an average weekday (TST), as well as how often they experience certain sleep problems, including problems of increased sleep onset latency (SOL), intermittent wake times (IWT), problems with early awakenings (EAW), and problems with nonrestorative sleep (NRS). These sleep problems were rated on a Likert scale (1=Never, 2=Rarely, 3=A few nights a month, 4=A few nights a week, 5=Every night or almost every night). Responses were divided into two groups, those reporting disturbance "a few nights a month" or less and those reporting disturbance "a few nights a week" or more. A chi square analysis was performed for each reported problem type, relating the complaint to TST, measured in hours. Due to unreported information, analyses of SOL, IWT, EAW and NRS included 961, 960, 962 and 959 adults, respectively.

Figure 1



**Results:** Chi square analyses evaluated frequency of sleep complaints across reported hours of TST for SOL ( $\chi^2=42.562$ ), IWT ( $\chi^2=52.866$ ), EAW ( $\chi^2=31.071$ ) and NRS ( $\chi^2=46.704$ ). All p values were  $<0.0005$ , indicating that sleep problems were not consistent across all values of reported TST. Figure 1 illustrates these values and shows a U-shaped curve for each of the four complaints, indicating that for both short and long sleepers, sleep complaints are more prevalent than for those that sleep approximately 7 or 8 hours.

**Conclusions:** These results indicate that sleep problems are associated with long sleep in addition to short sleep. As little research has investigated problems associated with longer sleep, the causal mechanisms of this relationship are not known. It is demonstrated, however, that this relationship is maintained across a wide range of sleep complaints. A similar U-shaped distribution is noted for mortality, upon prospective follow-up (1). These data question the assumption that more sleep is always better than less, and they call for additional attention to the problems of the long sleeper. Further research may examine this relationship with respect to the efficacy of sleep restriction therapies, and disorders that are associated with both increased sleep time and increased sleep disturbance (e.g., depression and sleep apnea).

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**Research supported by The National Sleep Foundation, 1522 K Street, NW, Suite 500, Washington, DC 20005, kindly supplied the raw polling data used for these analyses. Supported by NIH AG12364 and by AG15763.**

## 425.E

## CIRCADIAN RHYTHMS OF CORE BODY TEMPERATURE AND PLASMA CORTISOL IN ANOVULATORY WOMEN.

Grundler CS,<sup>1</sup> Rogacz S,<sup>1</sup> Duffy JF<sup>1</sup>

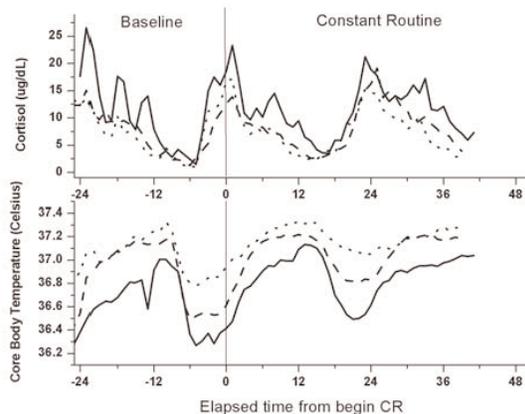
(1) Division of Sleep Medicine, Brigham and Women's Hospital, Boston, MA

**Introduction:** We carried out a study to examine circadian rhythms in women of reproductive age at different menstrual cycle phases (1). As part of the post-hoc analysis of those data, we identified two subjects who did not ovulate. Here we present preliminary analysis of their data.

**Methods:** Our original group included thirteen women who were not taking oral contraceptives and who had self-reported regular menstrual cycles. Subjects were studied more than once so as to record them at different phases of the menstrual cycle. Before study the women recorded basal body temperature and used a urinary LH test kit. Each study had two baseline days followed by a 40-hour constant routine [CR (2)]. Twice each day during the study, serum samples for estradiol, luteinizing hormone (LH), and progesterone were collected. Light levels during the wake episodes were ~150 lux.

Throughout the study core body temperature (CBT) was recorded at 1-minute intervals with a rectal thermistor. Blood was sampled ~three times per hour. Temperature data for each group were averaged with respect to wake time on the CR. Cortisol data were averaged per hour for each subject before averaging across subjects.

**Figure 1**



Average cortisol and temperature rhythms during baseline day and constant routine for anovulatory subjects (solid line), follicular subjects (long dashes and luteal subject (short dashes). Elapsed time begins 24-hours before the start of the 40 hour constant routine.

**Results:** Post-hoc analysis of the twice daily hormone samples identified two women who had LH surges but whose luteal phase progesterone levels indicated they did not ovulate. Mean (CBT) on the baseline day was significantly lower in the anovulatory women than in women in the follicular [ $37.02 \pm 0.12^\circ\text{C}$ ,  $p < 0.03$ ], or luteal phase [ $36.81 \pm 0.15^\circ\text{C}$  vs.  $37.18 \pm 0.13^\circ\text{C}$ ,  $p < 0.004$ ], and mean CBT on the CR was also significantly lower in the anovulatory women compared with the follicular [ $36.85 \pm 0.15^\circ\text{C}$  vs.  $37.06 \pm 0.12^\circ\text{C}$ ,  $p < 0.03$ ], and luteal phase [ $36.85 \pm 0.15^\circ\text{C}$  vs.  $37.18 \pm 0.11^\circ\text{C}$ ,  $p < 0.01$ ; see Figure]. Plasma cortisol levels were significantly higher in the anovulatory women than in the follicular phase women on the baseline day ( $9.76 \pm 2.02$  mg/dL vs.  $6.90 \pm 1.45$  mg/dL,  $p < 0.04$ ), but did not reach significance when compared with luteal phase women ( $9.76 \pm 2.02$  mg/dL vs.  $7.05 \pm 1.68$  mg/dL,  $p = 0.085$ ). Mean cortisol on the CR was significantly higher in the anovulatory women than in the luteal phase women ( $10.75 \pm 1.81$  mg/dL vs.  $7.60 \pm 1.53$  mg/dL,  $p < 0.05$ ), but did not reach significance when compared to the follicular phase women [ $10.75 \pm 1.81$  mg/dL vs.  $8.23 \pm 2.20$  mg/dL,  $p = 0.095$ ], see Figure]. Average cortisol and temperature rhythms during baseline day and constant routine for anovulatory subjects (solid line), follicular subjects (long dashes), and luteal subject (short dashes). Elapsed time begins 24-hours before the start of the 40 hour constant routine.

**Conclusions:** Our preliminary analysis of data from these two women during anovulatory menstrual cycles indicates that the daily variations of cortisol and core body temperature may be altered during anovulatory menstrual cycles. Additional studies are needed to determine causation.

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#### 426.E

#### SUBJECTIVE ADAPTATION DURING CHRONIC SLEEP RESTRICTION AT AN ADVERSE CIRCADIAN PHASE

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**Introduction:** Previous studies have described the course of physiological and psychological adaptation that takes place in response to chronic sleep deprivation (1). Most studies, however, have only examined the effects of 4 days or less of sleep restriction, with sleep typically placed nocturnally (normal circadian phase). Many people (e.g., shiftworkers) commonly experience chronically reduced sleep (quality and quantity) due to sleeping during the day (adverse circadian time). The present study aimed to examine subjective sleepiness during 3 doses of chronic (10d) sleep restriction (4h, 6h, 8h TIB) with sleep placed at an adverse circadian phase (i.e. diurnally).

**Methods:** Forty-four healthy subjects (29m; 15f; aged 21-44y) completed this 15-day (14-night) in-laboratory protocol. Following one night of baseline sleep (2330h-0730h) subjects remained awake for 28 hours, followed by an 8h diurnal sleep period (1130h-1930h). Subjects were randomly assigned to a diurnal sleep restriction condition (4h: 1530h-1930h; 6h: 1330h-1930h; 8h: 1130h-1930h) that was maintained for 10 consecutive days, followed by 2 recovery days with a 10h nocturnal sleep period (2330h-0930h). Subjects remained in the laboratory throughout the protocol, with light levels  $< 50$ lx and ambient temperature at  $24^\circ\text{C} \pm 1^\circ\text{C}$ . Every 2 hours during wakefulness subjects completed a 35-min neurobehavioral assessment battery (NAB), containing both objective tests of neurobehavioral performance and subjective measures of sleepiness (e.g. Karolinska sleepiness scale [KSS], Stanford Sleepiness Scale [SSS], Visual Analog Scale [VAS], Profile of Mood States [POMF]), mood, and effort (Subjective Effort Rating [SEQ]). Salivary melatonin and core body temperature were measured to assess changes in the circadian system. Polysomnographic recordings of sleep and wake periods were collected.

**Results:** Analyses of all scales (POMF, SSS, KSS, VAS) demonstrated initial increases in subjective sleepiness levels during the sleep restriction, relative to baseline for all these conditions. Sleepiness using the POMF demonstrated a significantly greater level of fatigue for the 4h condition relative to the 6 and 8h conditions ( $p = 0.0028$ ). Analysis of KSS ratings illustrated a trend for different levels of subjective sleepiness among conditions ( $p = 0.0785$ ). SSS and VAS ratings demon-

strated no significant difference among conditions.

**Conclusions:** These findings illustrate discrepancies between ratings on subjective sleepiness scales, indicating the difficulty in accurately defining and assessing subjective sleepiness. Such differences could be attributed to the different ways in which these scales ask subjects to assess their sleepiness. However, assessment of melatonin will allow comparisons between these subjects' assessments of their subjective sleepiness and an objective measure of circadian adaptation. Such comparisons may help determine the most sensitive subjective scale used.

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#### 427.E

##### MELATONIN PROMOTES SLEEP AND MEMORY FUNCTION THROUGH cAMP-DEPENDENT SIGNALING PATHWAY.

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**Introduction:** Our recent study has shown that acute daytime melatonin treatment can promote sleep-like state in zebrafish larvae, significantly reducing their locomotor activity and increasing arousal threshold (1). This effect is mediated via specific melatonin receptors, known to affect cAMP-dependent signaling pathway. We now present the results of our studies on the effects of acute treatment with melatonin and/or melatonin receptor agonists and antagonists on sleep-like state and memory function in larval zebrafish.

**Methods:** Daytime and nighttime locomotor activity was continuously monitored using high throughput image analysis system, FishWatch (1). The data were visually inspected using the SleepWatch program (MiniMitter, Sunriver, OR) and imported into StatView (SAS Institute, Inc., NC) for analysis. The escape test behavior was assessed using T-maze. Each animal was tested 3 times/day for 8 consecutive days. Treatments (melatonin, melatonin receptor analogs or forskolin) were administered in the medium. cAMP levels were measured using RIA (Amersham, UK) in larvae collected at different times of day or at intervals following treatment administration.

**Results:** A 12-hour overnight treatment with melatonin (100 nM in the medium), followed by a 3-hour washout period, augments zebrafish daytime exploratory activity in the T-maze ( $p=0.041$ ) and increases a number of correct choices in the escape test ( $p=0.049$ ,  $n=120$ ). Both sleep and memory-related effects of melatonin in zebrafish are mediated via specific melatonin receptors. They are produced by specific melatonin receptor agonists [(+) AMMTC and (-) AMMTC] and coun-

teracted by specific melatonin receptor antagonists (luzindole, 4P-PDOT, K185). We also show that cAMP levels in zebrafish larvae undergo a circadian variation, with lower levels observed at nighttime. An acute effect of melatonin treatment, induction of sleep-like behavior, is associated with a reduction of cAMP levels and counteracted by forskolin, a direct activator of adenylate cyclase. In contrast, facilitation of learning (increase in correct choices in the escape test) following prolonged melatonin treatment is associated with an increase in cAMP levels and augmentation of the amplitude of circadian rhythm of activity.

**Conclusions:** These results suggest that circadian alterations in cAMP levels in larval zebrafish are involved in the regulation of sleep and wake behaviors. Inhibition of cAMP levels has a sleep-promoting effect, while augmentation of cAMP production is associated with improved daytime memory function. Melatonin treatment has a dual effect on cAMP levels. The pineal hormone can acutely inhibit cAMP levels, promoting a sleep-like state. In contrast a prolonged overnight melatonin treatment (followed by a washout) results in increased cAMP levels, which appear to facilitate learning in zebrafish.

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#### 428.G

##### EEG SPECTRAL CHANGES DURING PERIPHERAL ARTERIAL TONOMETRY (PAT) ATTENUATION EVENTS IN 6-YEAR OLD CHILDREN.

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**Introduction:** A novel noninvasive probe developed for measurement of pulse arterial tonometry (PAT) has revealed that the enhancements in sympathetic nervous system tone can be reliably identified with PAT technology in adults (1). Bursts of alpha activity corresponding to the EEG arousals coincide with PAT signal attenuation, which have been proposed as a new way of detecting subclinical arousals, since the latter are not readily identified using conventional physiological measures as used in sleep studies. We hypothesized that changes in the EEG spectra occur during episodes of PAT attenuation in children.

**Methods:** Five healthy children underwent standard nocturnal polysomnography at the pediatric sleep laboratory with PAT signal (Itamar Medical Ltd., Israel) being simultaneously recorded throughout the night. A total of 63 PAT attenuations (PATa) that were not associated with visually recognizable EEG or behavioral arousals were selected from these recordings for analysis. EEG epochs of 2-sec duration corresponding to PATa were subjected to Fast Fourier Transformation (FFT) within delta, alpha, sigma and beta frequencies using a commercially available software routine (Luna, Stellate Systems, Montreal, Canada). EEG signals from C3, C4, Fp1, Fp2, O1, O2, T3, and T4 leads for a period of <6sec preceding PATa

(Pre), during PATa (PAT) and following PATa (Post) along with baseline (Base) intervals were analyzed. Mean of spectral powers for each frequency domain corresponding to Pre, PAT, Post and Base were compared by ANOVA with two-tailed t-tests. A p value <0.05 was considered statistically significant.

**Results:** Significant differences were found between Pre, PAT and Post intervals in most frequency domains. However, frequency domain and topographic location of changes in spectral power during PATa events were dependent on sleep stage. Indeed, differences were seen in all EEG leads during stage 2 sleep across all frequencies. In stage 4, only the central leads in the alpha and sigma range showed significant changes. REM sleep was characterized by spectral changes that occurred over the frontal areas in the delta and sigma range.

**Conclusions:** PAT events in children that are not associated with EEG or behavioral arousals demonstrated significant changes in EEG power spectra that were consistently observed across sleep stages, but varied in their location according to sleep stage. We speculate that these dynamic EEG changes may underlie autonomic responses that are not detected by traditional methods.

**References:**

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- (2) Lavie P, Shlitter A, Sheffy J, Schnall RP. Peripheral arterial tonometry: A novel and sensitive non-invasive monitor of brief arousals during sleep. *IMAJ* 2000;2:246-247.

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### 429.G

#### USE OF MELATONIN IN CHILDREN WITH INSOMNIA.

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**Introduction:** Melatonin has been widely studied and used for the treatment of various sleep disturbances in adults. In children, melatonin has been advocated for the management of sleep disturbances in patients with neurodevelopmental disabilities, visual impairment, epilepsy with abnormal sleep patterns, as well as in adolescents with delayed sleep-phase syndrome (1-3). Sleep patterns were reported to improve in these groups of children with no significant adverse reactions observed. The goal of the present study was to investigate the clinical response to melatonin among children with sleep initiation and sleep maintenance problems who were referred to the pediatric sleep medicine center.

**Methods:** The medical records of 30 (24 male) children and adolescents, ages 2-18 years (mean:9.3± 4.4) who were prescribed fast-release Melatonin after consultation at the pediatric sleep medicine clinic were examined. Parental reports in the form of sleep logs and clinical follow-up interviews were used for the effectiveness assessments.

**Results:** 24 children were diagnosed with sleep initiation

problems, 9 with frequent awakenings, and 3 children with delayed sleep-phase syndrome. Of note, 24 (80%) children had been previously diagnosed with another psychiatric disorder: 13 had a diagnosis of ADHD, 7 were diagnosed with an anxiety disorder, 3 were diagnosed with mood disturbances and 3 children had developmental delay. Only one child was diagnosed with periodic limb movement disorder and a mild degree of sleep apnea. 14 (46%) children were taking psychotropic medications (psychostimulant, antidepressant or mood stabilizer) at the time they were prescribed melatonin. 27 (90%) children showed improvement in the initiation and maintenance of their sleep according to the parental reports. An average effective dose of melatonin was 2.0±1.2 mg (0.3 to 6mg) administered 1 hour prior to bedtime. All children sustained a positive response at follow-up (mean: 2.2 months). There were no side effects reported by the parents, and melatonin seemed to be very well tolerated by the children.

**Conclusions:** In this uncontrolled study, melatonin appears to be effective in the treatment of chronic sleep initiation and maintenance problems in children without developmental disabilities. Melatonin can be potentially used as an adjuvant for children with ADHD and anxiety/mood disorders who present with significant sleep delay or frequent nocturnal awakenings as well as healthy children suffering from persistent sleep-wake cycle disturbances. However, more extensive research with clinical trials is needed before the clinical usefulness of melatonin can be fully defined in the pediatric setting.

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### 430.G

#### PULSE ARTERIAL TONOMETRY (PAT) SIGNAL ATTENUATION EVENTS AND EEG AROUSALS IN CHILDREN: PRELIMINARY OBSERVATIONS.

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**Introduction:** Overnight polysomnographic studies are considered the gold standard for the diagnosis of sleep disorders in children. Current methods employed for the scoring of arousals in children rely on criteria designed for adults and may therefore not be sensitive in children. In fact, substantial dynamic changes occur in EEG spectra during respiratory events in children without any visually recognizable change in the raw EEG. PAT is a noninvasive technique (finger mounted probe) (2) that allows for determination of moment-to-

moment changes in peripheral arterial bed vasomotor tone. In adults, PAT is exquisitely sensitive to changes in sympathetic autonomic nervous system tone, primarily those mediated by alpha sympathetic innervation. As such, arousals from sleep as defined by bursts of alpha and beta EEG frequencies were identified using PAT recordings in adult subjects (3). Our objective was to determine whether PAT signal attenuation during sleep corresponds to visually recognizable EEG arousals in children.

**Methods:** First grade children were recruited from schools within the Public School system of Louisville metropolitan area. All children underwent a standard polysomnographic evaluation in the sleep laboratory using a digital recording system. A PAT sensor was applied to the index finger and both raw and filtered signals were acquired using the digital record. Scoring of variables during sleep was performed blindly for PAT events and sleep record events using standard criteria. Arousals were divided into 2 subtypes: spontaneous arousals and respiratory arousals, and the arousal index was calculated. PAT events were defined as attenuations from baseline of >50%, and the PAT index was derived.

**Results:** 100 children (47 male) with no objective evidence of sleep-disordered breathing (SDB) were studied (mean age: 6.5 ± 0.8 years). TST was 7.9 ± 1.1 hours, and PAT recording time was 6.9 ± 1.7 hours. Sleep stage distribution was normal. Arousal index was 9.4 ± 3.5 and the PAT index was 9.5 ± 9.5. Scatterplot of PAT and Arousal indices revealed no significant correlation between these 2 measurements (r=0.06). We further examined 8 children with SDB (OAHl>5/hr) and PAT index appears to correlate with respiratory-related arousals in these children (r=0.70).

**Conclusions:** PAT events and EEG arousals may represent different neural activation patterns and their occurrence does not overlap in normal children. However, preliminary data supports the concept that autonomic arousals induced by obstructive respiratory events are recognizable using PAT technology in children with obstructive sleep apnea.

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**431.G**

**THE RELATIONSHIP BETWEEN PARENTAL INVOLVEMENT AND BEHAVIORAL SLEEP QUALITY IN PRESCHOOL AGED CHILDREN**

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**Introduction:** While there is evidence that child factors (e.g., temperament, medication status, health) are related to children’s sleep, the role of parent factors has received less attention (1). For preschool children, parental involvement in sleep-related practices may be especially important. Studies examining various sleep management techniques with children have cited the need for further investigation of parental involvement. This study investigated the following questions: (a) What is the level of parental involvement? (b) What is the nature of parental involvement? (c) What is the significance of parental involvement?

**Methods:** Participants were 111 non-clinical children (59 male, 52 female), ages 3 to 5 years. Sixty-eight percent of the children were Caucasian, and 31.5 % were African American and Hispanic. Parents completed a general information questionnaire, the Children’s Sleep Wake Scale (CSWS) and the Caretaker Sleep Participation Scale (CSPS). The CSPS assesses parental involvement along three sleep dimensions: bedtime, nighttime, and morning time. First, parents rated their usual level of involvement on a five-point likert scale, (1 = “Very Little” to 5 = “Very Much”). Items were summed across the three dimensions to obtain total level of involvement. Next, parents endorsed all practices in which they usually participated with their child (e.g., tucking in, bribing) for each of the three sleep dimensions. Practices were divided into “good” (recommended) and “poor” (not recommended) practices, based on anecdotal and clinical evidence. Finally, parents rated their usual affect during the parent-child interaction with a five-point faces scale (1 = “Very Happy” to 5 = “Very Unhappy”). Items were summed to obtain total affect score. The CSWS measured total sleep quality (2).

**Table 1**

**Percent of Parents Reporting Good Sleep Practices**

Item	BT	NT	MT
Bathing	64.0	1.8	9.0
Checking on Child	30.6	82.9	22.5
Cuddling	73.0	42.3	32.4
Making sure child has favorite toy, etc.	73.4	24.3	6.3
Playing Quiet Games	28.8	8.1	8.1
Praying	87.4	4.5	6.3
Reading a Story	82.0	9.0	8.1
Singing	42.3	14.4	18.9
Tucking In	80.2	7.2	.9

Note: BT = Bedtime, NT = Night Time, MT = Morning Time

**Results:** Twenty-eight percent of parents reported little or very little involvement, 43% reported some involvement, and 29% reported much or very much involvement. Good and poor sleep practices reported by parents are listed in Tables 1 and 2. Parents with higher levels of total sleep involvement (a) had children with lower total sleep quality (r = -.21, p < .05), (b) reported a greater number of poor sleep practices across the three sleep dimensions (r = .23, p < .05), and (c) rated their parent-child interactions more negatively (r = -.27, p < .01).

Parents who rated their parent-child interactions more positively reported a fewer number of poor sleep practices across the three sleep dimensions ( $r = -.32, p < .01$ ), and had children with higher total sleep quality ( $r = .27, p < .01$ ).

Table 2

Percent of Parents Reporting Poor Sleep Practices

Item	BT	NT	MT
Bribing	21.6	1.8	8.1
Begging	21.6	5.4	7.2
Going into Parent's Bed	17.1	43.2	18.9
Horseplaying	27.9	2.7	30.6
Punishing	19.8	1.8	6.3
Spanking	23.4	.9	6.3
Threatening	42.3	3.6	7.2
Turning on TV	25.2	9.9	43.2
Yelling	15.3	9.0	9.9

Note: BT = Bedtime; NT = Night Time; MT = Morning Time

**Conclusions:** Parents reported a moderate level of involvement in their preschool children's sleep. This involvement predominantly consisted of recommended practices thought to facilitate sleep (e.g., reading a story, cuddling). Interestingly however, increased parental involvement was related to decreased quality of sleep. This may be due to children with poor sleep needing more parental attention, but the basis of this relationship needs further exploration.

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**432.G**

**SLEEP HABITS AND SLEEP DISORDERS IN PRESCHOOL CHILDREN**

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**Introduction:** Few studies have been published about sleep habits and the prevalence of sleep disorders in preschool children. Latin American culture may play a role influencing bedtime, napping and time of waking. This is also of particular importance in residents of big cities whom may be sleep deprived because of the long distances parents must travel. The objective of this work was to describe sleep habits and estimate the prevalence of disorders sleep in preschool children.

**Methods:** We investigated the sleep habits and the associated sleep disorders in children from 2 to 6 years old recruited from 20 nursery schools located in Mexico City. Data were obtained from a Respiratory and Sleep Habits Questionnaire completed by a parent. All children had anthropometrics measurements.

**Results:** A total of 2240 children (51% males) were recruited. The participation rate was 85%. Regarding sleep habits the average time to go to bed was 9:04 p.m. ± 115 minutes, and wake up time was 6.07 a.m. ± 120 minutes. The reported nighttime sleep was 8.03 hours ± 1.96 hours. Majority of the children (70%) had one nap 1-2 times per week, with a length average of 2.41 hours ± 1.6 hours. The quality of sleep based on parents perception was reported as good in 77.8%, mediocre in 21% and bad in 1%. Resistance to sleep was reported in 306 children (13.2 %). Prevalence of sleep disorders were: habitual snoring (7%), nocturnal enuresis in 37 cases (1.58 %); nightmares in 3.35 %; restless sleep (defined as tossing and turning + falling off bed + daytime somnolence): 89 cases (2 %), leg movements: 317 (13.5%); sweating: 798 (34.1 %), sleep terrors: 85 children (1.96 %) and sleepwalking: 15 cases (0.34 %). Daytime sleepiness in our population was reported in 474 children (20.2%). When analyzing the possible causes for this symptom we found a significant association with obesity ( $p < 0.005$ ), leg movements ( $p: 0.018$ ), tossing and turning ( $p < 0.001$ ). The perceived bad or mediocre quality of sleep correlated best with snoring, excessive tossing and turning, sweating, sleepwalking and nocturnal enuresis ( $p < 0.001$ ). All these sleep disorders had a linear association with daytime symptoms: tiredness, irritability, headache and sleepiness ( $p < 0.001$ ).

**Conclusions:** Total daily sleep was enough for our group, however naps were frequent and long for 2-6 year old children. Parent's perception of a poor sleep quality in their children correlates with the presence of sleep disorders such as snoring, leg movements, sweating, sleepwalking and nocturnal enuresis, which in turn correlated with daytime symptoms (tiredness, irritability, headache and sleepiness). The prevalence of the sleep disorders in our children is lower to what has been reported for other groups.

**433.G**

**EPIDEMIOLOGICAL SURVEY OF PATIENTS WITH CONGENITAL CENTRAL HYPOVENTILATION SYNDROME: A PRELIMINARY REPORT.**

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**Introduction:** Congenital central hypoventilation syndrome (CCHS) is a rare lifelong disorder of respiratory control characterized by near-absent central chemosensitivity and inappropriately low ventilation, particularly during NREM sleep. Recent evidence suggests that the clinical manifestations of CCHS may in fact represent a large spectrum of neural crest dysfunction (1). Traditionally, CCHS patients would be managed by mechanical ventilation via a tracheostomy. However in recent years, transition to noninvasive ventilatory support

(NIPPV) during sleep has been successfully achieved (2). Thus, we conducted a survey of a large number of CCHS families to obtain updated information on the demographic characteristics and the ventilatory support strategies currently being applied in the homes of children with CCHS.

**Methods:** A confidential questionnaire was mailed to the families registered with various CCHS Family Networks in the US and Europe. Questionnaire items primarily addressed demographics, associated medical conditions, mode of ventilatory support in the past and in the present, and methods of cardiorespiratory monitoring. Data were tabulated and assessed using descriptive statistics.

**Results:** Thus far, 79 questionnaires have been received: 15% of the children are < 5 years of age, 44% are 5-12 years old, and 41% are >13 years old; 55.7% are female. Hirschprung's disease is present in 15 children (19%), and ocular problems are frequent (48%). Hypotonia (34%), syncope (34%), gastroesophageal reflux (19%) are frequent associated conditions. Of note, seizure activity was reported in 36.5%, with 13% receiving anti-seizure medication. In addition, cardiac arrhythmias occurred in 26% and cardiac pacemakers were required in 8%. Developmental delays, behavioral or learning problems occur in 49%. Hypothyroidism (3.8%), hypoglycemia (7.6%), and growth hormone deficiency (1.3%) were reported infrequently. The need for physician visits and hospital admissions was greater in younger patients. Only 10% of children require 24-hour ventilatory support, with the remainder are being ventilated at night only (83%), and during daytime naps as well (7%). 48 patients currently receive mechanical ventilation via a tracheostomy (61%), while an additional 22 (27.8) receive positive pressure ventilation via a nasal mask using either a conventional ventilator (n=9) or BiPAP (n=13). The youngest patient on NIPPV is 2 years old. Five patients undergo ventilatory support with diaphragmatic pacers, and 2 are on negative pressure ventilation. The vast majority of children have oxygen saturation monitors at home (88%), 56% use end-tidal carbon dioxide monitors, and only 14% currently use a cardiorespiratory monitor. 62% have a back-up ventilator, 72% have access to supplemental oxygen at home, 61% have a suction machine, and 44% have a nebulizer device.

**Conclusions:** CCHS is a complex condition of varying severity that affects multiple organ systems, and requires multidisciplinary comprehensive care. Transition to NIPPV is occurring more frequently and at younger ages. Institution of a national registry for this disorder is likely to improve the quality and access to care for these children and their families.

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### 434.G

#### CONTRIBUTION OF AUTONOMIC NERVOUS SYSTEM TO SUDDEN DEATH DURING SLEEP IN INFANTS

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**Introduction:** Future SIDS victims had a dysregulation of cardiac autonomic controls, fewer body movements, less cardiac autonomic reactivity after obstructive apneas (1). Environmental risk factors for SIDS, such as sleeping prone, prenatal smoking or high environmental temperature enhance a deficiency in autonomic and arousal controls. Changes in blood pressure (BP) were measured following auditory stimuli in the prone and the supine position to study the correlation between arousal from sleep and autonomic responses.

**Methods:** Two newborns born at term, 2 infants and 4 children were recorded polygraphically during one night, while sleeping in the prone and the supine position. They were exposed to white noises of increasing intensities during both REM and NREM sleep. BP was measured by Finapres in the children and by Pulse Transient Time (PTT) in the infants and newborns. PTT measured the interval from the ECG R-wave until the arrival of the pulse pressure wave at the periphery. Drops in PTT reflect a rise in BP. Heart rate (HR), BP and PTT were studied 10 sec. before and after auditory challenges. Cortical arousal was scored in the presence of EEG changes in frequency or amplitude, accompanied by changes in breathing, heart rate and/or body movement.

**Results:** Basal systolic BP was lower ( $p < .001$ ) and PTT was higher ( $p = .008$ ) in the prone than in the supine position. Baroreceptor sensibility was lower in prone position ( $p = .018$ ). 177 stimuli were administered. HR and BP responses to the auditory stimulus were biphasic with an increase followed by a decrease in children. PTT values varied inversely in infants. Rises in systolic BP and HR appeared with the onset of cortical arousals. BP response increased and PTT fell according to the intensity of decibels (respectively  $r = 0.50$   $p < .001$  and  $r = 0.49$   $p < .001$ ). Auditory thresholds were lower for autonomic responses than for cortical arousals in infants ( $p = .012$ ) and in children ( $p = .016$ ). During cortical arousals, increases in systolic BP ( $p = .024$ ) and decreases in PTT ( $p = .006$ ) were smaller in the prone than in the supine position, independently of sleep stage.

**Conclusions:** Children and infants sleeping prone had lower basal BP than when sleeping supine (2). In response to auditory stimulus, a biphasic response in BP was already found in infants (3). This finding could result from involvement of active brainstem centers regulating arousals. Changes in autonomic balance or decreases in afferent impulses from the baroreceptors could result in a reduced reactivity of the brain-

stem center and a reduced arousal from sleep.

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**435.G**

**COGNITIVE DYSFUNCTION IN 225 CHILDREN 7 TO 10 YEARS OLD WITH SLEEP DISORDERS.**

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**Introduction:** Cognitive function and behavior may be highly affected by sleep disorders (SD) as suggested clinically or by some experiments where the number of arousals was increased by auditory stimulation. We have shown that poor performance in school for 7 to 10 years old children in Brazilian schools is associated with SD and it is also demonstrated that treating disrupted sleep caused by adenoid/tonsils hypertrophy lead to an improvement in daily symptoms like hyperactivity and probably school performance. Because of a lacking of data assessing the relationship between SD and cognitive dysfunction (CD) in our country we start a research in a large sample of children from Brazilian elementary schools using an easier approach like Bender Test (BT). Objective: To study the association between SD and cognitive function in a sample of 7 to 10 years old children.

**Methods:** We studied 225 children from 8 elementary schools of São Paulo, Brazil. Each elementary school that participated in this research received consent forms to be signed by the principal and parents. One hundred and nine children were identified as having SD and 116 children were signed as having normal sleep (control group). To classify the children in those two groups we have used a SD questionnaire and the SD taken in account were: disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep wake transition disorders, disorders of excessive somnolence. To assess presence or absence of CD in the SD and control groups, two independent investigators blinded for the sleep variables applied the BT. We called CD in the BT if the subject had a score of mistakes above expected for his/her age. School failed children were excluded. There were no differences regarding age, gender, social and economic levels for both groups. We compared the SD and control groups for the presence or absence of CD according to gender, ages (7 to 10 years old), and grades (1st to 4th).

**Results:** There were no significant differences in CD regarding to the ages for boys and girls. We observed a trend for greater number of CD in the group of 7 years old SD girls

( $p=0.17$ ) and 10 years old SD boys ( $p=0.07$ ). Second ( $p=0.05$ ) and 4th ( $p=0.03$ ) grades children from SD group had more CD compared to the control group. When we take boys and girls of the 2nd and 4th grades separately we found out that just the boys were responsible for that difference ( $p < 0.05$ ). Discussion: The most striking result of this ongoing research is that in the Brazilian elementary schools we have studied until now, boys with SD are more likely to have CD disorders. Ten years old boys and those in the 4th grade are at risk for cognitive disorders. Ten years old SD boys had just a trend to CD, but there is a clear impairment in the expected performance for the grade, because the BT allows to different normal and abnormal results whether we consider ages or grades. We do not have any reasonable explanation at this time for why girls with SD are spared and also, whether a particular SD is more allowed to produce CD, but we suspect that disordered breathing will have a major weight in the explanation of our findings.

**Conclusions:** Girls with SD are apparently spared regarding to CD, and compared to the control group the association SD-CD was more frequent in boys of the 2nd and 4th grades.

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**436.G**

**A MEASURE OF CHILDREN'S SLEEP HYGIENE**

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**Introduction:** Sleep hygiene has been defined as a number of behavioral practices that can influence sleep initiation and maintenance (1). Examples of these practices for children include having a calm bedtime routine, keeping a stable bedtime and wake time, and avoiding caffeine consumption. While there is clinical evidence that such practices are important, there are no comprehensive measures of sleep hygiene for young children. This report provides developmental procedures and reliability data for the Children's Sleep Hygiene Scale (CSHS), a parental-report measure intended for use with preschool and early school-aged children. This scale requires caretakers to answer questions about sleep hygiene practices using a 6-point rating scale (Never, Once in Awhile, Sometimes, Quite Often, Frequently-if not Always, and Always). The mean of the items are computed to yield a total sleep hygiene scale score, with higher scores indicating better sleep hygiene.

**Methods:** During phase I of this project, content areas were defined and 24 items were derived from the existing sleep literature (2). Directions and items were written at or below a six-grade reading level. Pediatric sleep experts then reviewed

the items, which resulted in item deletion, addition, or revision. During Phase II, parents were recruited from local shopping malls, day-care centers, community activities, and via the World Wide Web. Data were collected on 246 children (130 male, 116 female), ages 2 to 8 years (mean = 4.07, SD = 1.47). The sample was 75% Caucasian, 19% African-American, and 6% Asian American, Hispanic, and multiracial. Parents were asked to complete a general demographic questionnaire and the CSHS. Seventy-one percent of the sample completed the questionnaire in person and the remaining 29% completed it via the World Wide Web.

**Results:** Item means, standard deviations, and corrected item-total correlations are reported in Table 1. Initial computation of reliability (Cronbach's alpha) yielded a value of  $\alpha = 0.74$  for all 24 items. Item analysis resulted in the deletion of 7 items due to low item-total correlations and skewed distribution shapes. Coefficient alpha for the remaining 17 items was  $\alpha = 0.76$ . Participants who completed the CSHS via the World Wide Web scored 1/3 to a 1/2 of a standard deviation higher on 14 of the 17 items.

**Table 1**

Item means, standard deviations, and corrected item-total correlations			
Item	Mean	SD	Item-Total Correlation
Naps 4 hours before bedtime	5.15	1.30	.2339
Caffeine 4 hours before bedtime	4.54	1.39	.3382
Does relaxing things before bedtime	3.82	1.43	.3144
Drinks lots of liquids before bedtime	4.07	1.55	.3259
Plays rough before bedtime	3.68	1.57	.4860
Does things that are alerting	3.21	1.61	.3986
Goes to bed about the same time	4.46	1.30	.3636
Complains about being hungry at bedtime	4.58	1.44	.2782
Does things in bed that keep him/her awake	4.39	1.39	.2678
Goes to bed in the same place	4.91	1.37	.3211
Goes to bed feeling upset	5.17	1.02	.3276
Goes to bed with worries*	5.56	.81	.1926
Sleeps in a darkened room*	3.93	2.12	.1092
Sleep is room that is too hot or too cold*	5.46	1.21	.0539
Sleeps in room where there are loud noises*	5.69	.89	.1488
Sleeps alone	3.55	2.05	.2713
Sleeps in a room that is "stuffy"	5.76	.67	.1846
Sleep in a bed that is comfortable*	5.76	.66	.2468
Sleep in home where someone smokes*	5.33	1.53	.1830
Has a calming bedtime routine	4.27	1.44	.4039
Uses bed for things other than sleep	4.07	1.77	.3754
Put to bed after falling asleep	4.64	1.36	.2676
Stays up past usual bedtime	4.14	1.23	.3933
Gets out of bed at same time in morning	4.64	1.13	.2847

\* Item removed

**Conclusions:** The internal consistency of the CSHS is adequate for studies of sleep hygiene in young children. In phase III, items related to the sleep environment will be revised and additional data will be collected for a factor analytic study to assess whether sleep hygiene, as measured by the CSHS, is a multi-dimensional construct. Further evaluation of the differences between community and World Wide Web samples is needed.

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**437.G**

**RELIABILITY AND VALIDITY OF THE CHILDREN'S SLEEP QUALITY ASSESSMENT QUESTIONNAIRE (CSAQ)**

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**Introduction:** The CSAQ was developed to provide a subjective analysis of pre-adolescent and adolescent children's sleep quality that could be used to reliably predict the presence of sleep disorders. The CSAQ is designed to allow parents to rate their child's symptoms on a four-point Likert scale based on the frequency of each symptom. It consists of five subscales: Breathing Disorders (BD), Periodic Limb Movements (PLM), Parasomnias (PS), Daytime Symptoms (DS), and Sleep Quality (SQ). This abstract describes the construction and empirical analysis of the CSAQ.

**Methods:** Questionnaires were completed by parents of children with attention-deficit/hyperactivity disorder (ADHD) and normal controls in part of an ongoing study into the relationship between ADHD and sleep (n= 54, 39 males, 15 females). Children ranged in age from 6 to 14 (mean = 10.09). Children with ADHD were referred from a developmental pediatrician. They were not selected on the basis of sleep complaints or symptoms of sleep disorders, nor did they have any comorbid psychological, developmental, or neurological disorders. Children in the control group had no history of neurological, psychiatric, or other medical problems. All subjects underwent a standard PSG, and results were scored by the standard criteria.

**Results:** Each subscale showed high inter-item reliability, as analyzed by Cronbach's alpha ( $\alpha$ ). The BD subscale had  $\alpha = .848$ , PLM  $\alpha = .767$ , DS  $\alpha = .938$ , and SQ  $\alpha = .840$ . Table 1 shows correlations and p-values for each subscale score related to objective measures of sleep disturbances as determined by PSG. Note that the parasomnia subscale has no objective measures so is not shown in Table 1.

**Table 1**

Correlations of CSAQ subscale scores with objective measures

	BD	PLM	DS	SQ
RDI	0.481*	.066	-0.163	0.056
RDI-REM	0.434*	0.151	-0.080	0.105
RDI-NREM	0.448*	0.029	-0.198	0.016
PLM	0.180	0.229**	0.358*	0.271*
SOL	0.256	0.278*	0.364*	0.534*
Slp. Efficiency	-0.280*	-0.054	-0.196	-0.395*

\* indicates significance at p = 0.05 \*\* indicates trend at p = 0.10

**Conclusions:** Because subscales of the CSAQ not only have very high inter-item reliability, but also were highly correlated with objective measures of sleep disturbances, they may be effective in predicting objective sleep disturbances from an analysis of subjective complaints. Furthermore, use of a Likert scale allows a more accurate description of the occurrence of symptoms as well as for more robust statistical analyses. The fact that the PLM subscale was not significantly correlated with objective measures of PLMs in our opinion reveals a bias

in parental perceptions. Parents are often highly alert to snoring as an indicator of sleep disturbance, but may not recognize or even be aware to look for unusual motor activity.

#### 438.G

##### TRENDS IN MORNING SLEEPINESS AMONG ADOLESCENTS - INTERNATIONAL COMPARISON

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**Introduction:** In the past hundred years the average sleep length has shortened significantly among adolescents. Several studies have suggested that inadequate and irregular sleep resulting from different reasons is associated with sleepiness and poor daytime functioning, which in some cases may lead to accidents, deteriorating school performance, and even makes future planning difficult. Morning sleepiness is one indicator of insufficient and irregular sleep. Investigating trends in morning sleepiness in several countries can help us to understand how widespread the phenomenon is. The present study examines trends in perceived morning sleepiness among 11, 13 and 15-year-old adolescents in many European countries and Canada in 1986, 1990, 1994 and 1998.

**Methods:** The study is part of the WHO-coordinated cross-national survey of school children's health and life-style (the HBSC-Study). The number of pupils increased from 39720 in 1986 to 125732 in 1998, and the number of countries from 11 in 1986 to 28 in 1998. Country representative data were collected using a standardized questionnaire. Perceived morning sleepiness was inquired about using the following question: how often do you feel tired when you go to school in the morning (rarely or never; occasionally; 1-3 times a week; 4 or more times a week). The focus in this study is in the last response category. Cross-tabulations and logistic regression analyses in SPSS Windows were used.

**Results:** In many countries the proportion of frequently (4 or more school mornings a week) sleepy pupils has increased. In some countries the proportion has almost doubled during survey years. Between 1986 and 1998 a linear trend in morning sleepiness was found in Norway, Scotland and Wales in many of the subgroups. For example among 11-year-old boys in Norway the proportion of sleepy pupils increased from 23% to 40%. Between 1990 and 1998 a linear rising trend was also found in Canada, Finland, and Sweden. Between a four year period (1994-98) a rising trend was found in countries such as Belgium, the Czech Republic, Germany, Latvia, and Poland. A more complex quadratic effect in morning sleepiness between 1990 and 1998 was discovered in Austria and Hungary making conclusions more difficult.

**Conclusions:** The increase in reported morning sleepiness reflects a decreased sleeping time during a school week in adolescents. Cross-cultural comparisons<sup>1</sup> have indicated that the problem of sleepiness is mainly a matter of many high-technology countries or countries situated in the North. The results of this study suggest that the phenomenon is not restricted to western countries with high technology. Reasons for increased sleepiness should be sought also from other sources such as changes in parents' control over children's

bedtimes, adolescents' alcohol use, and the way they spend their leisure time. The results suggest a need to strengthen the role of sleep education as an essential part of health education at schools.

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#### 439.G

##### ADOLESCENT SLEEP AND SCHOOL PERFORMANCE: AGE AND GENDER DIFFERENCES

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**Introduction:** During adolescence the timing of sleep is shifted towards later hours with increasing age, even when an early school start curtails their morning sleep. This results in a sleep loss during the school week and long sleep times during the weekend to make up for the sleep debt. A relation was found between this phase delay of sleep onset and awakening times (sleep lag) and poorer school performance. As most studies were conducted in schools with very early school start times this relationship was studied in Dutch schools where school starting times are 1 to 1.5 hours later. Possible age and gender differences are discussed, as well as the influence of being an evening type.

**Methods:** A sleep habit questionnaire consisting of 51 questions was filled out by 847 male and female students (age 12 to 18 years) of 6 high schools in the Netherlands. Information was obtained about sleep behavior, morningness-eveningness, general background, motivation for school, health and off-school activities. The average grade of a student for theory subjects was used as an indication of school performance.

**Results:** Bivariate regression analysis showed that sleep-lag increased with age ( $p < .001$ ), while the total time in bed ( $p < .001$ ) and the percentage of children getting enough sleep decreased with age ( $p < .01$  for boys and  $p < .05$  for girls). A series of models for the relationship between sleep characteristics and school performance was fitted to the data using path analysis (LISREL). The fitting of the general model was significant (Goodness of fit: 0.85). Better school performance was correlated with a smaller sleep lag ( $p < .001$ ), more time in bed ( $p < .05$ ), a later occurring trough in daytime alertness ( $p < .01$ ), a better subjective sleep quality ( $p < .05$ ) and less hours per week spent on a paid job ( $p < .01$ ). The most important factors influencing sleep lag and total bed time were evening type, more time spent in going out and longer travel times to school ( $p < .05$ ). Separate models were fitted for younger (12-14 years) and older children (15-18 years) to describe age differences and for boys and girls to describe gender differences. Age differences in the model described the

data significantly better than gender differences ( $p < 0.005$ ). In the older group school performance was mainly correlated with sleep lag and sleep quality whereas in the younger group other variables, like being an evening type and travel time to school also played a role. A negative relation was found between alcohol and nicotine use and school performance ( $p < 0.02$ ). Boys drank more alcohol than girls ( $p < 0.001$ ). This gender difference increased with age.

**Conclusions:** Also in Dutch schools where school starting times are not so extremely early as in other countries a sleep lag is developed in adolescents, which is increasing with age. Better school performance was related with less sleep lag and more sleep. Evening types had a bigger sleep lag and less time in bed. Although in the literature differences in gender have been found, in this study the relationship between variations in the sleep/wake rhythm was better explained by age than by gender.

#### 440.G

##### SLEEP COMPLAINTS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD): A COMPARISON OF SUB-TYPES

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**Introduction:** Numerous studies have documented an increased incidence of sleep complaints in children with ADHD. However, few studies have examined differentiated between the sub-types of ADHD. The question of sub-types is of particular interest because the different daytime symptom profiles suggest that differences in sleep complaints might also exist. The current study was designed to examine symptoms in children diagnosed with "combined-type" ADHD compared to the less common "inattentive" subtype.

**Methods:** 55 children with a confirmed diagnosis of ADHD were studied as part of an ongoing research study. These children were further stratified according to their ADHD-subtype into two groups: Combined-type ( $n=44$ ) and Inattentive-type ( $n=11$ ). The mean age of the children was 11.1 (range = 6-14) years and the groups did not differ in age after stratification. All children were referred from a developmental pediatrician specializing in ADHD and were not selected on the basis of sleep complaints or symptoms of sleep disorders. The parents of all subjects completed a variety of questionnaires including a Children's Sleep Assessment Questionnaire (CSAQ) and a one-week sleep diary during their participation. The CSAQ is a validated diagnostic tool described previously [1]. Groups were compared on CSAQ's scales (Global, Breathing Disorders, PLM, Sleep Quality, Daytime Symptoms, and Parasomnias). Responses to individual questionnaire items were also compared.

**Results:** The combined-type group showed a trend towards a greater PLM subscale score (4.7 vs. 2.8;  $p=.09$ ). This difference was primarily due to increased complaints about "leg cramps" in the combined-type group. In addition, the combined-type group demonstrated more symptoms of parasomnias (e.g., sleep walking and talking) as well as more daytime problems (all  $p < .05$ ).

**Conclusions:** These results suggest that subtle differences may exist between ADHD subtypes. In particular, it appears that the increased motor activity seen in the combined-type ADHD may continue even during sleep. Further studies, including objective PSG data, are clearly needed to better examine these differences.

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#### 441.H

##### SUBJECTIVE AND ACTIGRAPHIC RESPONSES OF RESTLESS & AGITATED ALZHEIMER'S DISEASE PATIENTS TO CITALOPRAM

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**Introduction:** Alzheimer's Disease (AD) affects about 10% of those over age 65. Behavior problems confronting caregivers include apathy, delusions, agitation, aggression, anxiety, insomnia, wandering, restlessness, depression and disinhibition. When behavioral modification techniques fail, pharmacotherapy is often tried, usually with antipsychotic or antidepressant drugs. Citalopram is a new SSRI reported by caregivers to be effective in controlling aberrant motor behaviors. It is well tolerated by the elderly.

**Methods:** Patients aged 50-90 yrs met diagnostic criteria for AD (NINCDS-ADRDA). They also had to have symptoms of aggressiveness or increased psychomotor activity. There had to be a principle caregiver who could attend clinic visits, complete questionnaires, administer medication and monitor the use of activity recorders. Patients with a psychiatric disorder prior to diagnosis of AD were excluded. Subjects participated for 12 weeks. At baseline, a medical history and medical & neurological exams were done. Citalopram 10 mg was then started and was titrated up to good effect or 40 mg/day. Patients were evaluated at baseline & after 4, 8 & 12 weeks of taking citalopram. Efficacy measures included the Neuropsychiatric Inventory (NPI; completed by caregiver interview), AD Assessment Scale, Efficacy of Function Scale (Lawton & Brodie) & wrist actigraphy (continuous for 7 days; IM Systems, Inc).

**Results:** 19 AD subjects (5M, 14F; mean age = 74.6) have been studied to date. NPI: The aberrant motor activity subscale of the NPI, which quantifies repetitive, stereotyped behaviors, decreased markedly after 4, 8 and 12 weeks of citalopram ( $p < 0.005$ ). Actigraphy: 6 AD subjects completed 1-3 study phases, and 13 completed all 4 phases. 1.9% of actigraphic data were missing & were replaced by mean motor activity at similar times on other days. At baseline, daytime motor activity levels were much lower than those of a group of younger (mean age = 39.1) normal subjects. Age-similar controls are being recruited. Motor activity did not change significantly when citalopram was administered. Mean actigraphic motor

activity & caregiver-rated aberrant motor activity were not correlated ( $r = -0.079$ , NS) among subjects. The mean, 24-hr function of activity level for treatment phases appeared to be phase delayed with respect to the pre-treatment baseline, by approximately 1.5 hours.

**Conclusions:** According to the caregivers of these agitated AD patients, citalopram was highly efficacious in reducing aberrant motor activity. Although objective measurement of motor activity did not confirm this, the caregivers rated specific behaviors, whereas actigraphy treated motor activity indiscriminately. The low level of AD motor activity at baseline accords with a previous finding, in which the daytime motor activity of community elders was found to be lower than that of age-similar caregivers (Pollak & Stokes, 1997). If confirmed, low motor-activity levels in AD would contrast with caregiver ratings of restlessness and agitation.

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**442.H**

**IMPACT OF SLEEP COMPLAINTS ON VIGILANCE AND COGNITIVE FUNCTIONING IN ELDERLY WOMEN: A NUN STUDY.**

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**Introduction:** Polysomnographic studies and questionnaire surveys reveal that sleep disturbances are a common problem in normal aging, especially among women (1). Although the etiology of these sleep disturbances can be manifold (e.g., underlying medical condition, dementia, normal physiological changes), they have a negative impact on both subjective well-being and objective health status. Another consequence of aging is a decrease in some aspects of cognitive functioning, but few studies have investigated the relationship between cognitive functioning and sleep quality. We present here preliminary results from an ongoing study of the relationship between quality of sleep, cognition, and level of daytime vigilance in a population of healthy elderly nuns.

**Methods:** Participants were thirteen women, all members of the same congregation, aged 68 to 91 (mean age  $79.7 \pm 8.6$ ). Participants were well educated, with a mean number of  $11.9 \pm 3.7$  years of schooling. All were in good health and none suffered from a medical condition that could affect either sleep and/or cognitive functioning (e.g., primary sleep disorder, dementia, head trauma, epilepsy, cerebrovascular accident, depression or other psychopathology). Exclusion criteria included scores of 24 or less on the Folstein Mini-Mental Scale (MMS), scores  $\geq 19$  on the Beck-II Depression (BDI-II), and scores  $\geq 15$  on the Beck Anxiety Inventory. Subjective sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI), and the level of daytime vigilance with the Epworth Sleepiness Scale. The cognitive evaluation included tests of memory, attention/vigilance, psycho-motor speed, and

verbal fluency. Participants also completed the Cognitive Failures Questionnaire (CFQ), a wide-ranging checklist of everyday mistakes in perception, memory and motor function.

**Results:** The mean score on the MMS was  $28.5 \pm 1.1$  out of a maximum of 30. The mean score on the BDI-II was  $6.3 \pm 4.3$ . For the Beck Anxiety, the mean score was  $7.6 \pm 6.7$ . No significant correlations were found between the global score on the PSQI and any of the cognitive tasks. A trend was also noted between the PSQI and anxiety ( $r = .56$ ;  $p = .07$ ). Trends were also found between the scores on the Epworth scale and the (CFQ) ( $r = .55$ ;  $p = .07$ ) and the number of omissions on the vigilance task ( $r = .54$ ;  $p = .08$ ).

**Conclusions:** The results suggest that minor complaints of subjective sleep quality have little impact on cognitive functioning when measured with formal tasks. Increased daytime sleepiness, however, appears to be associated with an increased number of daily mishaps which are not assessed by formal objective testing. It is possible that standard cognitive tests are not sensitive enough to detect small deteriorations resulting from either sleep degradation or decreased daytime alertness. These pilot data need to be interpreted with caution since it has been suggested that sleep quality is relatively better in nuns (2).

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**443.H**

**RESPIRATORY PERIODICITY AND HEART RATE VARIABILITY AS MARKERS OF AROUSAL DURING SLEEP IN OLDER ADULTS**

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**Introduction:** Respiratory periodicity and heart rate variability are important indicators of CNS integrity because they reflect the responsiveness of integrative brainstem systems to arousals during sleep<sup>1</sup>. Respiratory periodicity is a measure of the variability in the amplitude of breathing cycles. Heart rate variability (HRV) is a measure of the beat-to-beat variability in R-R intervals. While low respiratory periodicity may be associated with hypoxemia during sleep<sup>2</sup>, low HRV is thought to be associated with risk for ischemic injury during sleep<sup>3</sup>. This paper examines the relationship of respiratory periodicity and HRV during sleep in older adults.

**Methods:** Ten adults (5 males, mean age 74.3 yrs; mean BMI=26 Kg/M<sup>2</sup>) were observed during two, 2-night overnight stays on a GCRC. Monitoring included 6-hour recordings of

respiratory movements (Respirtrace, Ambulatory Monitoring Inc), R-R intervals (MiniLogger, Minimitter Company), and standard polysomnography. Each night's recording was divided into 72, 5-minute segments, yielding 288 segments/subject (4x72 segments). We used standard deviations to derive variables that measure the variability in the amplitude (sdAMP in volts) and frequency (sdIBF in cycles per minute) of breathing cycles in each 5-minute segment. The sdAMP and sdIBF were used to classify segments into 1 of 3 patterns of respiratory periodicity (1)low periodicity (sdAMP ≤ 0.1v and sdIBF ≤ 1.2cpm); (2)moderate periodicity (sdAMP /eq 0.1v and sdIBF>1.2 cpm); and (3)high periodicity (sdAMP>0.1v and sdIBF>1.2cpm). An algorithm, based on the percentage of patterns for each night, classified subjects into those with low and high periodicity. Two variables assessed HRV, the standard deviation of normal sinus rhythm beats (SDNN, a measure of overall ANS activity) and the percent of absolute differences between successive R-R intervals exceeding 50 milliseconds (%RR50, a measure of parasympathetic activity). Lower SDNN and %RR50 indicate greater risk of ischemic injury. Group differences in HRV were tested using repeated measures MANOVA.

**Results:** The magnitudes of respiratory periodicity and HRV variables were consistent across the four nights. Five adults exhibited low respiratory periodicity and five exhibited high periodicity. Adults with high periodicity had more EEG arousals than adults with low periodicity, but those with low periodicity had more awakenings. Adults with high periodicity had greater overall ANS activity than adults with low periodicity (SDNN: mean-low=73.4s mean-high=131.0s, F[1,4]=9.8, p<.01). Compared to adults with low periodicity, parasympathetic activity was greater in adults with high periodicity (%RR50 mean-low=4.54%; mean-high=15.70%; F[1,4]=3.4, p<.06). Frequency domain values will also be compared.

**Conclusions:** Respiratory periodicity and HRV are potentially useful methods for characterizing arousals during sleep. The association of low HRV with low respiratory periodicity may indicate abnormal responses to arousals during sleep and mark older adults at risk for hypoxic injury during sleep.

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**444.H**

**THE EFFECTS OF SLEEP SPINDLES ON EVOKED K-COMPLEX GENERATION.**

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**Introduction:** Sleep spindles are 12-14 Hz oscillations in the EEG that are thought to reflect a state of thalamo-cortical hyperpolarization (Steriade, 2000). Previously, it has been suggested that spindles and spontaneous K-complexes reflect "two sides of a coin", with the spindle reflecting an inhibitory microstate and the K-complex reflecting an excitatory or aroused microstate (Halasz, 1993). This hypothesis would predict that stimuli presented during a spindle should decrease the likelihood of a K-complex being elicited by that stimulus. The present study sought to test this hypothesis in young and elderly subjects.

**Methods:** Ten young and seven elderly adults were neurologically healthy and free from medications spent one night in the sleep laboratory. EEG was recorded from six gold plate electrodes (Fz, Fcz, Cz, Cpz, Pz and O2) referenced to A1 + A2. 1000Hz tone clicks at 80 decibels above measured awake detection thresholds were presented binaurally either during a spindle (SP+) or in the absence of a spindle (SP-). This was achieved by viewing a central EEG channel filtered to pass only the frequencies between 12 and 14 Hz. Trials were further classified based on whether or not they produced a K-complex (KC). KC trials were averaged to assess the amplitude of the N550 evoked potential component. KC probability N550 amplitude data were assessed using a two-way ANOVA with main effects of age and spindle presence/absence.

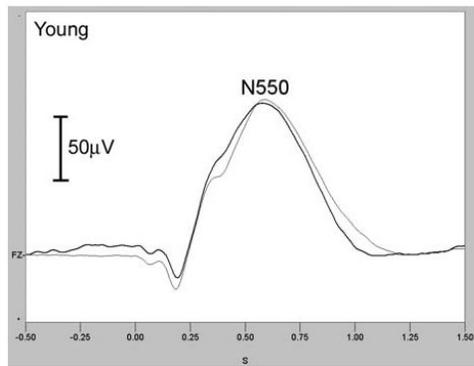
**Results:** Means (SD) are presented in Table 1. There were significant effects of age on both KC%, F(1,15) = 37.2, p<.001 and N550 amplitude, F(1,15) = 32.6, p<.001. Neither variable displayed a significant effect of spindle presence/absence (see figure 1) or an age x spindle interaction effect.

**Table 1**

**Means (SD) for old and young subjects for the proportion of KCs produced by stimuli (KC%) and the amplitude of the N550 component in the average of KC responses (N550 Amp.) Data are presented separately for trials in which tones were presented in the presence or absence of a sleep spindle.**

	Spindle absent	Spindle Present
N550 Amp. (µV) Young	-138 (27)	-137 (31)
Old	-63 (27)	-63 (25)
KC % Young	74 (10)	79 (8)
KC % Old	44 (14)	50 (15)

Figure 1



Grand Mean evoked potentials for the Young subjects. Data are drawn from KC+ averages in the SP+ (thick lines) and SP- (thin lines) conditions. Data are presented from 0.5 seconds prior to the stimuli to 1.5 second after them. Negative voltages are plotted up the Y-axis.

**Conclusions:** The data fail to support the hypothesis that sleep spindles are antagonistic to the production of K-complexes, both in terms of the likelihood of K-complexes being elicited or in their amplitude when elicited (N550). They are more supportive of the two processes being independent.

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**445.H**

**SLEEP COMPLAINTS IN A POPULATION-BASED SAMPLE OF MINORITY WOMEN**

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**Introduction:** Studies focusing on the epidemiology of sleep complaints have shown ethnic differences in reported difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), and early morning awakening (EMA).<sup>1</sup> However, until recently investigators did not specifically consider the possibility of within-group differences in sleep complaints. Using data collected from community-dwelling older adults, we recently found that 49% of US-born African Americans expressed these three complaints, whereas 40% of Caribbean Americans reported such complaints.<sup>2</sup> These findings suggested that sleep duration, which is an important correlate of morbidity and mortality,<sup>3</sup> may also differ between these two ethnic subgroups. The purpose of this study was to investigate sleep complaints and sleep duration in a sample of minority women.

**Methods:** Respondents in this study were 506 women (ages: 49-70 years, mean = 59.32 ± 6.78) that have participated in an on-going study assessing health-related risk factors among community-residing African Americans (AA, 22%), Haitian Americans (HA, 43%), and English-Speaking Caribbean Americans (ESCA, 35%) living in Brooklyn, New York. They were recruited using a stratified, cluster sampling technique. Trained interviewers collected data during face-to-face interviews conducted either in the respondent's home or another location of their choice. These interviews lasted approximately 1.5 hours, and those that provided valid data received \$25 for their participation. Demographic information such as age, sex, ethnicity, education, and family income was collected. Physical health was measured with the Comprehensive Assessment and Referral Evaluation; five sub-scales were included: heart disease, respiratory disease, arthritis, sleep disorder, and hypertension. The sleep disorders subscale included five questions: 'Do you depend on medicine to sleep?'; 'Do you have difficulty falling asleep?'; 'Do you wake up often during the night?'; 'Do you wake up early in the morning feeling tired?'; and 'Do you sleep during the day?'. Additionally, respondents provided estimates of habitual sleep duration and time spent in bed; they also rated their sleep satisfaction on a four-point scale from 1, 'very satisfied' to 4, 'very troubled'.

**Results:** Table 1 shows the sociodemographic data for the three subgroups (AA, HA, and ESCA). Reports of sleep-related complaints, sleep duration, time in bed, and sleep satisfaction for each group are compared in Table 2 [Chi Square tests were used to assess between-group differences in sleep complaints. Univariate F tests were used to determine between-group differences in sleep duration and satisfaction (\*p < 0.01)]. Chi Square tests have also shown significant between-group disparities in reported health complaints potentially influencing sleep patterns. The percentages of AA, HA, and ESCA reporting somatic complaints were: 69.9%; 64.1%; and 22.7%, respectively (X<sup>2</sup> = 87.27\*). For arthritis, complaint rates were: 74.3%; 78.8%; and 42.0%, respectively (X<sup>2</sup> = 63.28\*). For respiratory problems, rates were: 58.4%; 15.7%; and 9.1% respectively (X<sup>2</sup> = 106.05\*). For heart problems, rates were: 41.6%; 57.1%; and 13.1% respectively (X<sup>2</sup> = 80.51\*). For hypertension, rates were: 63.7%; 61.8%; and 60.2% respectively (X<sup>2</sup> = .36).

Table 1

Volunteer's Sociodemographic Data			
Measures	AA	HA	ESCA
Age	59.00±6.41	60.65±6.48	57.97±7.13
BMI	22.39±4.38	20.28±3.47	21.19±3.21
% Inc < 35K	74.2	85.7	47.2
% No HS Deg	8.8	46.1	11.4

Table 2

Comparison of Sleep Measures by Ethnicity				
Measures	AA	HA	ESCA	$\chi^2/F$
DIS (%)	19.5	19.8	6.3	16.27*
DMS (%)	61.1	25.8	15.9	70.05*
EMA (%)	46.9	18.4	8.5	62.30*
DS (%)	21.2	4.1	2.8	39.72*
SM (%)	5.3	5.5	1.7	4.07
TST (SE)	7.72 (.15)	8.05 (.11)	7.53 (.12)	3.47*
TIB (SE)	6.37 (.14)	6.74 (.10)	6.84 (.11)	5.23*
SS (SE)	1.71 (.08)	1.68 (.06)	1.34 (.06)	10.02*

**Conclusions:** Findings of this study are consistent with trends observed in the previous cohort surveyed between 1995 and 1999 regarding differences in reported DIM, DMS, and EMA between African Americans and Caribbean Americans living in Brooklyn, New York. It is important to note that differences in sleep complaints were also observed even within the Caribbean subgroup. This further suggests that other factors might explain observed differences in sleep patterns, over and above variances accounted for by ethnicity alone. Indeed, when we controlled for sociodemographic disparities, ethnic differences were less pronounced. Furthermore, results support the hypothesis that individuals' sleep duration and satisfaction would vary as a function of their ethnic grouping, which reflected observed variations in the rates of sleep complaints.

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## 446.I

### SLEEP DEPRIVATION-INDUCED CHANGES IN GROWTH HORMONE RELEASING HORMONE RECEPTOR (GHRH-R) MRNA IN RAT HYPOTHALAMUS

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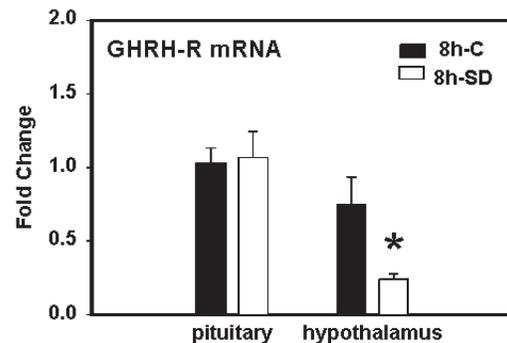
**Introduction:** GHRH plays a critical role in pituitary somatotroph GH release and in sleep regulation. Microinjection of GHRH into the anterior hypothalamus increases non-rapid eye movement sleep (NREMS), suggesting that the GHRH-Rs responsible for sleep regulation are localized in the anterior hypothalamus (Zhang et al., 1999). An acute suppression of

endogenous GHRH with a competitive receptor antagonist inhibits spontaneous sleep (Obal et al., 1991). Studying the regulation of these GHRH-Rs will facilitate our understanding of the role of this peptide in the regulation of NREMS. Sleep loss increases GHRH mRNA levels in the hypothalamus (Zhang et al, 1998) and GHRH release (Gardi et al, 1999). The effects of sleep loss on GHRH-R mRNA in the hypothalamus or pituitary have not heretofore been determined. In this study, we hypothesized that sleep deprivation will decrease the GHRH-R mRNA levels.

**Methods:** GHRH-R mRNA was measured using real-time RT-PCR. Sprague-Dawley rats (250-350 gm), kept on a 12:12 h L/D cycle at 23°C, were deprived of sleep for 8 h beginning at light onset (n=8). Another group was allowed to recover for 2 h after 8 h of sleep loss (n=8). Two time-matched control groups of 8 rats each were also used.

**Results:** After 8 h of sleep deprivation, hypothalamic GHRH-R mRNA levels were about half of those observed in control animals (Fig. 1). Sleep loss did not affect pituitary GHRH-R mRNA levels. After 2 h of sleep recovery, hypothalamic GHRH-R levels were similar to control values. In another experiment performed in our laboratory, we showed that specific binding of radio-labeled GHRH to cell membranes decreased after sleep deprivation in hypothalamic preparations but not in pituitary preparations. These results are consistent with the mRNA results presented here.

Figure 1



**Conclusions:** Enhanced exposure to GHRH is a major factor down-regulating GHRH-R. The current results are consistent with the previous findings demonstrating increased GHRH release in response to sleep deprivation. The results also suggest that GHRH-Rs in the brain are regulated independently and differently from that in the pituitary.

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#### 447.I

##### THE EFFECTS OF REM SLEEP DEPRIVATION ON RETENTION OF A CUED CONDITIONING TASK

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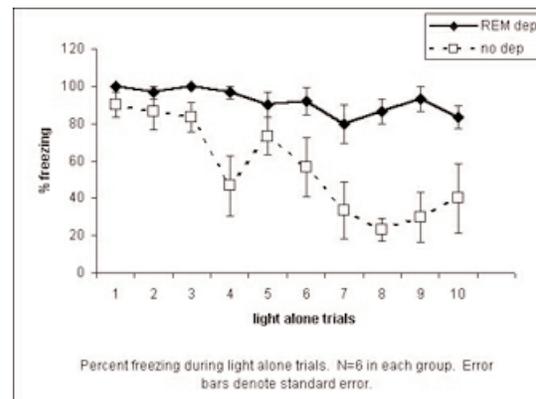
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**Introduction:** A growing body of literature indicates that sleep and learning are interconnected. Contextual learning, in which an animal is required to learn the location of various stimuli in its environment, produces an increase in subsequent rapid eye movement sleep (REM), while REM deprivation impairs retention of a contextual learning task<sup>1</sup>. The results seen after cued learning, in which a specific cue predicts a biologically significant event (e.g. footshock), differ from those seen after contextual learning. Cued learning tasks produce a decrease in subsequent REM1, with this decrease being most prominent during the first 2 hours of post-conditioning sleep<sup>2</sup>. This experiment is the first investigation of the effects of REM deprivation on retention of a cued learning task.

**Methods:** Twelve animals were trained in a 3-phase cued conditioning procedure. During phase 1, animals were exposed to the experimental chamber for approximately 30 minutes to habituate them to the context. Forty-eight hours later, phase 2 began. Each animal was presented with 5 light (5sec) + footshock (0.5sec, 0.5mA) pairings. Immediately following this conditioning session, 6 animals were subjected to REM deprivation for 6 hours. REM deprivation was accomplished with the "flowerpot" technique, which selectively reduces REM without affecting non-REM. The remaining 6 animals were placed in a control apparatus. Following the 6h of REM deprivation or control condition, animals were returned to their home cages. During phase 3, 48 hours later, each animal was returned to the conditioning chamber and was presented with 10 light alone (i.e., extinction) trials. Trained observers recorded freezing (a reliable indicator of conditioning) during each second of each of the 10 light alone presentations.

**Results:** When data for freezing behavior during each light alone trial were collapsed across each second of the light and analyzed by trials, the REM-deprived animals froze more than the controls ( $F_{(9,90)}=8.82, p<.001$ ; Figure 1). There was also a group by trials interaction, with the control animals showing a decrease in freezing across the 10 trials but no such effect in the REM-deprived animals ( $F_{(9,90)}=4.17, p<.001$ ). When data for freezing behavior during each second of the light were collapsed across all 10 light trials and analyzed by seconds of light presentation, REM-deprived animals also froze more than controls ( $F_{(1,10)}=12.42, p<.005$ ).

Figure 1



**Conclusions:** These results demonstrate that REM deprivation produced enhanced freezing in a cued conditioning task. This pattern of behavior can be interpreted one of two ways: either enhanced learning of the light-shock association or a failure of extinction in the REM-deprived animals; that is, the REM-deprived animals failed to learn during phase 3 that the light no longer predicted shock. Further research will be necessary to determine the specific nature of this REM deprivation-induced enhancement of freezing to a conditioned stimulus.

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#### 448.I

##### WHEN DOES FATIGUE AFFECTS SLEEP DEPRIVED DRIVERS?

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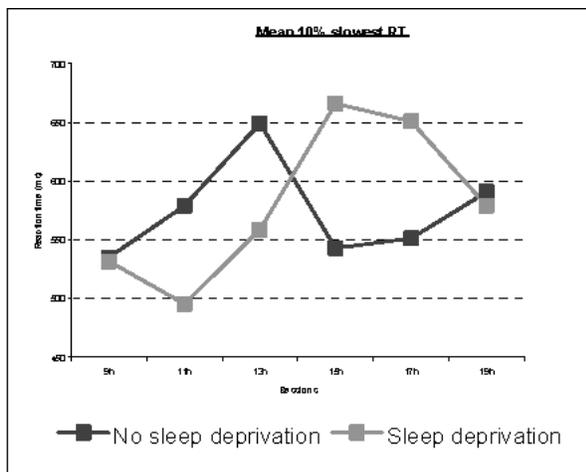
**Introduction:** Fatigue and sleepiness at the wheel are major risk factors for traffic accidents nevertheless many drivers combine sleep loss and extensive driving<sup>1</sup>. The effects on human performances of sleep loss associated to fatigue are still poorly known therefore we conducted a study on the neurobehavioral consequences of sleep deprivation combined with long distance automobile driving.

**Methods:** 10 healthy subjects were recruited for the experi-

ment. Clinical interview with a sleep specialist, actimetry and nocturnal polygraphy were performed to rule out any sleep disorder. After controlling for nocturnal sleep (11.30 pm- 8 am versus 11.30-1 am), we asked to 10 healthy young subjects to drive for 1000 Km on a freeway. Every 105 minutes (9:00, 10:45, 12:45, 14:45, 16:45, 18:45) subjects were asked to stop to self rate their fatigue and sleepiness on visual analog scales and to perform a simple reaction time test. All driving episodes were recorded through a video camera to quantify lateral deviations of the vehicle.

**Results:** During the non sleep deprived condition subjects were able to drive 9 hours without affecting their performances. In contrast, a severe sleep restriction preceding the trip affected significantly their reaction time during cognitive tests. Subjects during their 3 pm and 5 pm tests performed significantly worse (wilcoxon,  $p < 0.05$  and  $p < 0.01$ ) than without sleep loss. Lateral deviations during driving quantified by video analysis were significantly more frequent during the sleep deprivation condition. After 3 episodes of 105 minutes of driving, subjects deviated significantly more (wilcoxon,  $p < 0.05$  and  $p < 0.01$ ) than during the first two hours of driving. Drivers complained along the trip of an increasing fatigue and sleepiness especially during sleep deprivation condition (Freedman,  $p < 0.05$ ). No correlation was found between the lateral deviations and the self perception of fatigue as measured by visual analog scales for the 6 periods of driving and the two conditions.

Figure 1



**Conclusions:** We suggest that sleep deprived drivers should reduce seriously their daytime duration of driving in order to minimize their driving risks.

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#### 449.I

#### TOTAL SLEEP DEPRIVATION INDUCES AN INCREASE IN HIPPOCAMPAL 5-HT RELEASE MEASURED WITH MICRODIALYSIS

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**Introduction:** An increase in 5-HT activity has been implicated in the mechanism of action of antidepressant drugs. However, chronic administration is required to induce certain changes in the 5HT system (down-regulation of autoreceptors), which have been hypothesized to be responsible for the behavioral response. In contrast, sleep deprivation induces antidepressant effects within 24 hours. Accordingly, we wished to test the hypothesis that total sleep deprivation increases 5HT after 24 hours. In this study, we report the effect of total sleep deprivation on extracellular 5HT in the posterior hippocampus.

**Methods:** Rats were sleep deprived using the disk-over-water method. Rats were housed in a clear plastic cage, with a 46 cm diameter smooth plastic disk providing a partial floor on top of a container holding water 1 cm deep. Disk rotation caused rats to move to avoid falling into the water. Experiments lasted three days, during which EEG and EMG activities were recorded for analysis of sleep and wakefulness, and microdialysis samples were collected every three hours from the posterior hippocampus for 5HT analysis. On Day One (baseline), rats were left undisturbed. The experimental manipulation took place during Day Two, as follows. In the sleep deprived rat the disk rotated every time quiet sleep was detected. In the stress control rat, the amount of disk rotation was made equivalent to that previously measured in the sleep deprived rat, but at different intervals so as to allow the rat to sleep. On Day Three, rats were again left undisturbed (recovery sleep). Each experimental day started at the onset of the dark period.

**Results:** In the sleep deprived rats, 5HT levels remained elevated during the 24 hours of Day Two (i.e., during sleep deprivation). In the stress control rats, 5HT was elevated during the dark phase of Day Two (i.e., the first 12 hours of the stress control paradigm), but not during the light phase. During the recovery day 5HT decreased to baseline levels in the stress control rats, but remained elevated in the sleep deprived rats. Total amount of sleep was slightly elevated during the recovery day compared to baseline in both groups of rats.

**Conclusions:** 5HT was elevated during sleep deprivation. This result was expected since 5HT release is high during periods of wakefulness. Surprisingly, 5HT levels remained elevated during the recovery day, although total wake duration was slightly less than during baseline. The increase in 5HT on recovery day might be due to a desensitization or down-regulation of 5HT<sub>1a</sub> and/or 5HT<sub>1b</sub> autoreceptors as a consequence

of maintained high levels of 5HT during sleep deprivation.

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**450.I**

**SENSITIVITY OF A DRIVING SIMULATOR/COGNITIVE TEST TO SLEEP RESTRICTION IN ADOLESCENTS: A PILOT STUDY**

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**Introduction:** Our group is developing a performance test combining “overlearned” skills of a driving simulator with a numerical computation cognitive task (SimCog) in an effort to increase sensitivity to sleepiness and to provide a corollary for dual-task challenges encountered while driving. In an ongoing study of adolescents involving moderate sleep restriction, we examined whether performance would deteriorate over days of sleep restriction, especially in the morning.

**Methods:** Volunteers were 6 healthy, normal-sleeping adolescents (4 boys, 2 girls, ages 12 – 14 years) enrolled in a larger project. Participants slept at home from 2100 to 0700 for ten nights (confirmed by actigraphy) followed by four consecutive nights of in-lab testing with sleep from 0100 to 0700 hours. Following 1.5 hours of practice, participants performed SimCog for 20 minutes at 2000 and 0730 each day. SimCog runs on a PC with a color monitor and peripheral steering wheel, accelerator, and brake. The driving task has been described previously.<sup>Begin 1 End.</sup> Instructions are to stay centered in the right lane and keep speed at 60 mph. Participants simultaneously perform a three-condition cognitive task: *Begin count, compute, rest End.* For *Begin count End* and *Begin compute End*, participants detect whether numbers on the screen count forward by 1 and subtract by 7, respectively; for *Begin rest End*, participants drive only. Dependent measures were selected based on previous studies as variables likely to respond to sleepiness. Driving variables included lane position variability (standard deviation of lane position) across the full task and aggregated by cognitive conditions, and speed variability (standard deviation of deviation from 60 mph) and off-roads across the test (Table 1). Cognitive variables were percent correct and reaction time for *Begin count End* and *Begin compute End* aggregated over the test (Table 2). Dependent measures were analysed using repeated measures ANOVA with test day (1 to 4), time (morning vs. evening), and task (*Begin rest,*

*count, compute End*) as within subjects factors.

**Results:** Lane position variability showed a main effect of time (greater in the morning [*Begin F End*(1,5)=7.90, *Begin p End*<.05]) and task (greater for *Begin count End* and *Begin compute End* compared to *Begin rest End* [*Begin F End*(2,10)=4.24, *Begin p End*<.05]). Speed variability decreased linearly across days [*Begin F End*(1,5)=9.08, *Begin p End*<.05]. Off-road incidents did not change significantly. The cognitive task showed only a trend for slower reaction time on the *Begin count End* task in the morning [*Begin F End*(1,5)=5.92, *Begin p End*<.06]. No interactions of test day and time were found.

**Table 1**

Mean (SD) for driving variables.

Variable		Day 1	Day 2	Day 3	Day 4
Lane Position Variability (units from lane center)	pm	6.1 (1.3)	5.7 (0.9)	6.1 (1.2)	5.7 (0.8)
	am	6.2 (1.3)	6.5 (1.3)	6.5 (1.1)	6.3 (0.9)
Speed Variability (mph)	pm	5.5 (3.7)	3.2 (1.2)	3.2 (0.8)	2.9 (0.7)
	am	4.8 (1.5)	4.6 (3.2)	3.2 (0.8)	2.6 (0.6)
Off-road Incidents (number)	pm	0.3 (0.8)	0.2 (0.4)	0.2 (0.4)	0.0 (0.0)
	am	1.0 (1.5)	0.3 (0.5)	0.3 (0.8)	0.0 (0.0)

**Table 2**

Mean (SD) for cognitive variables.

Variable		Day 1	Day 2	Day 3	Day 4
% correct Count Task	pm	89.9 (5.0)	91.9 (6.0)	93.1 (4.7)	89.1 (11.9)
	am	88.7 (7.9)	88.3 (7.2)	90.3 (6.1)	86.5 (12.4)
% correct Compute Task	pm	78.8 (9.8)	82.2 (11.2)	82.4 (11.8)	82.9 (15.5)
	am	78.5 (11.6)	80.2 (11.1)	82.8 (13.7)	84.0 (15.3)
RT Count Task (sec)	pm	.79 (.10)	.70 (.14)	.73 (.14)	.70 (.14)
	am	.83 (.14)	.78 (.16)	.81 (.17)	.76 (.21)
RT Compute Task (sec)	pm	.92 (.16)	.81 (.16)	.82 (.17)	.77 (.13)
	am	.88 (.18)	.85 (.18)	.84 (.16)	.80 (.20)

**Conclusions:** The data did not support our hypothesis, indicating that this version of SimCog was not sensitive to sleep restriction and only minimally sensitive to time of day in young adolescent nondrivers. Continued learning beyond the training session—evidenced by improvements in speed variability—may have masked effects of sleep restriction. Although we have shown previously that a single 10-minute session is sufficient practice on the driving task alone.<sup>Begin 1 End.</sup> additional complexity of the cognitive task may increase learning time, particularly for young participants. We plan to

adjust cognitive task parameters to achieve the goal of increasing task sensitivity to sleepiness.

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**Research supported by Brown Medical School Department of Psychiatry and Human Behavior, MH52415, and MH01358 to Mary A. Carskadon**

#### 451.I

##### **EFFECT OF MODAFINIL ON WORKING MEMORY AFTER SLEEP DEPRIVATION: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY.**

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**Introduction:** Obstructive sleep apnea and sleep deprivation impair executive and other functions of the prefrontal cortex (1). Working memory, the short-term "online" maintenance and manipulation of information for various cognitive tasks, is a critical executive function, but functional imaging of working memory after sleep deprivation has not been previously reported. We have used functional magnetic resonance imaging (fMRI) to study working memory after overnight sleep deprivation, and we have evaluated the effect of modafinil on cortical activation and task performance.

**Methods:** The study is a randomized, placebo controlled, double blind evaluation of the effects of modafinil on functional activation and working memory performance following overnight sleep deprivation. Subjects are healthy males, ages 21-35 years, who have been screened for medical, psychiatric and sleep disorders. Each subject is scanned 4 times: after a night of sleep deprivation or sleep, and after treatment with 200 mg modafinil or placebo 2 hours before scanning. All imaging is done between 8 and 10 A.M. The task paradigm is a block design, verbal 2-back test, with 6 blocks of alternating baseline (a simple discrimination of the \* and + symbols) and task. Each task block lasts 60 seconds, each baseline 30 seconds, and each run lasts 9.5 minutes. As measures of vigilance, 10-minute PVT reaction times are obtained before and after scanning, a modified PVT-type task is performed in the scanner, and the Karolinska Sleepiness Scale is administered before and after the scanning session.

**Results:** Preliminary analysis indicates that sleep deprivation results in reduced activation of the dorsolateral prefrontal cortex during the 2-back test. In addition, the blood oxygen level dependent fMRI signal tends to decrease with time on task following sleep deprivation. In contrast, activation of the anterior cingulate cortex and posterior parietal cortex are relatively well preserved. Reaction times on the task are roughly doubled by sleep deprivation. Complete sets data will be available for 8 subjects at the time of presentation.

**Conclusions:** Sleep deprivation appears to impair working memory in association with decreased activation of dorsolateral prefrontal cortex. Further analysis should help determine whether this impairment is improved by modafinil. These

results have implications for complex decision making in the sleep deprived state, such as physicians on call, armed forces personnel, and emergency services

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#### 452.I

##### **GENDER DIFFERENCES IN TIME IN BED IN SLEEP DISORDERS PATIENTS: A PRELIMINARY REPORT**

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**Introduction:** It has been estimated that approximately one third of the general population are sleep deprived.(1) If the one third estimate of sleep deprivation in the general population is applicable to a population of sleep laboratory patients, then the standard sleep parameters obtained from the first night in the laboratory may be a function of both the sleep disorder and the patients' prior sleep schedule. Hublin et al (2) obtained questionnaire data from 12,432 respondents in Finland and found that women show a greater amount of sleep deprivation. There are few studies on gender differences in the amount of time in bed of sleep disorders center patients and our knowledge of gender differences in prior sleep deprivation for sleep disorders population is limited.

**Methods:** In the present study we examined the two week sleep diaries of 113 consecutive patients (47 female, 66 male). Each patient filled in a two week sleep diary prior to their sleep laboratory study. Time in bed was calculated from the time recorded by the patients of intent to go to sleep until the patients recorded the time they left their bed.

**Results:** The age ranges for males and females were comparable (female = 49.57 years, SD=13.36, males = 52.15 years, SD = 14.01). The gender differences in average time in bed were statistically non-significant (females = 8.51 hrs, SD = 1.27, males = 8.08, SD = 1.35,  $p > .05$ ). However, when sleep deprivation was arbitrarily defined as 7 or less hours in bed there was a statistically significant difference between the number of males and females who reported they spent 7 or less hours in bed. Of the total of 47 females in the study, 2 reported seven or less hours in bed (4%), while of the 66 males, 13 reported 7 or less hours in bed (20%). ( $\text{Chi}^2 = 5.69, p < .02$ .)

**Conclusions:** It is clear from our findings that the sleep diary is an important source of information for interpreting polysomnographic data in sleep laboratory patients. Our findings do differ from the Hublin study where females reported a higher incidence of sleep deprivation. Future research should focus on a further breakdown of variables contributing to gender differences in sleep deprivation in sleep laboratory patients (age, vocation, type of sleep disorder, etc.).

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(2) Hublin C, Kaprio J, Partinen M, Koskenvuo M: Insufficient Sleep - A Population-Based Study in Adults. *Sleep*

2001;24:392-400.

**453.I****SLEEP REBOUND AFTER MODAFINIL AND SLEEP DEPRIVATION IN MICE IS SIMILAR**Kopp C,<sup>1</sup> Petit JM,<sup>1</sup> Magistretti P,<sup>2</sup> Borbély AA,<sup>2</sup> Tobler I<sup>1</sup>

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**Introduction:** Modafinil is a wakefulness-promoting substance which is used to treat excessive daytime sleepiness in narcoleptic patients. In contrast to traditional psychostimulants such as amphetamines, modafinil is reported to have only minimal side effects and is not followed by hypersomnolence in rats (1). However, whether modafinil-induced wakefulness and spontaneous waking are similar in respect to their effects on subsequent sleep is still unknown. It is well established that EEG slow-wave activity (SWA; EEG power density in the 0.75-4 Hz band) in non-rapid eye-movement sleep (NREMS) changes as a function of the previous sleep-waking history. This was shown to be the case also in several mouse strains after sleep deprivation (SD) (2,3) as well as after spontaneous waking (2). The aim of the present study was to compare the effect of enforced waking to modafinil-induced waking on subsequent sleep in mice.

**Methods:** Two groups of mice (OF1 strain; n=7 per group) were treated at light onset either with modafinil (200 mg/kg i.p.) alone, or were sleep-deprived after vehicle administration (i.p.). SD duration was matched to the duration of the waking episode elicited by modafinil in the first group (range in min: modafinil: 197.7- 360.1; SD: 216.7-355.2). Occipital and frontal EEG, and EMG recordings were obtained continuously during the 24-h period before treatment (baseline) and the 12-h light period after treatment. SD was performed by introducing new objects into the cages whenever the animals looked drowsy or attempted to adopt a sleeping posture (2). Vigilance states and EEG spectra were analyzed as previously (2) over the 5 first hours after sleep onset.

**Results:** The effect of the two treatments on vigilance states did not differ: NREMS was not affected while REMS was initially reduced. Modafinil and SD induced a prominent enhancement of SWA, which was more pronounced over the frontal than over the occipital cortex. Except for a short initial difference where the SWA increase was higher after SD than after modafinil, this effect was similar for both treatments (Fig.1).

**Conclusions:** The changes of sleep and the sleep EEG after modafinil-induced wakefulness correspond largely to the well-known homeostatic responses induced by an extended non-pharmacological waking episode.

**References:**

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**Research supported by a scientific grant from Laboratoire L. Lafon (France).**

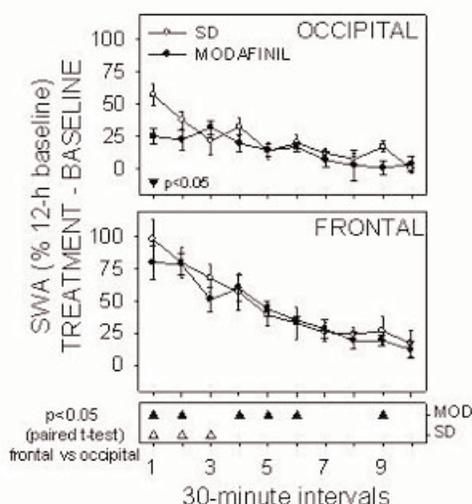
**454.I****THE EFFECTS OF EXPERIENCE ON PERFORMANCE DURING SLEEP DEPRIVATION IN AN AVIATION ENVIRONMENT**Prazinko B,<sup>1</sup> Caldwell JA<sup>1</sup>

(1) US Army Aeromedical Research Laboratory,

**Introduction:** Little research has examined the relationship between experience and performance while undergoing sleep deprivation (SD). Most of the research has not shown any significant differences between inexperienced and experienced driver's abilities to maintain driving performance during sleep-deprived conditions, while other research remains largely inconclusive. The purpose of the analysis was to further investigate these effects (if any) and to also introduce performance in an aviation setting, instead of a driving one.

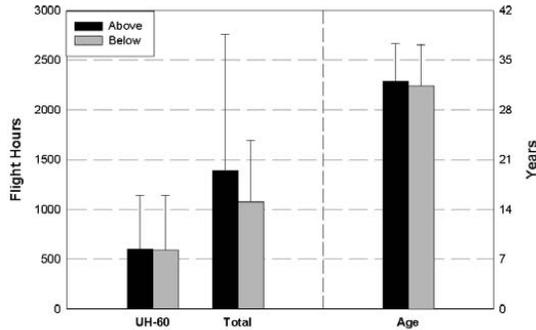
**Methods:** Data from 33 male and female UH-60 aviators between the ages of 24 and 46 from a total of five different SD studies were pooled together for analyses. In all the studies there was a 40-hour period of continuous wakefulness during which sessions in a UH-60 simulator/aircraft, eyes closed waking electroencephalographic (EEG) recording sessions, and the Profile of Mood States (POMS) were administered in cycles of 4-hour testing blocks. For the purpose of this analysis only the sessions that have previously been shown to be most susceptible to the effects of SD were used. A difference from baseline score was calculated for each session and the mean was used to separate all subjects into an above mean or below mean group.

**Results:** Analyses determined that there were no significant differences between the 2 groups' age, UH-60 flight hours, and total flight hours during any of the tests. The figure below

**Figure 1**

illustrates this (above/below groups were determined by performance during the 0500 flight).

Figure 1



**Conclusions:** These results indicate that there are no major differences in the demographic data, based on aviators' performance scores. This also suggests that experience is no substitute when it comes to sustaining performance during sleep deprivation, an issue that is extremely important in today's aviation environment.

**References:**

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**455.I**

**EXERCISE AFTER SLEEP DEPRIVATION: HEART RATE, HEART RATE VARIABILITY, FEELINGS OF SLEEPINESS, AND THEIR INTERRELATIONSHIPS.**

Crabbe JB,<sup>1,2</sup> O'Connor PJ,<sup>1,2</sup> Dishman RK<sup>1</sup>

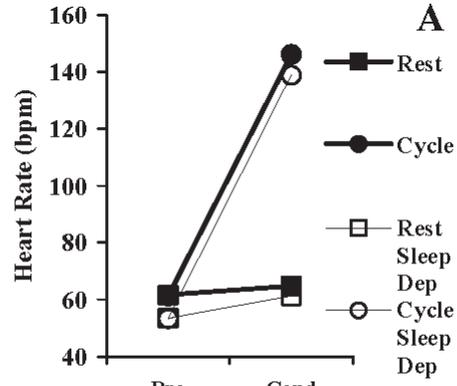
(1) University of Georgia, Department of Exercise Science, Athens, GA, (2) University of Pennsylvania, Division of Sleep and Chronobiology, Department of Psychiatry, Philadelphia, PA,

**Introduction:** The effect of sleep deprivation on heart rate (HR) and autonomic balance is unclear. HR during exercise is lower after sleep deprivation (1). However, it is not clear whether autonomic balance is altered during exercise after sleep deprivation. Sleepiness is transiently attenuated by low intensity physical activity (2), but the effect of intense exercise on feelings of sleepiness is unknown, as is whether changes in sleepiness are related to changes in HR and/or autonomic balance.

**Methods:** In a counterbalanced, 2 (sleep manipulation) x 2 (activity condition) x 2 (time) repeated measures design, 11 healthy males (19-27 years) either rested or cycled (70 ± 6% of maximal oxygen uptake, 146 ± 32 Watts) for 25 minutes following a regular night of sleep at home or after a laborato-

ry monitored night of no sleep. Hence, exercise or rest conditions were performed at about 0900 hour. Eight minutes of heart rate (HR; R-R intervals) and concurrent feelings of sleepiness (VAS) were collected just before (i.e., baseline) and during each condition.

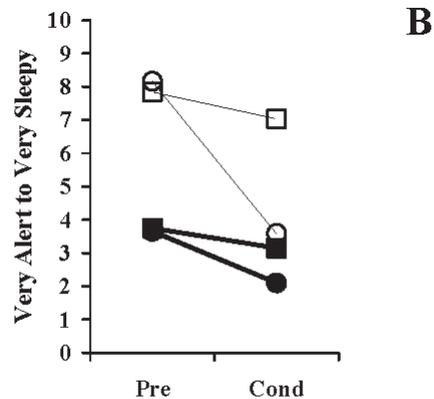
Figure 1



The decrease in heart rate after sleep deprivation was maintained during exercise

**Results:** HR before exercise was 7 bpm less following sleep deprivation ( $F(1,10)=25.9, p<.001, \eta^2 = 0.72$ ) compared to a normal night of sleep (Figure A). This 7 bpm difference was maintained throughout the subsequent exercise bout (Figure A). Sleep deprivation resulted in an increase in heart rate variability (HRV; measured by the standard deviation of R-R intervals (SDRR);  $F(1,10)=10.7, p=.008, \eta^2 = 0.52$ ), which also was maintained during exercise ( $t(10)=1.60, p=.07, d=0.48$ ). Ratings of sleepiness were increased by sleep deprivation, and that increase was abolished during the exercise bout ( $t(10)=0.72, p=.244, d=0.21$ ; Figure B). Changes in sleepiness were unrelated to changes in HR or HRV from before to during conditions. However, multiple correlations showed that increases in feelings of sleepiness were negatively related to HR ( $r = -.45$ ) and positively related to HRV ( $r = .44$ ).

Figure 2



Feelings of sleepiness after sleep deprivation were abolished during cycling.

**Conclusions:** These results indicate that sleep deprivation decreases HR during rest and during exercise and these effects may be mediated by increased parasympathetic nervous system (PNS) activity. Feelings of sleepiness may also be mediated by increases in PNS activity.

**References:**

- (1) Martin BJ. Sleep deprivation and exercise. *Exercise and Sport Science Reviews*, 1986; 14, 213-29.
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**Research supported by The Polar Research Grant on Controlled Heart Rate Zone Exercise from the American College of Sports Medicine Foundation, and in part by NASA Cooperative agreement NCC9-58 with The National Space Biomedical Research Institute.**

**456.I**

**SIMULATED DRIVING PERFORMANCE DETERIORATES UNDER CONDITIONS OF PROLONGED WAKEFULNESS BUT NOT REPEATED TESTING**

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(1) Department of Psychology, Queen's University, Kingston, Ontario, Canada,

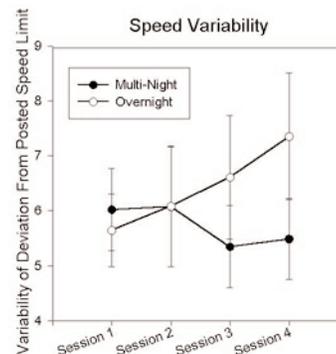
**Introduction:** Performance on a number of tasks, including simulated driving, has consistently been shown to deteriorate with sleep loss. This is often demonstrated by repeated testing over a period of prolonged wakefulness. Such a procedure confounds the effects of prolonged wakefulness and circadian rhythm changes with repeated exposure to the task. The effects of the latter might facilitate performance (practice) or increase deterioration (boredom). The objective of the present study was to examine the effects of prolonged wakefulness on performance while controlling for repeated exposure.

**Methods:** Thirty-six undergraduate students (18 males, 18 females, mean age 19 years) completed four 30-minute driving sessions on the York Driving Simulator. Each subject completed an initial practice session prior to their first experimental session. Participants were randomly assigned to one of the following conditions: Overnight condition - subjects remained awake overnight completing four driving sessions at 21:00, 24:00, 02:30, and 05:00; Multi-night condition- subjects kept usual sleep wake cycles and completed a 30-minute driving session at 21:00 on four consecutive nights. In both conditions, subjects were required to drive along a monotonous stretch of 4-lane highway whilst staying as close to the posted speed limits and centre of their lane as possible.

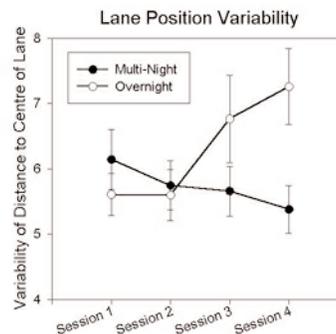
**Results:** ANOVAs with session and 5-minute block as within-subject variables and condition and gender as between-subject variables were conducted. In the multi-night condition, performance on the following variables remained constant or improved slightly with each session, whereas in the overnight condition, performance declined as the sessions progressed and participants reported increased sleepiness: variability of deviation of the vehicle speed from posted limits ( $F[3,96] = 4.35, p < .05$ ; see figure below); variability of lane position

( $F[3,96] = 13.06, p < .001$ ; see figure below); collisions with other vehicles or driver vehicle leaving the road ( $F[3,96] = 3.46, p < .05$ ); and percentage of time spent inside a designated safe zone ( $F[3,96] = 5.52, p < .01$ ). Performance of the overnight group deteriorated as time on task increased for: variability of speed deviation ( $F[5,160] = 2.70, p < .05$ ); variability of lane position ( $F[5,160] = 2.58, p < .05$ ); and time in safe zone ( $F[5,160] = 2.60, p < .05$ ). Lane position variability also increased more rapidly with time on task in later sessions ( $F[15,480] = 2.15, p < .05$ ).

**Figure 1**



**Figure 2**



**Conclusions:** Prolonged wakefulness led to deterioration in simulated driving performance on a number of measures. These changes could not be accounted for by the effects of repeated exposure to the task as such decrements were not seen in the absence of sleep loss. These results are consistent with a larger body of evidence which suggests that prolonged wakefulness puts the driver at greater risk for an accident.1-2

**References:**

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## 457.I

**GLYCOGEN IS PRESENT IN DROSOPHILA BRAIN AND CHANGES WITH REST DEPRIVATION**

Zimmerman JE,<sup>1</sup> Mackiewicz M,<sup>1</sup> Zhang L,<sup>1</sup> Zoh C,<sup>1</sup> Hendricks JC,<sup>1</sup> Galante RJ,<sup>1</sup> Pack AI<sup>1</sup>

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**Introduction:** Rest in *Drosophila melanogaster* meets criteria to be considered sleep-like [1,2]. It is unknown if there is glycogen present in the brain of *Drosophila* and, if so, whether it changes with rest deprivation. Determining this is necessary to use *Drosophila* to evaluate the energy hypothesis of sleep/wake regulation. Evaluating glycogen changes in the whole fly is necessary to determine whether changes in brain are part of a general metabolic response.

**Methods:** Animals: eyes absent<sup>2</sup> females. Glycogen assays: Animals in all groups were sacrificed by rapid immersion in >90°C. Glycogen was measured fluorometrically in 10 µl of homogenate using an enzymatic hydrolysis assay.

**Staining:** Sections of 10 µm were stained for glycogen using a Periodic Acid-Schiff (PAS) stain. **Deprivation:** Flies were placed in different treatment groups for 3 or 6 hours of rest deprivation: control group (Con); handled group (Han) where the container was tapped once and then left undisturbed; rest deprived group (RD), which were deprived by repetitive tapping of their container.

**Results:** Coronal sections show a diffuse stain specific for glycogen throughout the brain of *Drosophila melanogaster*. Rest deprivation for 3 hours leads to a significant decrease in glycogen levels in RD brains compared to Con brains, 0.074±0.022 and 0.111±0.029 µmoles glucose/mg protein respectively (p=0.041). After 6 hours of rest deprivation, the glycogen levels are not significantly different between RD and Con brains, 0.151±0.05 and 0.178±0.06 µmoles glucose/mg protein respectively. Rest deprivation has different effects on glycogen in the head and body. After 3 hours, in the head, the RD group is significantly lower than Con (0.61±0.14, 1.20±0.26 µmoles glucose/mg protein, respectively (p<0.001)). For 3 hours of deprivation, there is no significant difference between experimental groups in glycogen in the body. After 6 hours of rest deprivation, RD are significantly lower than the Con in both heads and bodies (p=0.0054, p=0.0016, respectively).

**Conclusions:** We have demonstrated that glycogen is present in the brain of *Drosophila melanogaster*. In the brain, glycogen levels decline with short-term rest deprivation, but recover to control levels if rest deprivation is maintained. The temporal change in brain glycogen is different from that of the body. Here, glycogen levels progressively decrease with increasing duration of rest deprivation. The change in glycogen in brain with early decline and later recovery is compatible with the changes in glycogen found when wake active neurotransmitters are applied to astrocytes in culture [3]. These data add further support to the use of *Drosophila melanogaster* as a sleep model, and specifically to investigate the energy hypothesis of sleep regulation.

**References:**

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JA, Sehgal A, Pack AI. Rest in *Drosophila* in a sleep-like state. *Neuron* 25:129-138, 2000.

(2) Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. Correlates of sleep and waking in *Drosophila melanogaster*. *Science* 287:1834-1837, 2000.

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Research supported by NIH grant HL-60287.

## 458.J

**DOES NCPAP TREATMENT OF OBSTRUCTIVE SLEEP APNEA SYNDROME LEAD TO A DECREASE IN PSYCHOTROPIC MEDICATION USE?**

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(1) Mayo Clinic, Rochester, Minnesota

**Introduction:** Mood symptoms are frequently reported in patients with obstructive sleep apnea syndrome (OSAS) and are often attributed to an independent psychiatric disorder resulting in treatment with psychotropic medications. Previous studies demonstrated that effective treatment with nasal continuous positive airway pressure (nCPAP) improves mood and sleep symptoms. If nCPAP therapy improves mood and normalizes sleep symptoms, one might expect a decrease in psychotropic use. To our knowledge, there are no published data regarding a decrease in psychotropic use after treatment with OSAS. The purpose of this study is to determine the change in psychotropic use in OSAS patients after treatment with nCPAP.

**Methods:** Retrospective chart review of patients with polysomnographic diagnosis of OSAS. Patients greater than 18 years old prescribed nCPAP therapy that were on psychotropic medications were selected. Patients with chronic medical illnesses, including metabolic (i.e. diabetes, renal failure), pulmonary (i.e. chronic obstructive lung disease), cardiovascular (i.e. congestive heart failure, coronary artery disease, myocardial infarction) except for hypertension, neurologic (i.e. dementia, seizures, strokes), that in themselves might account for mood symptoms were excluded. Psychotropic drug use history was reassessed at follow-up.

**Results:** 59 patients met the selection criteria. 25 were female and 34 male. Ages ranged between 20 and 69 years, with an average of 48. Average respiratory disturbance index (RDI) was 49. Patients had follow-up at a mean of 8 months (range 1-17 months). 55 patients had the diagnosis of mood disorders, 12 of anxiety disorders, 4 of somatic disorders, 1 with a thought disorder, and 10 with other psychiatric diagnosis (the total number is greater than 59 because many patients carried more than one diagnosis). All patients were on at least one antidepressant medication. The changes in the psychotropic use prior to OSAS diagnosis and after treatment with nCPAP are documented in Table 1. 20 patients out of 59 (34 %) decreased the number, the dose, or completely eliminated all psychotropic medications.

**Table 1**

1 <sup>st</sup> Visit		Follow-up Visit						
# Med	# Pts	NO Med	No change	↓ Dose only	↑ Dose only	↓ # med only	↓ # and ↓ dose	↑ # Med
1	35	5	22	2	4	0	0	2
2	14	0	4	2	4	1	2	1
3	6	1	1	1	0	2	1	0
4	4	0	1	1	0	1	1	0
	59	6	28	6	8	4	4	3

**Conclusions:** These results show that correct diagnosis and treatment of OSAS is associated with a substantial decrease in the use of psychotropic medications. It seems likely that the original psychiatric diagnosis may have erroneously resulted because of symptoms that were ultimately ascribable to OSAS, symptoms that resolved with correct diagnosis and therapy. Alternatively, diagnosis and treatment of OSAS may enhance treatment of psychiatric disorders. In any event, these results highlight the need for increased awareness of OSAS among primary physicians and psychiatrists.

**References:**

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- (2) Flemons W, Tsai W: Quality of life consequences of sleep-disordered breathing. *The J Allergy Clin Immunol*, 1997, 99(2),750-756.
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**459.J**

**EXPERIENCE WITH CPAP TITRATION IN CHILDREN WITH SEVERE OSAS**

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(1) National Institute of Respiratory Diseases,

**Introduction:** We have previously described a prevalence of 7% and 1% for snoring and obstructive sleep apnea syndrome (OSAS) respectively, in children in Mexico City (1). The major cause being enlarged tonsils and adenoids, and adenotonsillectomy the recognized and effective treatment (2), however children with severe OSAS have a high risk of complications during and after the surgery particularly at Mexico City's altitude. In a group of children with severe OSAS, we have successfully used CPAP for 1-2 months prior to the surgery. The aim of this work was to describe our experience with CPAP titration in 3 to 13 year old children with severe OSAS secondary to enlarged tonsils and/or adenoids.

**Methods:** All patients were referred from the hospital's ENT clinic for evaluation of sleep disordered breathing. All were evaluated by a sleep doctor and a Respiratory and Sleep Habits Questionnaire was completed by a parent. The children underwent a simplified overnight study registering snoring, finger pulse oximetry and body position. Evaluation was completed with a daytime full sleep study in which CPAP titration was completed. The CPAP pressure was considered as optimal when oxygen saturation (SaO<sub>2</sub>) and end tidal CO<sub>2</sub> (EtCO<sub>2</sub>) levels reached normal values, snoring was eliminated and obstructive events were significantly reduced.

**Results:** : A total of 20 children with severe OSAS were recruited (70% males). Basal polysomnographic values showed a high A/H I with an elevated number of arousals per hour of sleep (38±24), with severe hypoxemia and hypercapnia. During the CPAP titration there was a considerable improvement, and finally when the adequate values for respiratory values were reached without awakening the patients, we let them sleep for 60-90 minutes with the best fixed pressure. The mean CPAP pressure needed was 7.2 ± 1.2 cmH<sub>2</sub>O. The nasal mask was well tolerated by all the children.

**Table 1**

	A/H Index	Mean SaO <sub>2</sub> (%)	Min SaO <sub>2</sub> (%)	Max EtCO <sub>2</sub> (mmHg)
Basal	73\pm 50	83.3\pm 10	68\pm 16	47.6\pm 12
During CPAP	14.2\pm 10.6	89\pm 3.3	76\pm 13	41.5\pm 9
Optimal CPAP	10.6\pm 9.5	90.4\pm 4	87\pm 6	37\pm 6

Changes in respiratory parameters during CPAP titration

**Conclusions:** CPAP can be effectively titrated in the Sleep Center in children with severe OSAS, and is well tolerated. The mean pressure needed to normalize breathing parameters during sleep is similar to what has been reported for adults.

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## 460.J

**THE EFFECTS OF NCPAP THERAPY AND EXERCISE TRAINING ON MEASURES OF HEART RATE VARIABILITY, BLOOD PRESSURE, AND EXERCISE PERFORMANCE - A CASE STUDY FROM A 12 WEEK CLINICAL TRIAL**

Kaleth AS,<sup>1</sup> Chittenden TW,<sup>1</sup> Hawkins BJ,<sup>1</sup> Blevins JS,<sup>1</sup> Gregg JM,<sup>2</sup> Zedalis D,<sup>3,4</sup> Herbert WG<sup>3,4</sup>

(1) Laboratory for Health and Exercise Sciences, Department of Human Nutrition, Foods and Exercise, Virginia Tech, Blacksburg, VA, (2) Department of Exercise Science, Northern Arizona University, Flagstaff, AZ, (3) Sleep Disorders Network of Southwest Virginia, Christiansburg, VA, (4) Health Research Group, Blacksburg, VA,

**Introduction:** PURPOSE: To illustrate with case subject data, a design of an ongoing clinical trial to assess if exercise training, when added to nasal continuous positive airway pressure (nCPAP) therapy, improves blood pressure (BP), cardiovascular autonomic function, and cardiovascular exercise performance. HISTORY: The 50-year-old male case subject (height = 180 cm; weight = 90 kg; Body Mass Index = 27.8 kg/m<sup>2</sup>) presented with complaints of snoring, witnessed apnea, and excessive daytime sleepiness (EDS). He was not receiving prescription medications and the medical history revealed no other significant findings. Overnight polysomnography (PSG) established moderate-severe Obstructive Sleep Apnea (OSA; Respiratory Distress Index, RDI = 33.8) and nCPAP was recommended and the patient fitted with a ResMed (San Diego, CA) AutoSet T nCPAP device.

**Methods:** All measures were obtained at baseline, 6 weeks, with the treatment endpoint being a 12-week follow up (not reported here). Measures taken at each interval were weight, questionnaire scores for daytime excessive drowsiness (Epworth Sleepiness Scale), daytime blood pressure using four measures/day with an automated digital blood pressure device, and heart rate variability (HRV) assessed from precise ( $\pm 1$  ms) heart rate records of 12-hour waking periods in which the patient wore a small battery powered single-lead ECG recorder. HRV was analyzed as the standard deviation (SD) of the R-R intervals, after correcting data for ECG artifact and extrasystoles. Cardiopulmonary exercise tolerance, including measures of oxygen consumption, heart rate, and blood pressure, also were obtained at each interval, using a ramping cycle ergometer test to maximal effort. Exercise training consisted of walking or cycling 3-4 days per week, 30-40 minutes per session, at 50-60% of peak exercise VO<sub>2</sub> for 6 weeks.

**Results:** After 6 weeks of combined exercise training and nCPAP therapy, the patient reported feeling less tired during the day (ESS = 5). Resting daytime blood pressure decreased 7.1% and HRV increased 118.2% suggesting improved cardiovascular autonomic balance. Moderate intensity exercise training resulted in an 11.3% improvement in peak oxygen consumption, but no change in peak BP or ventilatory threshold. At the same workload, several key responses suggested a trend toward improved cardiorespiratory efficiency of exercise at a submaximal exertion, e.g., HR (-5 beats/minute), BP (mean arterial pressure -3.3 mmHg), and ventilation (-6 Liters/minute).

Table 1

Variable	BASELINE	6 WEEKS
Body Mass Index (kg · m <sup>2</sup> )	27.8	27.5
Epworth Sleep Score (X/24)	15	5
HRV: Standard Deviation (ms)	43.4	94.7
Daytime Mean Arterial Pressure (mmHg)	109.5	101.7
Exercise Test Time (minutes)	9:00	11:00
Peak Workload (watts)	160	190
Submaximal Exercise Heart Rate (beats · min <sup>-1</sup> ) at 100 watts	116	111
Submaximal Exercise BP (beats · min <sup>-1</sup> ) at 100 watts	218/100	200/104
Submaximal Exercise V <sub>E</sub> (L/min) at 100 watts	34.8	28.8
Ventilatory Threshold (VO <sub>2</sub> , L/min)	1.55	1.54
Peak Exercise VO <sub>2</sub> (L/min)	1.86	2.07
Peak Heart Rate (beats · min <sup>-1</sup> )	144	156
Peak BP (mmHg)	242/120	242/120

**Conclusions:** Clinical trials aimed at assessing treatment outcomes in OSA patients may be enhanced by including exercise testing, particularly if cardiovascular status is important. The addition of exercise training as an adjunct to principal therapies, such as nCPAP, adds a preventive dimension to treatment that may be especially important when goals of treatment include risk reduction for comorbid conditions, e.g., obesity and hypertension, that have a strikingly high prevalence in OSA.

**Research supported by ResMed Corporation (San Diego, CA)**

## 461.J

**DIFFERENTIAL NMDA GLUTAMATE RECEPTOR CHANGES FOLLOWING SUSTAINED OR INTERMITTENT HYPOXIA IN THE RAT BRAIN.**

Gozal E,<sup>1</sup> Rowell PP,<sup>1</sup> Sachleben Jr LR,<sup>1</sup> Guo SZ,<sup>1</sup> Gozal D<sup>1</sup>

(1) Kosair Children's Hospital Research Institute, Departments of Pediatrics, Pharmacology and Toxicology, University of Louisville, Louisville, KY.,

**Introduction:** NMDA receptors mediate critical components of learning and memory (1). However, excessive recruitment of NMDA receptors during hypoxia/ischemia may lead to neuronal excitotoxicity. In an animal model of obstructive sleep apnea (2), significant early decreases in the population of NMDA receptor expressing neurons were found in both hippocampal and cortical regions via apoptotic mechanisms (2). We hypothesized that changes in NMDA receptor subunit expression and binding properties will occur over time in surviving cortical neurons.

**Methods:** Adult Sprague-Dawley rats were exposed to either intermittent (10% O<sub>2</sub> alternating with room air every 90 sec; IH) or to sustained hypoxia (10% O<sub>2</sub>; SH) for up to 14 days

using computer-driven environmental chambers. Cortical tissue lysates were prepared at 0,1, 3, 7, and 14 days exposure and western blots of protein equivalents were conducted for NR1, NR2A, and NR2B NMDA receptor subunits. Similarly, tissue lysates were analyzed for NMDA receptor binding properties using the labeled selective antagonist [3H]MK-801 as ligand. Blots were analyzed using scanning densitometry, and loading differences were corrected using actin western blots on the same membrane. The Kd (receptor affinity) and Bmax (maximal binding) values of NMDA receptor binding were determined by Scatchard analysis using specialized software.

**Results:** NR1 NMDA receptor subunit density was not affected by either SH or IH over time. However, increased expression of the NR2A subunit occurred with hypoxic exposures, and was particularly prominent in IH. The NR2A/NR1 ratio further reinforced these findings. No significant changes in NR2B subunit expression occurred. The overall affinity of NMDA receptors for [3H]MK-801 was not altered by either SH or IH. However in both SH and IH, Bmax increased, and the increase in maximal binding was more prominent in IH.

**Conclusions:** Both IH and SH are associated with changes in NMDA receptor binding and NR2A subunit composition. However, the more prominent changes induced by IH suggest that slowly evolving excitotoxicity associated with NMDA receptor changes may underlie the more severe neurocognitive deficits induced by IH.

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**462.J**

**THE POTENTIAL UTILITY OF POST-EXERCISE SYSTOLIC BLOOD PRESSURE RESPONSE FOR THE ASSESSMENT OF CARDIOVASCULAR CO-MORBIDITY IN OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Obstructive sleep apnea (OSA) is associated with both acute and long-term sympathoexcitation that involves increased vascular tone. It has been postulated that the increased vascular tone in OSA leads to disturbed diurnal blood pressure control and increases in the incidence of myocardial infarction and stroke. Hypertension (HTN) is pres-

ent in 50% of OSA patients, and daytime systemic HTN is the cardiovascular marker most often studied when attempting to establish a link between OSA and cardiovascular disease (CVD) [1]. In an attempt to develop a reliable, noninvasive measure for the assessment of HTN, researchers have determined that the normal decline in systolic blood pressure (SBP) during the recovery phase of exercise does not occur in some patients afflicted with various pathologic conditions such as coronary artery disease (CAD). Amon et al. [2] examined the diagnostic value of this observation in 56 CAD patients and 31 age-matched, healthy controls. Derivation of post-exercise SBP ratios was achieved by dividing the SBP at 1, 2, and 3 min in exercise recovery by the peak exercise SBP. The 1, 2, and 3 min ratios in the control subjects showed a steady decline from  $0.85 \pm 0.07$  (SD) to  $0.79 \pm 0.06$  and to  $0.73 \pm 0.06$ , however, the ratios in the CAD patients remained elevated at  $0.97 \pm 0.12$  to  $0.97 \pm 0.11$  to  $0.93 \pm 0.13$ , respectively (Fig.1). They concluded that post-exercise SBP ratios provide a valid diagnostic marker of CAD. Our research team is presenting illustrative data suggesting how the aforementioned methodology might also be utilized for the assessment cardiovascular co-morbidity in OSA.

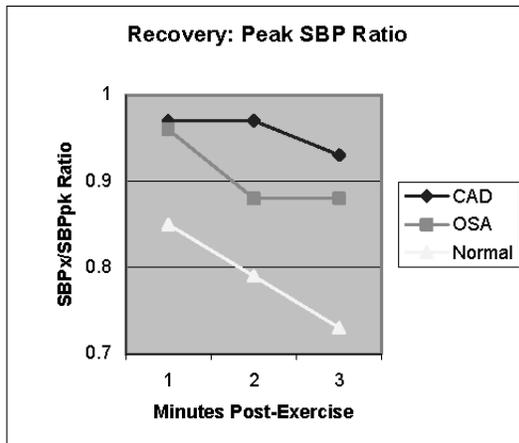
**Methods:** After the initial polysomnographic sleep study, patients diagnosed with mild to high moderate OSA (Table 1) performed a ramping ergometric exercise test to maximal effort on an electronically braked cycle ergometer. Oxygen consumption, heart rate, and blood pressure were monitored throughout exercise and into a seated active recovery. Post-exercise SBP ratios were determined as previously described [2]. Exclusion criteria included antihypertensive medications.

**Table 1**

Patient Demographics						
Patient	Gender	Age	RDI	Epworth Score	Neck Cir	BM I
1	Male	50	33.8	15	15	28
2	Female	58	11.4	19	15	38
3	Female	25	26	9	16	45
4	Female	27	29.6	14	15.50	38
Mean	N/A	42.5	25.2	14.25	15.38	37.25

**Results:** Preliminary data analysis on four patients (1 male and 3 females) revealed elevated post-exercise SBP ratios compared to normal controls reported in the literature [2]. Figure 1 presents SBP recovery ratio values for OSA patients of  $0.96 \pm 0.005$  (SD),  $0.88 \pm 0.03$ , and  $0.83 \pm 0.01$  for 1, 2, and 3 min, respectively.

Figure 1



Post-exercise SBP ratios for CAD and OSA patients and normal adults at minutes 1, 2, and 3 of recovery.

**Conclusions:** An elevated post-exercise SBP ratio response witnessed in four patients after maximal exercise suggests the value of a definitive clinical study to determine the utility of this measure for assessment of cardiovascular co-morbidity in OSA.

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**463.J**

**AUTO-ADAPTING CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP): IS NIGHT-TO-NIGHT PRESSURE VARIATION RELATED TO COMPLIANCE WITH CPAP THERAPY?**

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**Introduction:** Auto-adapting CPAP varies the CPAP pressure to respond to respiratory events in obstructive sleep apnoea (OSA) patients. By adapting the pressure, the mean pressure used per night should be lower than if a fixed pressure is used and the number of hours of use of the device should increase. There is little data investigating the night-to-night variation in CPAP pressure and whether the magnitude of the pressure variation ( $\delta P$ ) is related to the number of hours of actual night-time usage. We wished to assess a) the magnitude of pressure variation night-to-night occurring over seven consecutive nights and b) whether the degree of variation was related to the number of hours of CPAP use per night.

**Methods:** Patients with varying degrees of OSA were included in the study and completed a single night auto-titrating CPAP study in the laboratory. They then used an auto-adapting nasal CPAP device (Goodnight 418P, Mallinckrodt) for 14 nights, with data being analysed over the second 7 nights. The data recorded each night was the mean pressure, the magnitude of pressure variation ( $\delta P$ ) and the number of hours of pressurized use. Local ethics approval was obtained for the study. Data are presented as mean  $\pm$  standard deviation. Analysis of variance was used to assess variation over the 7 nights and regression analysis to assess the relationship between  $\delta P$  and CPAP usage.

**Results:** Variation over 7 nights: 20 patients recorded more than 11 hours of use and used CPAP for >70% of the time (mean 91%) over the 7 nights. Mean hours/night over the 7 nights ranged from 1.8 to 6.9 hours. Data for each night and the mean for all 7 nights are shown in Table 1. There was no significant variation in CPAP usage, mean pressure or  $\delta P$  over the 7 nights. There was however, a trend in CPAP usage with lower usage on Sunday, increasing to a peak on Thursday. CPAP usage and  $\delta P$ : There was a weak, but significant correlation between CPAP usage and DP over the 7 nights of study, where CPAP Usage =  $3.14 + 0.19\delta P \pm 2.1$ ,  $n = 126$ ,  $r^2 = 0.10$ ,  $p < 0.001$

Table 1

	Usage	Mean P	$\Delta P$
Sunday	3.2 $\pm$ 2.4	8.5 $\pm$ 3.3	8.1 $\pm$ 4.5
Monday	3.8 $\pm$ 3.3	8.2 $\pm$ 3.2	8.9 $\pm$ 3.3
Tuesday	4.1 $\pm$ 2.1	7.7 $\pm$ 3.0	7.8 $\pm$ 3.9
Wednesday	4.3 $\pm$ 2.6	7.3 $\pm$ 2.7	7.3 $\pm$ 3.7
Thursday	4.9 $\pm$ 2.5	8.3 $\pm$ 3.3	9.4 $\pm$ 3.5
Friday	4.5 $\pm$ 2.4	7.8 $\pm$ 3.1	7.9 $\pm$ 4.2
Saturday	4.8 $\pm$ 2.1	7.6 $\pm$ 3.3	8.7 $\pm$ 4.0
Mean - 7 Days	4.6 $\pm$ 1.6	7.8 $\pm$ 2.9	7.9 $\pm$ 3.3

**Conclusions:** Over seven consecutive days - 1) Both mean pressure and the variability of pressure show little variation 2) CPAP usage varies over the working week, with the lowest usage at the start of the week, increasing towards the end of the week. Assessment of variability in CPAP usage should be assessed over a longer time to determine any possible trends in usage. 3) The degree of variation - DP in CPAP pressure is weakly linked to CPAP usage and is one of a number of factors that may contribute to CPAP usage.

**464.J**

**EARLY POSTNATAL EXPOSURE TO INTERMITTENT HYPOXIA ATTENUATES BAROREFLEX SENSITIVITY IN ADULT RATS.**

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**Introduction:** It is now widely accepted that the baroreflex sensitivity is attenuated in adult patients with obstructive sleep apnea (OSA). Long-standing intermittent hypoxia (IH), one of the hallmarks of OSA has been mechanistically implicated in the changes of baroreceptor function that ultimately lead to systemic hypertension (1). These changes are reversible in adults upon discontinuation of IH exposures. OSA affects up to 2% of children and induces blood pressure elevation. However, little is known about the long-term effects of IH when it occurs during development. We hypothesized that IH exposures in developing rats may lead to altered baroreflex control of cardiovascular responses during adulthood.

**Methods:** We exposed neonatal male Sprague-Dawley rats (n=6) to IH (10% O<sub>2</sub> alternating with 21% O<sub>2</sub> every 90 sec) or normoxia (Co) for 30 days, after which exposures were discontinued. Baroreflex (BR) function was assessed at 4-5 months of age. Rats were anesthetized, tracheotomized, femoral vein and carotid artery catheters were inserted and vasoactive drugs were administered (phenylephrine, 100 g/ml, and sodium nitroprusside, 100 g/ml ; infusion rate 60 l/min) while continuously monitoring heart rate (HR) and mean arterial pressure (MAP). In both groups of rats BR sensitivity was assessed in two experimental conditions -during room air (RA) and after 18 min of IH (6 cycles of 90-sec 10%-21% O<sub>2</sub> alternations; IHA). Changes in HR were plotted against the changes in MAP, and logistic regression analysis was used to calculate baroreflex sensitivity (2).

**Results:** The resting MAP was similar in Co and IH rats (110.9 ± 5.6 and 108.0 ± 4.5 mm Hg respectively), and mean resting HR were also similar (332.5 ± 22.3 in Co and 315.0 ± 11.3 bpm in IH). However, HR chronotropic responses were enhanced, in Co (range 53 to 66 bpm) compared to IH (19 to 20 bpm). In Co, baroreflex sensitivity was significantly attenuated by IHA. The slope of the regression line in Co following IHA decreased by 42% (P<0.05), from -0.64 ± 0.12 bpm/mmHg in RA to -0.37 ± 0.06 bpm/mmHg after IHA. In contrast, postnatal exposures to IH demonstrated attenuated baroreceptor reflex sensitivity in RA, which was not altered by IHA. Indeed, BR slopes in IH rats were approximately 50-60% (P<0.05) smaller compared to Co in RA but were similar to CO after IHA.

**Conclusions:** Acute IH exposures lasting as little as 18 minutes induce BR reductions in naïve rats. Postnatal IH exposures induce BR sensitivity reductions that will last into adulthood, such that no further changes in BR sensitivity are elicited when IH is re-applied. We speculate that IH-induced long-lasting alterations in baroreceptor properties during childhood may predispose for the early onset of hypertension during adulthood in susceptible individuals.

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**465.J**

**CORRELATION OF THE SLEEP DISORDERS QUESTIONNAIRE'S "SLEEP APNEA" SCALE TO POLYSOMNOGRAPHIC VARIABLES.**

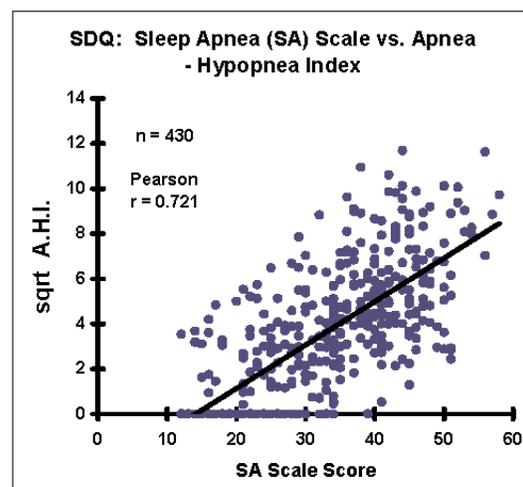
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**Introduction:** The development of the Sleep Disorders Questionnaire (SDQ) from Stanford's Sleep Questionnaire and Assessment of Wakefulness (SQAW) (1) using multivariate methods was previously reported (2). This abstract reports the next step in the development of SDQ, the construct validation of the Sleep Apnea (SA) subscale. The definition of a person suffering sleep apnea was operationalized as an apnea-hypopnea index (AHI) of 20 per hour or greater. The validation is made via a correlation of the SA raw scale score to relevant polysomnography variables.

**Methods:** The same subjects that were reported in detail in (2) were used, so all sleep lab procedures have been published. There were 435 clinical sleep disorder patients with full polysomnography: sleep apnea (n=158), narcolepsy (n=73), inpatient psychiatric (n=108), and PLMS (n=96). Non-blind sleep disorder diagnoses were made by the patient's treating sleep clinician according to the Diagnostic Classification of Sleep and Arousal Disorders (3). All variables were assessed for normality. We operationally defined normality as an absolute value of skew and kurtosis less than 2.0, and a Shapiro-Wilk "W" test for normality greater than 0.90. Any variable not meeting these standards was mathematically transformed so that criteria were met. Multiple regression was then performed with all polysomnography variables as the predictor variables and SA Scale raw score as the predicted variable.

Figure 1



**Results:** Only the square root transform of AHI, body weight increase since age 20, and the number of night awakenings,

were significant contributors to the multiple regression. Their R-squared partial correlations were 0.326, 0.125, and 0.116 respectively (all significant at  $p = 0.02$  or less). AHI was by far the best predictor of the SA score, and vice-versa. The graph below shows a Pearson univariate correlation of AHI vs. SA score.

**Conclusions:** The psychometric construct of "sleep apnea" embodied in the SDQ's SA scale has been validated. The raw SA score predicts the AHI with a high correlation, while other PSG variables contribute little. The SDQ is one of the few sleep questionnaires to have been designed for the purpose of predicting sleep disorder patient diagnosis, rather than assessing subjective dimensions of sleep quality.

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Research supported by a grant from SleepLab Software Ltd., Ann Arbor MI, [www.sleeplabsoftware.com](http://www.sleeplabsoftware.com)

#### 466.J

##### EFFECTS OF SLEEP DISRUPTION ON THE SYMPATHETIC NERVOUS SYSTEM ACTIVITY OF NORMAL SUBJECTS

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**Introduction:** We have reported that sleep disruptions by movement arousals independently predict daytime plasma norepinephrine in sleep apnea patients. Others have reported that RDI, even in the normal range, is a risk factor for the development of hypertension. In this study we hypothesized that sleep disruptions at the level seen in normal subjects contribute to their sympathetic nervous system (SNS) activity.

**Methods:** Thirty-one normal subjects were recruited to undergo an overnight polysomnogram as part of a protocol to compare SNS differences between African-Americans and Caucasians. A 24-hour urine collection for norepinephrine (NE) was started the night of admission. All were free from antihypertensive medications.

**Results:** Age ranged from 29 to 49 years. Body mass index was  $25.9 \pm 2.9$ , and all subjects consumed an isocaloric diet providing 170 mEq Na and 100 mEq K per day during the study period. Respiratory disturbance index (RDI) was  $2.1 \pm 2.1$  and the periodic leg movement during sleep index was  $0.17 \pm 0.38$ . Movement arousal index and total arousal index were  $9.4 \pm 5.0$  and  $11.3 \pm 5.7$ /hour respectively. The percent time spent at saturation (SpO<sub>2</sub>) below 90% was  $0.9 \pm 1.9$ %. None of these potential sleep disruption parameters correlated with 24-hour urine norepinephrine. The subjects were then divided by race. African-Americans ( $n = 23$ ) had a significant-

ly greater urinary NE level than Caucasians ( $n = 8$ ), ( $29,625 \pm 14,786$  Vs  $18,392 \pm 7,952$  pg/ml,  $p = 0.021$ ) and significantly greater BMI ( $26.6 \pm 2.7$  Vs  $24.0 \pm 2.8$ ,  $p = 0.04$ ). In African-Americans, RDI was correlated with urine norepinephrine ( $r = 0.604$ ,  $p = 0.005$ ). Arousal indices, periodic leg movement index, saturation, BMI and age did not correlate with urine norepinephrine. None of the above parameters correlated with urine norepinephrine in Caucasians. Linear regression analysis revealed that RDI was an independent predictor of 24-Hour urine norepinephrine in African-American subjects after controlling for BMI and total arousal index ( $t_{14} = 2.71$ ;  $p = 0.02$ ).

**Table 1**

##### Pearson Correlation Between 24-Hour Urine NE and sleep disruptive events in African-Americans

Variable	r	p Value
RDI	0.604	0.005 *
Total Arousal Index	-0.321	0.225
Movement Arousal Index	-0.335	0.205
Periodic Leg Movement Index	-0.090	0.707
% Time SpO <sub>2</sub> <90%	0.305	0.234
BMI	0.352	0.139
Age	-0.235	0.319

\*Based on Bonferroni's correction, a significant p value was determined to be  $\leq 0.007$

**Conclusions:** Urine NE levels were significantly higher in African-Americans. These data suggest that RDI, even when clinically within the normal range, is associated with SNS activity in African Americans but not in Caucasians.

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#### 467.J

##### HYPERACTIVITY IN CHILDREN WITH OBSTRUCTIVE SLEEP APNEA

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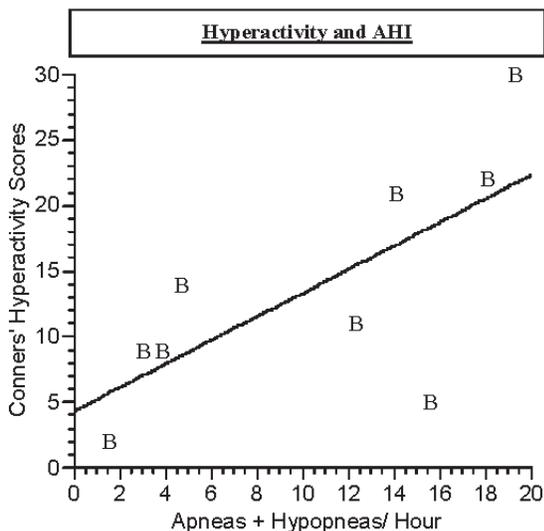
**Introduction:** The association of inattention and hyperactivity with snoring children has been suggested by parental reports (1). Parents of hyperactive children have reported more frequent awakenings in those children (2). It is possible that the daytime repercussions of children with obstructive sleep apnea (OSA) may include both inattention and hyperactivity. To further explore this hypothesis, we prospectively evaluated children with tonsillar hypertrophy and snoring using parental

reports of hyperactivity, restlessness, conduct or behavioral problems by Conner's questionnaire and polysomnography.

**Methods:** Children 3 through 14 years of age with tonsillar hypertrophy and snoring were prospectively studied by nocturnal polysomnography. Parents were asked to fill out a Conners' Global Index Parent Questionnaire (CGIPQ) prior to the sleep study. Sixteen children were enrolled with parental consent. Children with circadian rhythm disorders or neurodevelopmental problems were excluded. Standard nocturnal polysomnography was performed in an American Academy of Sleep Medicine-certified sleep disorders center and scored by a registered polysomnographic technologist according to the most recent criteria (3). All obstructive apneas and hypopneas were scored only if accompanied by a 4% decrease in oxygen saturation or 25% decrease in heart rate. An apnea index of at least one obstructive apnea/hour of sleep was considered sufficient to make the diagnosis of OSA.

**Results:** Nine subjects, 7 boys and 2 girls, age  $5.9 \pm 3.1$  (SD) years, had OSA with a mean apnea+hypopnea index (AHI) of  $10.4 \pm 7$  apneas+hypopneas/hour, while the remaining seven subjects, 4 boys and 3 girls, age  $4.8 \pm 1.95$  years, had primary snoring disorder (PSD) without significant OSA, with mean AHI =  $0.3 \pm 0.3$  apneas+hypopneas/hour,  $p < 0.005$ . There were significant differences in arousals ( $11.3 \pm 5.2$  vs  $4.7 \pm 1.6$  arousals/hour,  $p < 0.005$ ) and oxygen saturation nadir ( $82.7 \pm 7.2\%$  vs  $96.6 \pm 2.2\%$ ,  $p < 0.0005$ ), but there were no significant differences in age or in CGIPQ scores between those with and without OSA. However, among those with OSA there was a significant Pearson correlation ( $r = 0.7$ ,  $p = 0.036$ ) between AHI and hyperactivity scores on the CGIPQ (fig.1).

Figure 1



**Conclusions:** Hyperactivity scores on the Conners' Global Index Parent Questionnaire correlate with apnea+hypopnea index in children with obstructive sleep apnea. Among snoring children with tonsillar hypertrophy, there was no significant difference in reported behavior between those with and without sleep apnea. It is possible that among those without

sleep apnea, some children may have upper airway resistance syndrome or behavior problems which are unrelated to sleep-disordered breathing.

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**468.J**

**SLEEP APNEA MAY NOT ADVERSELY AFFECT PATIENTS UNDERGOING CARDIAC SURGERY.**

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**Introduction:** Obstructive sleep apnea (OSA) and coronary artery disease (CAD) share many risk factors including male gender, advancing age, obesity and diabetes mellitus. The apnea-hypopnea index (AHI) and the percent of sleep time in hypoxemia are fairly strongly correlated with prevalent CAD. (1) Sleep apnea may contribute to increasing morbidity and mortality in cardiovascular disease. Literature addressing the effect of sleep apnea in patients undergoing cardiac surgery is sparse. In addition to difficulties in airway management in these patients, they are also sensitive to central depressant drugs such as opioids. Post operative hypoxemia may have deleterious cardiac and cerebral consequences. We undertook this study to a) assess the incidence of peri-operative complications in patients with sleep apnea who underwent cardiac surgery and b) to identify clinical and/or polysomnographic (PSG) markers of adverse outcomes in these patients.

**Methods:** Retrospective observational study. The database of patients who underwent an overnight PSG from '96-'00 was matched with the database of patients who underwent open heart surgery within 2 years of the date of the PSG. Information collected included demographics, PSG variables (AHI, Lowest oxygen saturation and % of sleep time below 90% oxygen saturation), peri-operative complications such as respiratory failure, myocardial infarction (MI), stroke, arrhythmias, ICU and hospital length of stays and mortality. Univariate and multivariate analysis were performed. "Morbidity or Mortality" was calculated as any patient with any one of the following: respiratory failure, post-operative MI, stroke, arrhythmia or post-operative death.

**Results:** Among patients who underwent cardiac surgery from 1995 to 2000, 47 patients were diagnosed to have OSA by PSG. There were 37 males and 10 females aged  $60.11 \pm 11.79$  (mean  $\pm$  SD) years, with a BMI of  $39.41 \pm 41.19$  (Mean  $\pm$  SD). Co-morbidities included hypertension (77%), history of smoking (64%), history of MI (45%), Carotid disease (26%) and arrhythmias (9%). The ejection fraction by catheterization was  $45.3 \pm 10.5$  (mean  $\pm$  SD). The diagnosis of OSA was made in 17 out of 47 patients prior to open heart surgery but none were treated post-operatively with con-

tinous positive pressure(CPAP)therapy. The AHI was 23±20.5(mean±SD), the lowest oxygen saturation during PSG was 76.3 ±16.4(mean±SD)and 19.7%±24%(mean±SD) of the sleep time was spent below 90%.These PSG variables did not correlate with length of hospital or ICU length of stay,arrythmias or other post-operative complications by univariate or multivariate analysis although there was a trend towards increased length of ICU stay in patients with OSA. COPD and hypertension correlated with increased length of stay. Patients whose cardiac surgery was CABG alone had shorter ICU and hospital length of stay.

**Conclusions:** 1.OSA did not affect the outcome of cardiac surgery adversely in the immediate post-operative period until hospital discharge.2.A prospective study of patients with OSA who undergo cardiac surgery may be needed to confirm our findings.3.Among our group of patients,COPD and hypertension were found to prolong hospital length of stay.

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**469.J**

**SLEEP-DISORDERED BREATHING (SDB) AND CPAP USE IN AN URBAN, POOR POPULATION: ANALYSIS BY GENDER**

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**Introduction:** The prevalence and severity of SDB is influenced by risk factors such as obesity, gender, and underlying medical conditions. In addition, African-Americans also appear to demonstrate a higher risk and severity of SDB. Gender comparisons suggest that women with SDB typically display a lower AHI and less severe desaturation, despite a higher BMI. However, little information on the diagnosis and treatment adherence among urban, poor, populations with SDB is available. This study involves analysis of prospectively collected data from an urban, county hospital sleep clinic serving a predominantly uninsured, African-American population. We describe presenting features, PSG findings, and longitudinal CPAP usage patterns.

**Methods:** Data was prospectively collected from a population referred for evaluation of SDB. Subjects were asked to complete a health questionnaire including the Epworth sleepiness scale, Beck depression inventory, SF-36, and sleep hygiene questions. Polysomnographic information was collected utilizing a single laboratory with CPAP titration and PSG scoring performed according to standardized criteria. More than 80% of subjects underwent a split-night CPAP protocol. Subjects prescribed CPAP were provided downloadable CPAP equipment utilizing microchip technology, educated on proper use, and followed according to clinic protocol. This included clinic return one month after initiation of CPAP and every three months or sooner depending on treatment adherence. Information on subjects diagnosed with SDB and prescribed CPAP is presented here. Statistical analysis utilized t-test and chi-

square testing using SPSS version 9 software.

**Table 1**

	Male (n=135)	Female (n=113)	p value
Age (years)	42.0	50.8	<.001
BMI	44.4	49.0	.002
Percent Married	31%	18%	.032
Beck	14.6	16	.463
Epworth	15.8	16.4	.643
SF-36 Vitality	47	33	.021
SF-36 Pain	67	48	.013
Sleep Time	6.3 hrs	5.9 hrs	.027
Sleep Efficiency	81.5%	75.5%	.001
AHI	85	59	<.001
Effective CPAP Pressure	13.3 cm H2O	12.1 cm H2O	.002
CPAP Use Month 1	3.8 hr/d	4.0 hr/d	.721
CPAP Use Month 3	4.1 hr/d	4.4 hr/d	.518
CPAP Use Month 6	4.9 hr/d	4.4 hr/d	.591
CPAP Use Month 1 (Married Subjects)	4.1 hr/d	2.1 hr/d	.021

**Results:** Gender comparisons were performed on baseline presentation and questionnaire responses. PSG features, and CPAP adherence patterns are also illustrated in the table.

**Conclusions:** This study illustrates a pattern of severe SDB in an urban, poor population with distinct gender differences. Specifically, females present older, have several lower self-report quality of life scores, a higher BMI, but less severe SDB with lower effective CPAP pressures. Despite a lower AHI, self reported sleepiness was not different and sleep efficiency was lower. Treatment adherence with CPAP was similar over a 6 month study period although married males have a higher use of CPAP compared to married females. A better understanding of these differences may help facilitate gender-specific diagnostic and treatment approaches for SDB.

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**470.J**

**SLEEP-DISORDERED BREATHING IN A PREDOMINANTLY MINORITY SAMPLE**

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**Introduction:** Sleep-disordered breathing (SDB), which may be observed in the absence of daytime sleepiness and snoring, is estimated to affect as much as 25-50% of the US adult population.1 Investigators have found a consistent association between SDB and hypertension (HBP).2 It is also important to note that the prevalence of hypertension tends to be higher with increasing SDB severity. It has also been found that SDB is a correlate of reported morning headache.3 The present study examined sleep-disordered breathing in a predominant-

ly minority sample. Furthermore, we explored whether SDB measures differed between individuals reporting both a family history and a current diagnosis of HBP and those that did not. **Methods:** Data were collected as part of an-going study of sleep-disordered breathing in a minority population. Included in the present analysis were individuals (n = 61, age range = 23-94, mean BMI = 36 ± 8) who were initially referred to the sleep clinic because of a complaint of sleep difficulties. Fifty-two percent of the participants were female. The ethnic composition of the sample was as follows: Black = 77%, Hispanic = 7%, White = 16%). Participants spent a night in the laboratory where a comprehensive sleep recording was performed using the Biologic Systems. Standard physiological parameters were monitored including, sleep structure, SaO<sub>2</sub>, heart rate, respiratory effort, airflow, and EEG- and snoring-related arousals; all parameters were analysed by a trained polysomnographer using standard criteria.

**Results:** In the initial interview, 43% of the participants indicated that they suffered from high blood pressure and 44% reported a family history of HPB. Twenty-one percent reported that they were depressed and 24% reported morning headache. Of the individuals reporting HPB, 44% received a diagnosis of sleep apnea (using the 30-event apnea rule). The percentage of participants receiving the diagnosis was 63% when we considered both a family history of HBP as well as a current diagnosis of HPB. We also noted that 33% of the participants with HPB also reported morning headache, whereas 40% of those with both a family history and a current diagnosis of HBP reported morning headache. Table 1 compares sleep-disordered breathing measures of participants reporting both a family history and a current diagnosis of HBP vs. those that did not. Of note, the apnea-hypopnea index was substantially greater for Blacks (mean = 40±34), compared with Hispanics (mean = 15±14), or White (mean = 29±33).

Table 1

Comparison of Sleep-Disordered Breathing Measures		
Variable	HPB	HBP + FH
AHI	38±39	42±37
AHI (supine)	33±35	36±34
AHI (REM)	40±35	47±37
Obstructive	76±26	86±17
Central	21±27	10±16
Mixed	3±5	3±3
SaO <sub>2</sub> (%)	87±23	92±5
# Dessat	125±133	158±142
EEG AI	62±56	79±84
Snoring AI	35±53	35±39

**Conclusions:** These results are consistent with estimates of sleep-disordered breathing from previous epidemiological and clinical studies, demonstrating greater apnea-hypopnea indices for Blacks. The percentages of participants reporting high blood pressure and morning headache are also in agreement with previous findings. Our data further support the

associations between hypertension and SDB. However, they suggest that it is also important to consider family history of hypertension. Indeed, as shown in the table SDB was worse for individuals reporting both a family history and a current diagnosis of high blood pressure

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**471.J**

**DSM-IV DIAGNOSES IN CHILDREN SCHEDULED FOR ADENOTONSILLECTOMY OR HERNIA REPAIR**

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**Introduction:** Sleep-disordered breathing (SDB) is an explicit indication in 40% of children undergoing adenotonsillectomy (AT),<sup>1</sup> while among the remaining 60%, many may have undiagnosed SDB.<sup>2</sup> Although polysomnographically documented SDB in children is associated with inattentive and hyperactive behavior,<sup>3</sup> few children having ATs undergo polysomnography or psychiatric evaluation.<sup>1</sup> Behavioral problems of children who have AT are not well studied, and even among those with laboratory-documented SDB, the frequency of formal DSM-IV-based diagnoses is unknown.

**Methods:** Subjects were 53 children (28 boys and 25 girls), aged 5 to 12 (mean 7.8 ± 1.9) years who took part in an ongoing study of sleep and behavior in children. Each child had been scheduled for AT (n = 45) or seen at a general surgery clinic (n = 8 controls, most scheduled for hernia repair). A board-certified child and adolescent psychiatrist interviewed the parent(s) of each subject with the computerized Diagnostic Interview Schedule for Children (DISC), a well-validated instrument widely employed in behavioral research to make DSM-IV diagnoses. Further interviewing of subject and parent(s) verified DISC-based diagnoses. Diagnoses reported here were assigned in strict conformity with DSM-IV criteria, based upon all available data.

**Results:** Disruptive behavior disorders—attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, or conduct disorder - were diagnosed in 20 (44%) of the AT children but in 0 (0%) of the controls (Fisher's 2-tail exact test, p = 0.019). Differences between groups on individual diagnoses were not statistically significant (all p > 0.10) owing to sample size. Children were also evaluated for other DSM-IV diagnoses (Table 2), but none were more frequent

among AT subjects (all p > 0.10).

**Table 1**

DSM-IV disruptive behavior disorders in children [number (%)] scheduled for adenotonsillectomies (AT) or other procedures (controls).

Diagnosis (D = Disorder)	AT (n = 45)	Controls (n = 8)
ADHD-inattentive subtype	7 (16)	0 (0)
ADHD-hyperactive subtype	2 (4)	0 (0)
ADHD-combined	6 (13)	0 (0)
Oppositional Defiant D	9 (20)	0 (0)
Conduct D	0 (0)	0 (0)
Any DBD	20 (44%)	0 (0)

**Table 2**

Other DSM-IV disorders in children [number (%)] scheduled for adenotonsillectomies (AT) or other procedures (controls).

Diagnosis (D = Disorder)	AT (n = 45)	Controls (n = 8)
Social Phobia	3 (7)	1 (13)
Separation Anxiety D	2 (4)	2 (25)
Generalized Anxiety D	3 (7)	0 (0)
Obsessive Compulsive D	2 (4)	0 (0)
Post-Traumatic Stress D	0 (0)	0 (0)
Enuresis	10 (22)	3 (38)
Encopresis	1 (2)	0 (0)
Tic Disorder	1 (2)	0 (0)
Major Depressive D	0 (0)	0 (0)
Dysthymia	0 (0)	0 (0)
Mania	0 (0)	0 (0)
Hypomania	0 (0)	0 (0)
Pervasive Development D*	2 (4)	0 (0)

\*clinical diagnosis, not covered by DISC

**Conclusions:** Disruptive behavior disorders occurred in 44% of children scheduled for AT - many of whom have SDB - but in none of those scheduled for unrelated surgeries. The most frequent individual diagnosis, seen in 20% of the AT subjects, was oppositional defiant disorder, a condition often associated with crankiness and irritability. Disorders of attention comprised another large group (29%). Other DSM-IV diagnoses, however, were not more common in AT children. Although behavioral concerns are sometimes a major indication for AT, children rarely undergo formal behavioral evaluation prior to surgery.<sup>1</sup> These results suggest that such evaluations may be useful in some cases.

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**472.J**

**COGNITION AND BEHAVIOUR IN CHILDREN WHO SNORE COMPARED TO NON SNORERS AND RESTLESS SLEEPERS**

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**Introduction:** Although snoring can be a benign condition, it can also be an indicator of sleep related breathing disorders (SRBD). While not universal, children who snore have also reported fragmented sleep. Preliminary research indicates that children with SRBD exhibit attentional deficits, cognitive impairment and increased behavioural problems. Generally these studies have used selective patient groups referred to sleep units for assessment of snoring and related upper airway obstruction. However it remains to be established if similar deficits exist in children from the community who report a history of snoring and/or restless sleep.

**Methods:** A subset of 84 children (age range 6-16y) (Snorers with restless sleep = 15, Snorers without restless sleep = 14, Non Snorers = 36, Restless sleepers = 19; 38 males) from an epidemiological survey, underwent psychometric testing using age appropriate standardised instruments.[ie.intelligence (Wechsler Abbreviated Scale of Intelligence-WASI), memory (Numbers subtest, Children's Memory Scale-CMS; Word pairs subtest, CMS), attention (Auditory Continuous Performance Test - ACPT; Code Transmission subtest-CT, Test of Everyday Attention in Children-TEA-Ch), behaviour (Child Behaviour Checklist-(CBCL) Sleep history was assessed with the Sleep Disturbance Scale for Children (SDSC).

**Table 1**

Measure	Group status			
	Snorers with RS	Snorers without RS	Non snorers	Restless sleepers
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Intelligence				
Global IQ	86.1(7.3) ****	92.9 (10.9)	99.4 (11.1)	95.4 (10.1)
Attention				
Selective attn (# errors)	14.2 (8.5) *	11.6 (8.1)	7.6 (8.2)	6.6 (4.4)
Impulsivity	8.9 (3.8) ***	8.2 (5.0)	4.6 (4.5)	5.7 (3.5)
Sustained attn	6.5 (3.1) *	6.6 (3.9)	8.9 (2.4)	7.9 (2.6)
Memory				
Numbers backward	7.9 (1.8) *	10.2 (1.8)	9.6 (2.3)	8.6 (2.30)
Total numbers	6.9 (1.6) *	9.1 (1.5)	8.7 (2.6)	7.5 (2.7)
Behaviour				
Total behaviour	61.4(13.2) ****	53.9 (11.4)	46.7 (11.4)	61.6 (10.1)

denotes p<0.05,\*\*p<0.01,\*\*\*p<0.005,\*\*\*\*p<0.001

**Results:** Preliminary analyses reveal significant between group differences (ANOVA). Children who snore show poorer cognitive performance and attention and increased problematic behaviour than children who do not snore. Children with restless sleep show poorer memory than both other groups and similar problematic behaviour to snorers.

**Conclusions:** These preliminary results support emerging evidence of neuropsychological impairment in children who snore. As well they present new data that fragmented sleep without snoring can also effect neuropsychological functioning and behaviour.

Research supported by Adelaide Northern Division of General Practice, Australia

**473.J**

**PREDICTORS OF POSTOPERATIVE RESPIRATORY COMPROMISE IN CHILDREN WITH SNORING UNDERGOING TONSILLECTOMY (T) AND OR ADENOIDECTOMY (A)**

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**Introduction:** Obstructive breathing during sleep is a common indication for T and or A surgery in children. Morbidity and mortality associated with this procedure has declined significantly with advances in anesthetic and surgical techniques. However postoperative respiratory complications continue to represent a significant morbidity following the procedure. We hypothesized that patients who develop postoperative respiratory complications after T and A surgery for obstructive breathing during sleep differ from the group that do not have postoperative respiratory complications in their demographic characteristics and presence of co-morbid conditions. The goal of this study is to identify the factors that predict postoperative complications.

**Methods:** A total of 3986 patients underwent T and or A surgery at Children’s Hospital from June 2000 to May 2001. Obstructive breathing during sleep was the indication in 1842 children. 103 (4.7%) patients, who developed postoperative respiratory complication requiring intervention, constituted our study group. 103 patients who had T and or A surgery for obstructive breathing during sleep on the same date as the study group, but did not have any respiratory complication, were selected as the control group. We performed retrospective review of the chart records of the two groups and compared them for age, weight, race, sex, and for presence of co-morbid conditions. Results are expressed as mean ± standard deviation. Student’s t test and Chi-square analysis were performed to measure the difference in demographics between the two groups. Bivariate correlation and multiple regression analysis were performed to measure the association between different variables.

**Results:** The two groups differed in age, weight, racial composition, gender and presence of co morbid conditions. Asthma was the most common co morbid condition in the study group.(Table1).Bivariate correlation showed a significant correlation between occurrence of postoperative complications and younger age (p< .001), presence of associated medical

condition (p<. 001), and African American race (p <. 003). Multiple regression analysis showed that the strongest predictor for post operative complication was young age, followed by presence of co morbid condition, followed by African American race. A model that included age, presence of co morbid conditions, and African American race explained 35 % of the variability (p value <. 0001). Out of the 103 patients who developed complications, 100 had oxygen desaturations below 90% requiring O2 supplementation, 34 required Nasal airway, 8 required continuous positive airway pressure support and 15 required endotracheal intubations. Chest radiograph was abnormal in 21 patients.

**Table 1**

Variable	Study Group N=103	Control Group N=103	P value
Age (years)	3.77 ± 2.45	6.98 ± 3.52	<. 0001
Weight( Kg)	20.98 ± 17.63	30.21 ± 17.49	.0021
African American race (N)	40	17	<. 0005
Male Sex (N)	71	49	<. 0005
Co morbid condition (N)	50	18	<. 0005
Asthma (N)	29	17	<. 05

**Conclusions:** We concluded that young age, presence of co morbid conditions especially reactive airway disease, and African American race are associated with increased incidence of postoperative respiratory complications.

**474.J**

**WOMEN WITH FIBROMYALGIA ARE PREDISPOSED TO SLEEP-RELATED BREATHING DISORDERS**

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**Introduction:** Fibromyalgia (FM) is commonly associated with sleep complaints, such as nonrestorative sleep and daytime sleepiness, that are supported by altered polysomnographic findings including increased arousals, decreased slow wave sleep, and alpha intrusion into delta wave sleep. Sleep-related breathing disorders (SRBD) such as obstructive sleep apnea syndrome (OSAS) and upper airway resistance syndrome (UARS) have been described in males with FM, but this association was not found among females with FM (May et. al, 1993). Another study did not find significant association with sleep apnea in either group (Molony et. al, 1986). Our objective is to investigate the prevalence of SRBD in women

with FM.

**Methods:** We retrospectively studied 34 women with a diagnosis of FM. Complaints consisted of excessive daytime sleepiness (EDS), insomnia, awakenings, snoring, and witnessed apneas. Objective data such as age, Epworth Sleepiness Scale (ESS), Body Mass Index (BMI), and respiratory data (apnea-hypopnea index (AHI), arousal index, and UARS) were reviewed. An ESS > 10 and BMI > 27.3 Kg/M<sup>2</sup> were defined as abnormal. OSAS was grouped into mild (AHI: 5-20), moderate (>20-40), and severe (>40). UARS was defined by snoring associated with an arousal index >10, paradoxical respiratory effort, and repetitive desaturations.

**Results:** Of the 34 subjects, the most common complaints were EDS and snoring (70%). Other complaints were insomnia (53%) and frequent awakenings (24%). The least common complaint was witnessed apneas (17.6%). The average age was 51 years (range 36-75). The mean ESS was 12.6 (range 2-33) and the mean BMI was 32 (range 21-73). SRBD was present in 62% (OSAS: 47%; UARS: 15%) of the women. Thirteen women had mild OSAS, one woman had moderate, while two women had severe OSAS. The mean AHI was 9.1 (range 0-80). Primary snoring was present in nine (26%) women. Four women (12%) had no evidence of SRBD.

**Conclusions:** A high proportion of women with FM have SRBD (62%), compared to that reported in women in the general population (9%) (Young et al, 1993). SRBD may contribute to their sleep complaints.

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#### 475.J

##### SLEEP-DISORDERED BREATHING IN WOMEN WITH CORONARY HEART DISEASE

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**Introduction:** Women appear to be increasingly susceptible to regular snoring and sleep apnea after menopause. Whether sleep apnea increases risk of coronary artery disease (CAD) in postmenopausal women remains unclear. We investigated the prevalence of sleep-disordered breathing, such as the sleep apnea syndrome (SAS), in women with CAD.

**Methods:** Among 113 patients with CAD, verified by coronary angiography, 41 women were compared with 72 men. Overnight polysomnographic recordings were performed in a stable condition of CAD.

**Results:** The prevalence of SAS with an apnea-hypopnea index (AHI; the number of apneas or hypopneas per hour of

sleep) >5 was 62 of the 113 subjects (54.9%). Women with CAD had AHI>5, 61.0% (n=25), and AHI>30, 26.8% (n=11), while men with CAD had 51.4% (n=37, ns), and 11.1% (n=8, P<0.05), respectively. The mean age of female subjects was older than that of male subjects (57.7 }9.9 vs 66.2 }7.1 years of old, P<0.01), and women with both of CAD and SAS were postmenopausal.

**Conclusions:** Since a complication of SAS in CAD was a high incidence, all patients with CAD should lead to evaluation for sleep-disordered breathing. We consider SAS as one of the causative factors of CAD, especially in postmenopausal women.

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#### 476.J

##### THYROID MASS ASSOCIATED WITH TRACHEAL DISTORTION AND OBSTRUCTIVE SLEEP APNEA

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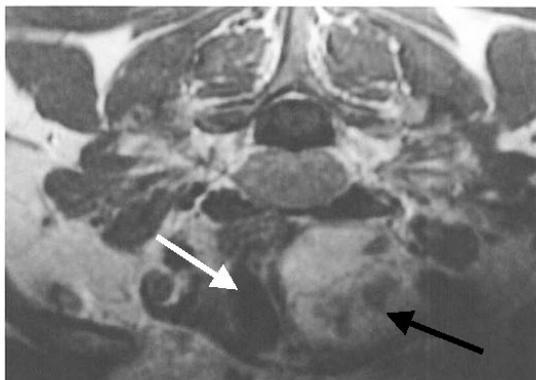
**Introduction:** A relationship between tracheal deviation and obstructive sleep apnea (OSA) has not been well documented in the medical literature. We report the case of a gentleman who developed a thyroid mass associated with severe OSA.

**Methods:** A 46-year-old, 70 inch, 223 pound gentleman, under our care since 1992 for the treatment of REM Sleep Behavioral Disorder and mild idiopathic daytime hypersomnia, presented in December of 1999 with a dramatic worsening of daytime sleepiness. There was no change in baseline medications, weight gain or alteration of sleep hygiene. Sleepiness was problematic and he was involved in a minor automobile accident. An MRI of the cervical spine obtained following the accident revealed an anterior neck mass extending to the right of the midline, compressing and deviating the trachea (Figure 1). The mass and tracheal deviation were obvious on physical examination. Work up included a severely abnormal daytime Multiple Sleep Latency Test (MSLT) with an average sleep latency of 1.9 minutes and no REM intrusions. A polysomnogram revealed severe obstructive sleep apnea with an overall apnea+hypopnea index of 77/hour with desaturations down to 73% and severe sleep fragmentation. Prior polysomnograms of 1992 and 1997 revealed no evidence of clinically significant obstructive sleep apnea (Table 1). The patient responded to treatment with CPAP at a pressure of 8 cm.

**Results:** Complete thyroid function studies were entirely normal and the patient underwent total thyroidectomy in July 2000. Pathological diagnosis was adenomatoid colloid goiter with Hurthle-cell changes and follicular adenoma in the right lobe and adenomatoid colloid goiter for the left lobe. Repeat polysomnography in January 2001 after a 3 week hiatus in

CPAP treatment revealed improvement in OSA to pre-morbid levels with the exception of rare events associated with oxygen desaturations down to 80%. (Table 1) Excessive daytime sleepiness also gradually improved to his baseline level.

Figure 1



MRI scan of neck revealing right cystic thyroid mass (black arrow) and compressed, deviated trachea (white arrow).

Table 1

	Apnea+Hypopnea Index (per hour)	Total Sleep Time (min)	Mean Duration (sec)	Greatest Desaturation
Jun-92	5.9	497	10-12	92%
May-97	13	456	13	90%
Dec-99	77	428	16	73%
Jan-01	12	364	13	80%

Overnight polysomnographic data obtained with standard 16 channel recording including EEG, Chin EMG, EOG, nasal thermister (1992 & 1997 studies), nasal flow pressure (1999, 2001), oral thermister, chest and abdominal movements, EKG, limb EMG, snore and oxygen saturation. Studies were all hand scored by Emsellem.

**Conclusions:** This case documents a thyroid mass associated with tracheal deviation and compression causing OSA. There was no evidence of tracheomalacia to suggest that obstruction occurred due to failure of tracheal integrity. In a prior report of two cases of OSA seen in association with thyroid enlargement it was postulated that thyroid enlargement might impair the function of muscles attached to the hyoid bone, thereby increasing the risk of OSA.<sup>1</sup> We hypothesize that tracheal deviation may have produced torsional forces on the upper airway resulting in distortion of the airway and increased risk of obstruction. The possibility of OSA should be considered in any patient with significant thyroid enlargement, particularly if there is associated loud disruptive snoring and disproportionate hypersomnia. Tiredness generally attributed to thyroid dysfunction may be due to the presence of OSA.

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**477.J**

**GENIOGLOSSUS NEGATIVE PRESSURE REFLEX RESPONSES AND UPPER AIRWAY COLLAPSIBILITY DURING THE INSPIRATORY AND EXPIRATORY PHASES OF RESPIRATION**

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**Introduction:** Phasic respiratory controller and negative pressure (NP) reflex activation of upper airway (UA) dilator muscles are thought to play a major role in promoting UA patency during inspiration. In support of this hypothesis, UA anaesthesia in humans has been shown to attenuate the genioglossus (EMGgg) reflex response to UA NP and increase UA collapsibility during inspiration. In anaesthetized animals, the EMGgg response to UA NP is markedly attenuated during expiration.<sup>1</sup> In humans, there is remarkably little information regarding UA collapsibility and dilator muscle reflex responses during expiration, when phasic activation of UA dilator muscles is absent. The aim of this study was to compare UA collapsibility and EMGgg NP responses during inspiration and expiration.

**Methods:** Seven healthy males (mean  $\pm$  SEM age  $25 \pm 2$  years, BMI  $25.0 \pm 1.7$  kg.m<sup>-2</sup>) participated, breathing via a nasal mask and pneumotachograph. A computer-controlled rapid actuating solenoid valve system was used to examine UA collapsibility (peak choanal-epiglottic pressure) and the EMGgg (bipolar intramuscular electrodes) reflex response to ~200 msec pulses of UA NP (-10 to -12 cmH<sub>2</sub>O choanal pressure). NP pulses were delivered for 25-min every 3-7 breaths during early inspiration and mid-late expiration. Data from replicate pulses were compared between inspiration and expiration using Student's t-tests.

**Results:** Subjects received  $52 \pm 4$  inspiratory and  $49 \pm 3$  expiratory pulses. Whilst care was taken to deliver comparable NP stimuli, the minimum choanal pressure was more negative during inspiratory pulses ( $-12.3 \pm 0.6$  vs expiratory  $-10.4 \pm 0.6$  cmH<sub>2</sub>O,  $p < 0.001$ , Figure 1). Despite the smaller stimulus, UA collapsibility, as conventionally measured,<sup>2</sup> was greater during expiration ( $5.5 \pm 1.1$  vs inspiration  $3.1 \pm 0.4$  cmH<sub>2</sub>O,  $p = 0.026$ ). However, peak expiratory flow, measured during the NP pulse, was also greater during expiration ( $1.37 \pm 0.07$  vs inspiration  $1.00 \pm 0.08$  l.sec<sup>-1</sup>,  $p < 0.001$ ) such that flow resistance calculated at peak expiratory flow was not significantly higher during expiratory pulses ( $4.2 \pm 0.8$  vs inspiratory  $3.3 \pm 0.5$  cmH<sub>2</sub>O.l<sup>-1</sup>.sec respectively,  $p = 0.093$ ). Within ~30 msec of the NP stimulus onset there was an augmentation in the rectified and moving time averaged EMGgg activity, reaching a peak within ~200-250 msec. The peak response above baseline was not different between inspiratory ( $0.12 \pm 0.02$  au) and expiratory ( $0.11 \pm 0.02$  au,  $p = 0.524$ , Figure 1) pulses. Only 1 subject exhibited changes in the averaged raw EMGgg signal that were clearly reflex in origin (i.e. within the first 100 msec of the pulse). This response was qualitatively similar between inspiratory and expiratory pulses.

Figure 1A

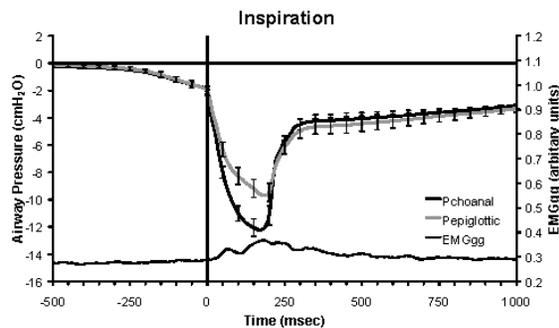
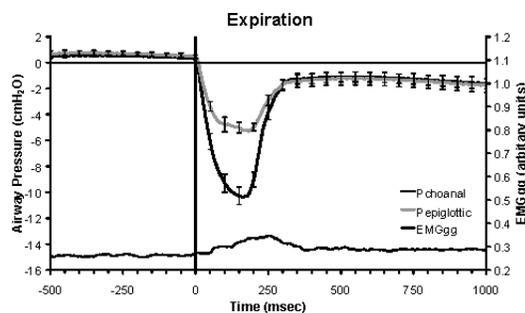


Figure 1B



Choanal and epiglottic pressures and the rectified and moving time (50 msec) averaged genioglossus (EMGgg) response to brief (~200 msec) negative pressure pulses applied during early inspiration (A) and mid-late expiration (B). Values are means $\pm$ SEM, n=7.

**Conclusions:** Although greater UA collapsibility during expiration compared to inspiration supports the hypothesis that phasic activation of UA dilating muscles is important for stabilizing the UA, collapsibility measured in this manner appears inadequate to support such a conclusion. The EMGgg response to NP does not appear to be attenuated during expiration. How much of this response is truly reflex in origin is unclear.

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## 478.J

### THE VENTILATORY RESPONSE TO AROUSAL FROM STAGE 2 SLEEP IN HEALTHY MEN AND WOMEN.

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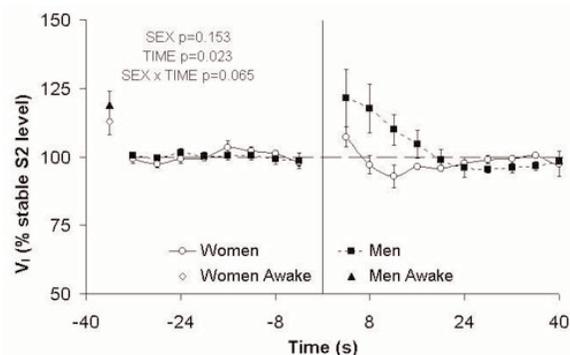
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**Introduction:** Obstructive Sleep Apnea (OSA) is more common in men than in women for reasons that are unclear. Respiratory control instability has been postulated as a possible mechanism for OSA. The ventilatory response to arousal from sleep may be an important determinant of respiratory stability/instability. For example, an excess ventilatory response could lead to acute changes in blood chemistry that may subsequently predispose to reduced respiratory drive and therefore upper airway obstruction on resumption of sleep. In this study we have compared the ventilatory response to auditory induced arousals from stage 2 sleep in men and women.

**Methods:** Healthy men and women in the follicular menstrual phase (5 of each sex to date) were fitted with a nasal mask connected to a pneumotacograph and capnograph for measurement of inspiratory minute ventilation ( $V_{s1s}$ ) and end tidal CO<sub>2</sub> (PETCO<sub>2s</sub>). Standard EEG, EOG and EMG were recorded for sleep staging and arousal scoring. Following 5 minutes of resting wakefulness subjects were asked to go to sleep. Once subjects were in stable stage 2 sleep (S2) in the left lateral position, they were briefly awoken with an auditory tone (0.5s, 1000Hz, 55-95dB) through ear-insert headphones. Sleep staging and arousal scoring was performed by a single trained sleep technician blinded to ventilatory and tone data. Tones associated with 3-15s arousals and not preceded or followed by another arousal (within 30s) were analysed. Data for 32s prior to and 40s following arousal were interpolated at 4s intervals and compared between genders with ANOVA for repeated measures. Wake and S2 data were compared between genders with Student's t-tests. Data are presented as mean  $\pm$  SEM and p<0.05 was considered significant.

**Results:** The men and women studied had normal lung function and did not differ in terms of age ( $27.1 \pm 2.5$  yrs) or BMI ( $22.8 \pm 0.8$  kg/m<sup>2</sup>). During wakefulness,  $V_{s1s}$  was higher in men than women ( $8.2 \pm 0.3$  vs  $6.3 \pm 0.3$  l/min) and PETCO<sub>2s</sub> levels were not different ( $40.3 \pm 2.1$  in men vs  $41.1 \pm 0.7$  mmHg in women). These differences persisted during S2 sleep ( $V_{s1s}$   $6.9 \pm 0.2$  and  $5.6 \pm 0.2$  l/min and PETCO<sub>2s</sub>  $43.1 \pm 1.2$  and  $42.3 \pm 0.7$  mmHg in men and women respectively). 95 tone-induced arousals were analysed. The arousal duration was  $6.4 \pm 0.3$ s and tone volume was  $61.5 \pm 0.9$ dB and neither were different between genders. The ventilatory response to arousal appeared to be higher and last for longer in men than in women (p=0.065, Figure 1). Correspondingly PETCO<sub>2s</sub> levels tended to fall in men following arousal but not in women ( $2.1 \pm 1.9$  vs  $0.1 \pm 0.2$  mmHg lower than S2 level in men and women respectively) although this was not significant.

Table 1



**Conclusions:** The men studied had a trend towards a larger increase in minute ventilation following brief arousal from sleep than women. If this finding is confirmed in a larger sample of men and women, then it may suggest that men are more prone than women to respiratory instability following arousal from NREM sleep.

Research supported by the NH&MRC Australia.

#### 479.J

##### CORRELATIONS BETWEEN BREATH HOLDING ABILITY WHILE AWAKE AND OBSTRUCTIVE SLEEP APNEA SEVERITY

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**Introduction:** An individual's ability to breath hold is affected by many factors. Some studies suggested the mechanism to be physiological (2) while others, psychological (1). As seen in skin divers, the ability to hold one's breath increases with training (1). Patients with obstructive sleep apnea (OSA) are subjected to chronic involuntary breath holding before the disease is diagnosed and treated. In addition, it has been shown that OSA patients have impaired hypoxic ventilatory response (HVR) which is an important predictor of breath-holding ability (2). Therefore, we hypothesize that OSA patients may have changes in their breathing-holding ability.

**Methods:** Patients presented for an evaluation of sleep-disordered breathing were recruited. Patients with significant cardiac, pulmonary or neurologic disease were excluded from the study. Each subject was asked to take 3 deep breaths and then hold breath at the total lung capacity for as long as possible. In addition to the total breath-holding time, blood pressure, heart rate and oxygen saturation were recorded before and after the breath holding. The patients then had a standard in-laboratory polysomnography. The breathing holding time was compared between patients with OSA (apnea/ hypopnea index, AHI>5) and controls (AHI< or = 5). Correlation coefficient was used to determine the relationship between the breath holding ability (using breath holding time) and the sleep-disordered breathing severity (using AHI and lowest oxygen saturation).

**Results:** Twenty-four patients met the criteria for entry into analysis (5 control [C] and 19 OSA [A]). No significant difference in the age ( $47.6 \pm 13.5$  [C] vs.  $52.6 \pm 10.8$  [A];  $p>0.05$ ) and awake baseline oxygen saturation ( $96.4 \pm 1.3$  [C] vs.  $95.6 \pm 1.6$  [A];  $p=>0.05$ ) was observed between the two groups. The breath holding duration in patients with obstructive sleep apnea was significantly longer than control ( $38.2 \pm 8.1$  [C] vs.  $59.3 \pm 18.9$  [A];  $p=0.02$ ). However, the correlation coefficient between the breath holding time and the AHI was  $-0.05$  and between the breath holding time and the lowest oxygen saturation during sleep was  $0.03$ .

**Conclusions:** This study demonstrates that patients with OSA have significant increase in breath-holding ability during awake, but there is no direct relationship between the breathing holding ability and severity of apnea or lowest oxygen saturation during sleep. It is speculated that chronic involuntary training during sleep increases the breath holding ability of OSA patients through a physiologic mechanism, but it is unclear whether modulation of HVR in this population plays a primary role.

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#### 480.J

##### TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN STROKE PATIENTS

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**Introduction:** Stroke patients demonstrate a high prevalence of Obstructive Sleep Apnea (OSA) (1) and treatment of OSA may improve stroke outcome (2). The variability of neurological deficits associated with stroke may cause variable CPAP pressure requirements. In order to evaluate the efficacy of auto-CPAP, we conducted this prospective treatment trial.

**Methods:** Forty-two stroke (hemorrhagic and ischemic) in patients were screened. Patients had stroke within a period of thirty days. Twenty-two patients were excluded due to unstable clinical conditions and/or no acceptance to participate. A total of twenty patients was enrolled. Baseline clinical evaluation: sleep history, ESS (Epworth Sleepiness Scale), NIH stroke scale, FIM (Functional Independence Measurement) scale and portable sleep study. Follow-up after 1, 4 and 8 weeks included clinical evaluation, ESS and FIM scales. Stroke was diagnosed by clinical examination and image studies (MRI, CT).

**Results:** Twelve patients met the final criteria of AHI >10 events/h (mean RDI: 12.8 events/hour). Mean age: 62 years old, mean BMI: 23.4 kg/m<sup>2</sup>, mean NIH stroke score: 6, 10M/2F. Patients started a treatment trial with Auto-CPAP with pressures ranging from 4-15 cmH<sub>2</sub>O. Six patients dropped out after starting Auto-CPAP for various reasons (feeling suffocated, uncomfortable with the mask). Six patients continued to use Auto-CPAP at home. Three patients reported a significant decrease of nocturnal awakenings

caused by nocturia (from 5 to 1 or 2 times). Five out of six patients reported a general decrease in nocturnal awakenings and improvement in sleep quality. Three patients reported subjective improvement in daytime sleepiness and increase in daytime energy. From the group of four patients who completed 8 weeks of Auto-CPAP, 3 patients wanted to continue to use Auto-CPAP due to improvement in sleep quality and daytime alertness.

**Conclusions:** Stroke patients may present a challenge for treatment, since their overall acceptance to therapy is lower and sensitivity to adverse effects higher than non stroke OSA patients. All patients presented an improvement in sleep quality and the majority showed an increase in daytime energy. Compared to other Auto-CPAP trials on OSA patients in similar settings, the drop-out rate is clearly higher. Patient and clinician education about OSA and the potential benefits of positive airway pressure treatment needs to be improved. The role of auto-titration devices should be assessed in order to optimize clinical outcomes in stroke patients.

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#### 481.J

##### RESPIRATORY MUSCLE STRENGTH ASSESSED NON-INVASIVELY IN RELATION TO CURRENT OR PREVIOUS NEED FOR MECHANICAL VENTILATORY SUPPORT AMONG POST-POLIO PATIENTS

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**Introduction:** Respiratory failure requiring nocturnal ventilatory support is a recognized late complication of previous poliomyelitis and is often related to weakness of the respiratory muscles.

**Methods:** We assessed 50 post-polio patients non-invasively to look at the relationship between the current or previous need for ventilatory assistance and respiratory muscle weakness. The seated forced vital capacity (FVC), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and sniff nasal inspiratory pressure (SNIP) were measured in each patient.

**Results:** At the time of testing, 21 patients were using nocturnal ventilatory assistance and 29 were on no ventilatory support. These two groups were similar in terms of age, BMI and time since acute polio. Thirteen of the 21 ventilated patients had been ventilated during the acute polio compared to 13 of the 29 non-ventilated patients. The % predicted FVC was significantly lower in the ventilated group than the non-ventilated group ( $P=0.01$ ), but there was no significant difference in either the MIP or the MEP value between the two groups. The SNIP (both absolute value and % predicted) was highly significantly associated with the need of current ventilatory support ( $P<0.0001$ ). There was also a significant difference in

the % predicted SNIP ( $P=0.04$ ) between the subgroup of non-ventilated patients who had been ventilated during their acute illness and the subgroup that had never been ventilated. However, both subgroups did not show significant differences as regards FVC, MIP and MEP. None of the test parameters showed any significant differences between the subgroup of currently ventilated patients who had been previously ventilated and the subgroup of currently ventilated with no previous ventilation. Also, both subgroups did not show any significant differences as regards age, body mass index, presence of kyphoscoliosis, or the time post polio.

**Conclusions:** Currently ventilated post-polio patients have significantly lower FVC and SNIP values (suggesting global inspiratory muscle weakness) compared to non-ventilated patients. Non-ventilated patients who were ventilated during the acute illness are still significantly weaker than patients who were never ventilated, raising the question that they may still need to be ventilated in the future.

#### 482.J

##### OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME IN WOMEN EVALUATED FOR GASTRIC BYPASS SURGERY

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**Introduction:** Obstructive sleep apnea hypopnea syndrome (OSAHS) is present in more than 50% of morbidly obese patients, with severe OSAHS occurring in over 15% of morbidly obese women<sup>1</sup>. In addition to vascular co-morbidities, the post-anesthetic state and subsequent use of narcotic analgesics following surgery may exacerbate OSAHS<sup>2</sup>. Identifying patients at risk for OSAHS may not only reduce long-term vascular risk, but also lead to fewer post-operative complications.

**Methods:** A series of 347 women were evaluated by a pulmonologist board certified in sleep medicine prior to Roux-en-Y gastric bypass surgery. The evaluation included a complete medical and sleep history, physical exam and spirometry. Patients were asked to rate sleep symptoms- snoring, observed apnea, gasping, morning headache, congestion, mouth breathing, sweating, persistent cough, reflux and restlessness in the following terms: (1) never to (5) nightly. Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS). Patients with symptoms consistent with OSAHS were referred for laboratory polysomnography (PSG); those with few or no clinical symptoms were referred for nocturnal oximetry, or testing was deferred. Abnormal oximetry was followed by laboratory PSG.

**Results:** The mean age for the sample was  $41 \pm 10$  yrs, BMI  $50 \pm 9$  kg/m<sup>2</sup>. Forty percent ( $n=139$ ) were referred for polysomnography; 58 received split-night studies according to AASM guidelines; 22% ( $n=78$ ) had normal oximetry, and in 29% ( $n=102$ ) testing was deferred. Only 27 (8%) of the 347 women had received prior PSG testing. This contrasts with 44 men evaluated during the same time period, in which 28 (64%) had prior PSG testing ( $p < 0.0001$ ). To assess which pre-test variables would predict clinically significant OSAHS in

women, those with current PSG data were divided into two groups: moderate to severe OSAHS: AHI  $\geq$  15 + SaO<sub>2</sub> nadir < 90% and mild or no OSAHS: AHI < 15 + SaO<sub>2</sub> nadir > 90%. Nineteen percent of patients had moderate to severe OSAHS. This group had higher ESS scores (10.3 vs. 8.5;  $p = 0.05$ ) and more frequent snoring (4.0 vs. 4.5;  $p = 0.01$ ). Body mass index, age and pulmonary function were not different between the two groups.

**Conclusions:** Moderate to severe OSAHS was present in 19% of this sample. Morbidly obese women were 8 times less likely than men to have had prior laboratory investigation of OSAHS, despite similar symptoms of daytime sleepiness and snoring. Identifying all patients at risk for significant OSAHS may reduce post-operative complications and prevent vascular co-morbidities.

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### 483.J

#### THE RELATION BETWEEN SLEEP HYGIENE BEHAVIORS AND SEVERITY OF SLEEP DISORDERED BREATHING

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**Introduction:** Poor sleep hygiene has been widely cited as a cause of poor sleep in patients with insomnia. However, patients with other sleep disorders also report engaging in poor sleep hygiene behaviors. Therefore, it is possible that poor sleep hygiene can be a consequence, rather than a cause, of disturbed sleep. The purpose of this study was to assess the presence of poor sleep hygiene behaviors in a sample of patients with obstructive sleep apnea syndrome (OSAS).

**Methods:** All patients completed a measure of 7 facets of sleep behaviors as measured by a sleep hygiene behavior checklist. This scale used a 7-point Likert scale to rate the following behaviors: watching television, reading, listening to the radio, eating, talking on the telephone, working or studying, and using the computer in the bedroom. Scores ranged from 1 (every night) to 7 (never), with lower scores representing poorer sleep hygiene. This instrument was administered consecutively to patients in our sleep disorders center. Patients identified as having sleep disordered breathing were retrospectively reviewed.

**Results:** As expected, the group with an AHI>20 also had worse sleep, as shown by shorter TST ( $p<.0001$ ), increased % stage one sleep ( $p<.0001$ ), and increased WASO ( $p<.0001$ ).

**Table 1**

	AHI <20 n=51		AHI > 20 n=107		P-VALUE
	Mean	SD	Mean	SD	
Total Sleep Hygiene	38.90	(8.10)	35.70	(9.46)	.019
Watching Television	4.41	(2.35)	3.21	(2.41)	.002
Reading	5.04	(2.05)	4.87	(1.90)	NS
Listening to the Radio	6.10	(1.65)	5.70	(1.91)	NS
Eating	5.59	(1.94)	5.14	(2.27)	NS
Talking on the Phone	5.80	(1.66)	5.28	(1.86)	.045
Work or Studying	6.00	(1.78)	5.42	(1.99)	.035
Using a Computer	5.96	(1.97)	5.84	(2.03)	NS

**Conclusions:** Patients with moderate-to-severe OSAS have significantly worse sleep hygiene, as characterized by increased rates of engaging in waking activities in the bedroom as compared to patients with mild OSAS. Since it is unlikely that poor sleep hygiene causes an increase in the AHI, these data are interpreted to support the view that increased sleep disturbance, whatever the cause, predisposes to an increase in poor sleep hygiene behaviors. These findings have implications for understanding the role (cause vs. consequence) of poor sleep hygiene in patients with insomnia.

### 484.J

#### REACTIVE AIRWAYS DISEASE, GERD AND OBSTRUCTIVE SLEEP APNEA: A RELATIONSHIP REVISITED

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**Introduction:** Obesity, hyperreactive airways disease (HAD), obstructive sleep apnea syndrome (OSA) and gastroesophageal reflux (GERD) are common in the U.S. population. All these disorders are associated with increased morbidity and mortality in affected individuals. For various reasons, including obesity (partially steroid-induced), rhinosinusitis, nasal obstruction, GERD and HAD may be predisposed to developing OSA. We describe 29 patients referred for evaluation of dyspnea in a pulmonary-allergy clinic, despite intensive treatment who had a symptom complex of GERD, HAD and OSA.

**Methods:** 29 patients referred to our clinic for evaluation of dyspnea were studied. Patient demographics including age, sex, blood pressure and body mass index (BMI) were noted. Data from the sleep questionnaire, pulmonary function tests (PFT), polysomnography (PSG) and 24 pH studies and history and physical examination were reviewed and analyzed.

**Results:** 16 out of 29 (16/29) patients (55%) had obstructive lung disease. 13/29 (45%) had evidence of bronchial reversibility. 23/29 (79%) had symptomatic GERD of which 5/7 (71%) had a positive 24 hour pH study so far. 25/29 patients (86%) had symptoms of rhinitis, cough and wheezing. 25/29 patients (86%) had a history of snoring, snort arousals, and witnessed apneic episodes. 28/29 (97%) had excessive daytime somnolence suggestive of OSA. So far, 17/17 (100%) patients who have had PSG have had documented evidence of OSA. The study is ongoing.

**Conclusions:** Patients referred for refractory dyspnea with above risk factors (such as GERD, rhinosinusitis and HAD) must be screened for OSA by primary care physicians and subspecialists caring for these patients. Diagnostic PSG and early treatment with CPAP could reduce morbidity and mortality in this subgroup of patients.

#### 485.J

##### NEONATAL INTERMITTENT HYPOXIA INDUCES HYPODOPAMINERGIC ACTIVITY IN THE STRIATUM, DECREASED WAKEFULNESS, HYPERACTIVITY, AND WORKING MEMORY IMPAIRMENT.

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**Introduction:** Derangements in dopaminergic (DA) signaling are hypothesized to contribute, at least in part, to disorders consistent with minimal brain dysfunction, such as attention deficit hyperactivity disorder (ADHD). We hypothesized that intermittent hypoxic insults, occurring during a period of critical brain development, would be sufficiently pathogenic to induce significant impairments in DA signaling leading to behavioral and cognitive impairments in the juvenile and young adult.

**Methods:** Following birth, Sprague-Dawley pups were undisturbed and maintained by the dam. On postnatal day (PN) 7, between the hours of 1000 and 1800, pups were assigned to either the intermittent hypoxia-inducing chamber, the normoxia chamber, or were returned to the dam. Between PN 7-11, pups were exposed to either 20-second bursts of isocapnic hypoxic gas (10% O<sub>2</sub>, 5% CO<sub>2</sub>, balance N<sub>2</sub>) or compressed air, followed by a 40-second burst of compressed air. Exposure was interrupted every two hours for a 45-minute feeding and grooming session. At the conclusion of the protocol on PN 11, all pups were returned to the dam where they remained, undisturbed, until weaning at PN 21. On PN 23 pups were instrumented with EEG/EMG electrodes and sleep-wake architecture characterized between PN days 27-30. Locomotor activity was assessed between PN 35 - 38 and learning and working memory were characterized between PN 53 -64. Rats were sacrificed on PN 80 and tyrosine hydroxylase (TH), vesicular monoamine transporter (VMAT2), dopamine transporter (DAT), and dopamine D1 receptors were quantified in the prefrontal cortex, primary sensorimotor cortex, and precommissural striatum by Western blot analyses.

**Results:** Behavioral data demonstrate that post-hypoxic pups (n=5) expressed significantly less wakefulness (32.9% ± 1 vs 41.1% ± 3, p= 0.021) and more REM sleep (10.8% ± 1 vs 7.9% ± 1, p= 0.037) than control littermates (n=6) during the lights-on phase of the circadian cycle. No between-group differences in sleep-wake architecture existed during the darkness phase of the circadian cycle. Post-hypoxic rats (n=4) were also hyperactive during the lights-on phase of the circadian cycle, traveling 57% further than control littermates (625 ± 94 cm vs 390 ± 36 cm, p=0.020). During darkness, post-hypoxic rats traveled 59% further than control littermates (1271 ± 163 cm vs 801 ± 49 cm, p=0.006). Post-hypoxic rats (n=7) also

required significantly more days to learn the delayed win-shift protocol (5 days vs 3 days) than control littermates (n=12) and made more errors during the first four days of testing. Neurochemical analyses demonstrate increased striatal VMAT2 (22.63 ± 2.99 vs 8.81 ± 0.95, p=0.001) and D1 receptor protein (28.25 ± 3.41 vs 16.15 ± 1.49, p=0.006) in post-hypoxic rats, consistent with depressed DA signaling.

**Conclusions:** Post-hypoxic rats express increased sleep, locomotor hyperactivity, and working memory deficits similar to those observed in ADHD. These behavioral aberrations are consistent with neurochemical analyses suggestive of dampened DA signaling in prefrontal-striatal circuits. This leads to the intriguing hypothesis that neonatal intermittent hypoxia evokes neurochemical and behavioral aberrations that persist through the juvenile period.

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#### 486.J

##### A COMPARISON OF HEART RATE, STROKE VOLUME AND CARDIAC OUTPUT IN OBSTRUCTIVE SLEEP APNEA PATIENTS SUCCESSFULLY TREATED WITH CPAP/BILEVEL

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**Introduction:** Studies investigating fluctuations in heart rate (HR), stroke volume (SV) and cardiac output (CO) in OSA patients have found decreases in CO during the recovery period of an apneic event to be associated with decreased SV1 or decreased HR.<sup>2</sup> Using a canine model, it was found that decreases in CO during repetitive apneas in comparison to normal breathing were associated with decreases in HR rather than SV.<sup>3</sup> Using non-invasive impedance cardiography, the present study looked at changes in HR, SV and CO by comparing periods of repetitive apneas during REM and Non-REM with periods of normal breathing.

**Methods:** Five male patients diagnosed with severe obstructive sleep apnea using routine polysomnography who were successfully titrated on CPAP/BiLevel were chosen for analysis. Non-invasive impedance cardiography was used during the course of both the baseline nights and CPAP/BiLevel titration nights. Polysomnographic data and impedance cardiography data were synchronized on a time line basis. The titration nights were first analyzed to find periods of uninterrupted breathing in both REM and non-REM sleep occurring the last half of the night. Periods of identical length from REM and non REM sleep also during the last half of the night of the baseline nights with repetitive obstructive apneas/hypopneas present were compared using paired sample t-tests.

**Results:** It was found that HR decreased during both REM (65.5 SE=6.0) and non-REM (66.0 SE=6.5) with normalized breathing in comparison to periods of repetitive apneas/hypopneas in REM (71.1 SE=6.0) and non-REM (70.7 SE=6.2), although not significantly in REM (p< 0.424) and non-REM (p< 0.331). Stroke volume decreased during both REM (78.4 SE=14.8) and non-REM (75.0 SE=10.7) in comparison to baseline REM (84.2 SE=9.9) and non-REM (78.2 SE=9.8), but not significantly in REM (p< 0.504) and non-REM (p<

0.555). During normalized breathing in REM (4.8 SE=0.61), CO was significantly decreased in comparison to baseline (5.8 SE=0.45,  $p < 0.013$ ). Cardiac output was also reduced during non-REM (4.8 SE=0.53) in comparison to baseline (5.3 SE=0.31), but not significantly ( $p < 0.284$ ). There were no significant differences between REM and non-REM within baseline or treatment nights in any of the three variables.

**Conclusions:** The results of this study do support previous research showing trends of decreased HR, CO and SV during normalized breathing, although only the decrease in CO from baseline to treatment during REM was statistically significant in this study.

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**487.J**

**SLEEP IMPAIRS THE RELATIONSHIP BETWEEN NEGATIVE PRESSURE AND GENIOGLOSSAL MUSCLE DURING PASSIVE VENTILATION**

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**Introduction:** It is well known that the activity of the pharyngeal dilator muscles, such as the genioglossus (GGEMG), is important in maintaining patency of the upper airway during wakefulness and sleep. It has previously been shown that the activity of this muscle can be affected by at least 3 separate inputs. These include Respiratory Pattern Generating Neurons (RPGN, which is the respiratory pacemaker), a negative pressure reflex (NPR, in which GGEMG increases or decreases with changes in pharyngeal negative pressure) and a wakefulness stimulus (withdrawn at sleep onset). However, the relative importance of each of these systems during wake and sleep on GGEMG has not previously been examined in humans.

**Methods:** To date, we have studied four healthy controls (1 female) during wakefulness and NREM sleep. Measures included ventilation, ETCO<sub>2</sub>, airway pressure (Millar catheters) and GGEMG (intramuscular electrodes, % of maximum) during basal breathing, and during increased pharyngeal negative pressure (passive ventilation in an iron-lung—decreased RPGN output). Both peak GGEMG and the slope of the GGEMG/Pepi relationship within a breath were analyzed.

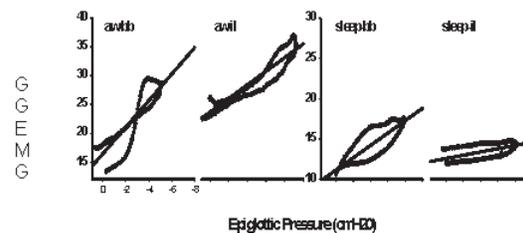
**Results:** Table 1 shows that with sleep onset during basal breathing (bb) there is a reduction primarily in Tonic GGEMG (loss of wake stim) and a smaller reduction in peak GGEMG

(decrease in NPR). During passive ventilation during wakefulness Peak GGEMG is highest (increased NPR) and during NREM sleep is lowest (loss of wakefulness, RPGN and NPR), and is associated with the highest pharyngeal resistance. The relationship between GGEMG and epiglottic pressure (slope GGEMG/Pepi) was also lowest during NREM sleep with passive ventilation (Figure 1).

**Table 1**

	WAKE	SLEEP	P
<b>Basal Breathing (bb):</b>			
TONIC GGEMG (% max)	16.82 +/- 6.68	10.53 +/- 2.55	0.29
PEAK GGEMG (% max)	32.87 +/- 10.23	20.13 +/- 5.32	0.22
R ph (cm H <sub>2</sub> O/L/S)	1.16 +/- 0.36	3.89 +/- 0.64	0.054
<b>Iron-Lung Ventilation (il):</b>			
TONIC GGEMG (% max)	17.64 +/- 6.16	10.74 +/- 3.20	0.26
PEAK GGEMG (% max)	44.67 +/- 12.50	14.83 +/- 5.01	0.05
R ph (cm H <sub>2</sub> O/L/S)	2.76 +/- 0.48	6.46 +/- 1.13	0.09

**Figure 1**



**Conclusions:** These data suggest that during wakefulness all three inputs are important in controlling GGEMG, and with sleep a reduction in the wake stimulus and NPR occurs normally, and that GGEMG is primarily maintained by RPGN activity.

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**488.J**

**ASSESSMENT THE VALIDITY OF PATIENT SLEEP QUESTIONNAIRE FOR SCREENING OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder that can result in medical, psychological, and social disturbances. A reliable and valid questionnaire can help the primary health-care providers make decisions for further testing. This research, using clinical data, examined the validity of the Patient Sleep Question-

naire (PSQ) in prioritizing sleep disturbance patients for polysomnography. The PSQ was designed for detecting sleep disorders in an outpatient clinic.

**Methods:** This research examined 665 records of persons seen in the clinical setting for a sleep problem between 1994 to 1999. Included in this study are 102 men and 35 women who filled out the PSQ and also underwent an overnight polysomnography in a sleep laboratory. Age ranged from 11 to 77 (M=46.9, SD=11.1). The PSQ consists of 20 questions regarding sleep habits, respiratory symptoms during sleep, witnessed sleep apnea, excessive daytime sleepiness (EDS), body mass index (BMI), alcohol consumption, and health problems. Diagnostic criteria of OSA were based on polysomnographic data done in a sleep center. Three diagnostic criteria were apnea hypopnea index (AHI), % of time SO2 less than 90, and minimum SO2.

**Results:** Among 137 subjects, 97% reported snoring, 80% had witness sleep apnea, 45.8% consumed alcohol regularly, and 49% had choking, 74% had gasping, 55% had coughing during sleep, and 66.2% had EDS. BMI ranged from 20.4 to 68.1 (M=35.2, SD=9.2), AHI ranged from 0-121.4 (M=38, SD=32.5), % of time SO2 less than 90 ranged from 0 to 100 (M=23.8, SD=27.8), and minimum SO2 ranged from 30 to 98 (M=75.5, SD= 13.8). According to the polysomnographic data, 84.7% were diagnosed as having OSA. Correlation analysis showed that EDS was positively correlated with AHI (r=.30, p<.001), % of time SO2 less than 90 (r=.40, p<.001); and negatively correlated with minimum SO2 (r=-.32, p<.001). BMI also had significant correlation with all three diagnostic criteria. BMI was positively correlated with AHI (r=.27, p<.005), % of time SO2 less than 90 (r=.53, p<.001); and negatively correlated with minimum SO2 (r=-.47, p<.001). The breath symptoms (choking, gasping, coughing) had a significant correlation with the AHI (r=.26, p<.005) and minimum SO2 (r=-.17, p<.05). Alcohol consumption was not significantly correlated with any diagnostic criteria. Principle component factor analysis demonstrated that 3 breath symptoms (choking, gasping, and coughing) and 7 (falling asleep while operating a machine, driving, talking, working, watching TV, reading, riding in a car) measures of EDS accounted for 59% of the variance. One factor was clearly defined by breath symptoms; the other was clearly defined by the EDS items.

**Conclusions:** Initial results indicate that the PSQ is a valid questionnaire for measuring the risk factors for sleep apnea. Further analysis will include a weighted scoring system that will facilitate the clinical predictability for OSA. The major implication of this study is that a brief, clear self-report questionnaire can be effectively used to identify patients in need of referral to sleep studies.

**489.J**

**SUBJECTIVE EVALUATION OF DAYTIME SLEEPINESS IN OSAS PATIENTS**

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**Introduction:** Excessive daytime sleepiness (EDS) is one of the most common symptoms reported by patients with obstructive sleep apnoea syndrome (OSAS). The most frequently used subjective evaluation is the Epworth Sleepiness Scale (ESS). ESS is a simple and quickly-administered questionnaire, which measures the general level of daytime sleepiness, or, to be more precise, the probability to falling asleep.

**Methods:** In order to study the relationship occurring between subjective daytime sleepiness and OSAS severity, we compared the results of ESS and those obtained with polygraphic recordings using EMBLETTA (Flaga®). Patients suffering from other sleep disorders were excluded from the study. The ESS scores obtained in 120 recorded patients were divided in three categories according to sleepiness level: I) 1-6; II) 7-8; III) >9. The polygraphic parameters analyzed were as follows: Apnoea/Hypopnoea Index (AHI), AHI in supine position, mean duration of the apnoeas, mean oxygen saturation (MOS), mean oxygen desaturation (MOD), minimum registered value of O2 saturation (MIN.SaO2), time spent with oxygen saturation <90% (T/S<90%). Non parametric test, multivariate analysis and linear regression were utilized for the statistical analysis of the data.

**Table 1**

Respiratory Parameters	Non-parametric Test*	Multivariate Analysis
AHI	(p < 0.001)	(p < 0.005)
MIN.SaO2	(p < 0.006)	(p < 0.042)
T/S<90%	(p < 0.014)	(p < 0.021)
BMI	(p < 0.020)	(p < 0.020)

\*Jonckheere-Terpstra Test

**Conclusions:** Subjective daytime sleepiness, for ESS scores >9, is significantly related to the severity of OSAS, as determined not only by the AHI, but also by the degree of hypoxaemia resulting.

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#### 490.J

##### PULSE TRANSIT TIME IN OSAS PATIENTS AND THE RELATION WITH DAY TIME FUNCTIONING

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**Introduction:** The most important symptoms of obstructive sleep apnea are daytime sleepiness, poor cognitive functioning and poor sleep quality. This is presumably caused by the sleep fragmentation due to the numerous arousals during sleep following an obstruction in the upper airway. An adequate quantification of sleep fragmentation to investigate the relation with daytime functioning is, however, difficult. Cortical EEG arousals and respiratory disturbances do not correlate very well with daytime sleepiness. However, it may be necessary to measure other indications of daytime functioning besides sleepiness. Also, alerting arousals may not cause a cortical response, but they may result in a reflex increase in sympathetic activity triggering autonomic responses. Beat-to-beat rises in blood pressure have been described as sensitive indices of transient arousal. An indirect but much easier way of measuring beat-to-beat changes in blood pressure than more conventional blood pressure measurements is Pulse transit time (PTT). This paper describes the relationship between various indices of sleep fragmentation (EEG arousals, autonomic arousals -PTT- and respiratory disturbances) in OSA patients and cognitive functioning, wellbeing and sleepiness during the day.

**Methods:** A group of 12 OSA patients and 10 healthy controls were measured with full polysomnography (REMbrandt system), including ECG and finger plethysmography. The morning after subjective sleep quality was measured with a Dutch sleep quality scale, mood with the Profile of Mood States and sleepiness with the ESS. Cognitive performance was measured with the Parasuraman vigilance task and the N-back continuous attention memory task. Indices of sleep disturbance were: cortical EEG arousals, PTT arousals and respiratory disturbances. PTT was calculated as the time between the R-wave and 50% of the height of the maximum value of the plethysmography pulse. As all signals were recorded with full disclosure polysomnography all recordings could be checked for artefacts due to movements, missed R-top detection or missed plethysmogram peak detection.

**Results:** The OSA patients had a lower sleep quality ( $p<.02$ ), were more sleepy ( $p<.001$ ), were more fatigued ( $p<.001$ ), had less vigor ( $p<.001$ ) and felt more tension ( $p<.05$ ) than the healthy controls. No difference could be found in the vigilance test between the two groups. The physiological data showed a trend towards more Pulse Transit Time arousals and EEG arousals in the patients than in the control subjects. In the apnea patients there seemed to be a better relation between the various indexes of sleep fragmentation and the indexes of daytime functioning than in the control subjects. However, the inter subject variation in PTT arousals was high and artefacts can obscure the PTT detection, especially in the presence of EEG arousals.

**Conclusions:** Pulse Transit Time arousals may give additional information about the fragmentation of sleep in apnea patients.

#### 491.J

##### DETECTION OF SLEEP DISORDERED BREATHING IN A GENERAL POPULATION BASED ON THE PERIPHERAL ARTERIAL TONE

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**Introduction:** Obstructive sleep apnea (OSA) is a major public health problem with consequences including daytime sleepiness and cardiovascular complications. Traditional measures of OSA have not proven to be closely related to severity or occurrence of these complications. Alternative measures for screening and identification of subjects at risk are therefore warranted. The newly developed peripheral arterial tone (PAT) signal is based on altered autonomic activity reflected by pulsatile volume changes in the digital arteries. In a portable diagnostic device PAT is combined with assessment of oxygen saturation. In this study we applied this new potential tool in a sub sample of an ongoing large general population study.

**Methods:** The Skaraborg Sleep Study (3-S) is an ongoing project to investigate a population based cohort of 400 subjects in the Skara Primary Health Care District, Sweden. This population has been enriched with a balanced number of diabetes type II and systemic hypertension cases. All subjects undergo a standard polysomnography (ambulatory recordings) in addition to the assessment of a number of cardiovascular risk factors, gene typing, sleep, QoL and other health related measures. A subgroup sample of 37 consecutive subjects were assessed at home by an continuous overnight monitoring session using a ambulatory PAT system (WP 100, Itamar, Israel) in parallel with a portable polysomnography (PSG) system (Embla, Flaga, Iceland). The Apnea Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI $<4\%$ ) determined by PSG were compared with the Respiratory Disturbance Index (RDI) obtained by the automatic algorithm of the ambulatory PAT device.

**Results:** Mean AHI and ODI determined by PSG were  $24.8\pm 19.0$  and  $11.4\pm 12.0$  compared with an RDI of  $24.0\pm 14.1$  determined by the PAT system. The number of subjects with AHI  $<10$  and  $<20$  by PSG were 7 and 20, respectively. The overall correlation coefficients between PSG-AHI/PSG-ODI and PAT-RDI were  $0.83$  ( $p<0.001$ )/ $0.72$  ( $p<0.001$ ). Sensitivity and specificity for the diagnosis of OSA (AHI threshold 20) by the PAT device were 92% and 70%, respectively. According to the recommendation of Altmann we determined a mean difference of the two methods of 0.8 events/hr with an error of 10.6.

**Conclusions:** The PAT device assesses a measure of vascular autonomic activation that is not reflected by standard PSG. The PAT provided a reasonable – good identification of the sleep related breathing disorder in the general population

when compared with a PSG gold standard. Additional analysis of an expanded material including OSA related symptoms and morbidity/mortality will show if the device may provide better identification of subjects at risk of OSA related complications.

#### 492.K

##### NARCOLEPSY WITH CATAPLEXY, MONOSYMPTOMATIC NARCOLEPSY AND PRIMARY HYPERSOMNIA: A PROSPECTIVE STUDY IN 24 PATIENTS INCLUDING CEREBROSPINAL FLUID HYPOCRETIN LEVELS

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**Introduction:** The nature and diagnosis of these three syndromes, narcolepsy with cataplexy (NC), primary hypersomnia (PH) and monosymptomatic narcolepsy (MN, syn. Narcolepsy without cataplexy), has been increasingly debated since Nishino et al. reported the absence of hypocretin in the CSF of patients with NC.[1] Much less is known about the role of hypocretin in IH and MN.[2] It has been suggested that CSF hypocretin (Hcrt) measures could be used as a diagnostic tool for narcolepsy.[1] The aim of this study was to confirm the CSF Hypocretin findings in our sample and secondly, to assess the clinical spectrum of these disorders using a multimodal diagnostic approach including CSF Hcrt-1 and, for the first time, CSF Hcrt-2 levels. Testing for HLA DQB1\*0602 rather than HLA-DR2 or HLA-DR15 has been recommended as sufficient to assist in the diagnosis of NC.[3]

**Methods:** The total sample size was 24 patients (pts, 17 women, 7 men; mean age of 40 years, range 19-67, a mean illness duration of 15 years). In all 24 patients assessment included a personal interview by a senior sleep physician (AJW) and the following: A standard sleep questionnaire; Conventional Nocturnal Polysomnography (NPSG); Multiple Sleep Latency Testing (MSLT); Epworth Sleepiness Score (ESS); Clinical Evaluation including weight and height; HLA typing; Measurement of CSF Hcrt-1 and Hcrt-2. The diagnosis of NC was presumed by the presence of the following: Excessive daytime sleepiness (EDS) > 6 months; ESS > 10; and; Presence of definite cataplexy. MN was diagnosed using the following criteria: EDS > 6 months; ESS > 10; No definite cataplexy; Sleep Latency (SL) < 8 minutes; MSLT with > 1 sleep onset REM periods (SOREMs); Apnea-Hypopnea Index (AHI) < 10 (in the absence of other respiratory pathology); No other evident cause(s) of EDS; No improvement in EDS following sleep extension. The diagnosis of PH was presumed in patients fulfilling the criteria for MN but with 0-1 SOREMPs and no set criteria on Sleep Latency.

**Results:** The sample was divided as follows: NC (n=13; 12 females and one male), MN (n=5; 4 females and one male) and PH (n=6; one female and 5 males). The ESS results are broad-

ly in keeping with the expected with the NC group having a mean score of 19.6, MN and PH groups scoring 18. MSLT analysis (available for 20 patients at time of abstract submission) reveals a mean SL for the sample of 4.6, the NC group (n =11) 3.58, the MN group (n = 4) 3.76 and the PH group (n = 5) scoring a mean of 7.58. SOREMs were present in 9 of the patients with NC, all 5 pts with MN and in only one patient with PH was there a single SOREM. HLA DQB1\*0602 (available for 18 pts at time of abstract submission) is positive in 8 of 9 pts with NC, 4 of the 5 pts with MN and 1 of 4 pts with PH. Polysomnography evaluations, and CSF-levels of hypocretin are currently being analysed.

**Conclusions:** Preliminary results suggest that NC is a distinct diagnosis on clinical grounds and the clinical heterogeneity of functional hypersomnia without cataplexy (PH and MN) is confirmed. We are currently testing the hypothesis that CSF-levels of hypocretin or a combination of different tests may help differentiating these subgroups of pts. This differentiation may have implications for a better understanding and management of these pts.

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#### 493.K

##### OREXIN NEURON-ABLATED MICE FAIL TO INCREASE VIGILANCE AND LOCOMOTOR ACTIVITY IN RESPONSE TO FASTING

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**Introduction:** Increased vigilance under food-restricted conditions has been described in several species. Orexin (hypocretin) neuropeptides have been implicated in both energy homeostasis and arousal control. Electrophysiological recordings on isolated, green fluorescent protein-labeled orexin neurons demonstrate that these neurons respond to changes in extracellular glucose, leptin and ghrelin levels, all of which reflect feeding status (Yamanaka et al., companion abstract). Mice in which the neurotoxic *ataxin-3* fragment is expressed under control of the human *prepro-orexin* promoter (*orexin/ataxin-3* transgenic mice) selectively and completely lose their orexin neurons during adolescence, resulting in narcolepsy and late-onset obesity //super1//super. Here we report the behavioral characterization of *orexin/ataxin-3* transgenic mice in response to fasting, by using locomotor activity monitoring and polysomnographic recording of vigilance states.

**Methods:** *Orexin/ataxin-3* transgenic mice (5 male hemizygous transgenic and 6 weight matched wildtype 10-week old

littermates, backcross generations 4 and 5 into C57BL/6J) were kept on LD 12:12 light cycle and standard chow (6% fat). An automated tracking system with infrared light detection of movements was used to record locomotor activities of mice between Zeitgeber time 9 and 16 under baseline and fasted (up to 31-hour food deprivation) conditions. Mice (6 male transgenic and 6 wildtype 13-weeks old littermates) were then chronically implanted with EEG/EMG electrodes, and sleep-wakefulness patterns were recorded at 15 weeks of age under similar baseline and fasted conditions. All data were evaluated using two-way ANOVA to detect interactions between genotype and feeding status.

Figure 1

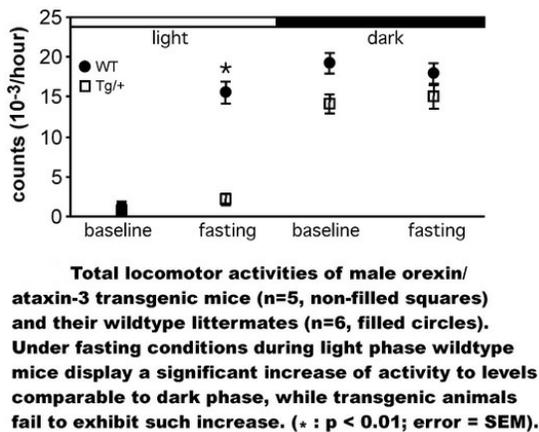
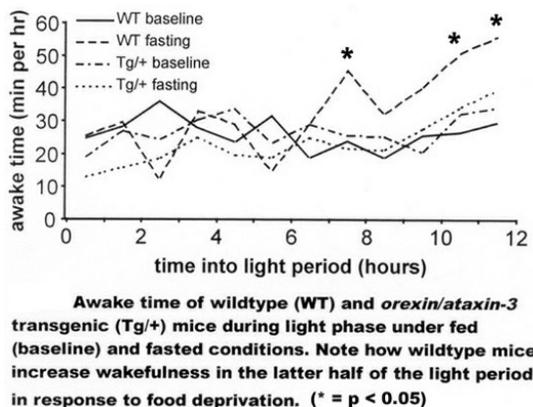


Figure 2



**Results:** Under food-deprived conditions during light phase, wildtype mice reduced resting time, increased ambulatory time and distance (food seeking), increased stereotypic behavior, and increased rearing and jumping (escape attempts). *Orexin/ataxin-3* transgenic mice failed to exhibit each of these responses (Fig.1). This behavioral phenotype of *orexin/ataxin-3* transgenic mice was not due to a simple motor dysfunction, since average ambulating speed did not differ between genotypes. During dark phase, no differences between genotypes could be observed. Polysomnographic characterization under fasting showed an increased wake time (Fig.2) concomitant

with a decreased non-REM sleep time in wildtype mice during the latter half of light phase, and decreased REM sleep time over the whole light phase, as compared with ad lib fed conditions. However, transgenic littermates failed to show any of these vigilance state changes in response to fasting. Again, no differences between genotypes were apparent during dark phase.

**Conclusions:** Wildtype mice respond to food deprivation with increased active wakefulness at the expense of non-REM sleep and REM sleep during the normal rest phase. Orexin neuron-ablated *orexin/ataxin-3* transgenic mice fail to show this adaptive behavior. Orexin neurons are likely involved in sensing the animal's nutritional state, and in initiating increased arousal and motor activity in times of food scarcity.

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**494.K**

**INCREASED NUMBER OF ASTROCYTES AND REDUCED DENSITY OF HYPOCRETIN/OREXIN FIBERS IN HUMAN NARCOLEPSY**

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**Introduction:** In previous work, we reported that human narcoleptics have an 85%-95% reduction in the number of hypocretin (Hcrt) neurons and gliosis in the hypocretin cell region (Thannickal et al., 2000). In this study we further examined the distribution of surviving hypocretin neurons and the distribution of hypocretin containing fibers in each hypothalamic nucleus, locus coeruleus, raphe dorsalis and raphe centralis of human narcoleptics and controls to determine the pattern of cell and fiber elimination. We also studied the density of glial fibrillary acidic protein(GFAP) labeled astrocytes in these nuclei to determine the pattern of gliosis.

**Methods:** The hypothalamus and brain stem areas of three narcoleptic and six age and sex matched normal individuals were used. Sections were cut at 40 μm and pretreated with 10 mM sodium citrate at 80 °C for antigen retrieval (Jiao et al., 1999). Sections were immunostained for Hcrt-1, Hcrt-2 (Orexin A & B, Oncogene Research Products) and GFAP (Rabbit anti-cow GFAP antibody, Dako) labeled astrocytes. The following nuclei were examined : anterior hypothalamus, periventricular, paraventricular, supraoptic, arcuate, dorsal, dorsomedial, ventromedial, lateral, posterior, tuberomammillary, mammillary hypothalamus, thalamus, locus coeruleus, raphe dorsalis and raphe centralis. All nuclei were systematically sampled for Hcrt cells, fibers and astrocytes. Analysis was performed using stereological techniques by tracing the outlines of each nucleus and systematic sampling of every tenth square

(250 x 250  $\mu\text{m}$ ) in each of each section using the NeuroLucida program (Microbright Corp).

**Results:** Hcrt cells were distributed in dorsomedial, dorsal, posterior, lateral and anterior hypothalamic nuclei in both normal and narcoleptic brain. There was difference in the density of Hcrt cells in these nuclei in normal and narcoleptic brains. In the normal brain, Hcrt cell density was highest in the dorsomedial hypothalamus (41.41 cells/mm<sup>2</sup>) and lowest in anterior hypothalamus (2.2 cells/mm<sup>2</sup>). In narcoleptics, maximum loss of Hcrt cells occurred in the posterior hypothalamus (96.65%). In control brain, Hcrt fiber density was maximal in paraventricular (69.66 fibers/mm<sup>2</sup>) and periventricular nuclei (59.0 fibers/mm<sup>2</sup>). Compared to normals, narcoleptics had significant ( $p < 0.001$ ) loss of hypocretin fibers and increase of GFAP ( $p < 0.001$ ) in anterior hypothalamus, paraventricular, periventricular, arcuate, dorsal, dorsomedial, ventromedial, lateral hypothalamus, tuberomammillary nucleus and locus coeruleus. There was no significant fiber loss or increase of astrocytes in supraoptic, mammillary, thalamus, raphe centralis and raphe dorsalis. Maximum gliosis occurred in posterior hypothalamus ( $p < 0.0007$ , with a 290% increase). There was a significant correlation between the increase in GFAP density and decrease in Hcrt fibers ( $r = 0.82$ ,  $p < 0.0001$ ) in narcoleptics.

**Conclusions:** We found a coupled pattern of gliosis and Hcrt fiber loss within narcoleptic brains. Gliosis is not restricted to regions of cell loss, suggesting that the degenerative process underlying narcolepsy is targeted at Hcrt terminals as well as or instead of Hcrt somas.

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## 495.K

### HLA AND HYPOCRETIN STUDIES IN KOREAN PATIENTS WITH NARCOLEPSY

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**Introduction:** Narcolepsy, a sleep disorder characterized by sleepiness and symptoms of abnormal rapid eye movement sleep such as cataplexy, is known to be tightly associated with the human leukocyte antigen (HLA) DQB1\*0602. Recent discoveries has shown that the pathophysiology of narcolepsy involves abnormal hypocretin transmission. Very few studies have evaluated narcolepsy in Asian countries. In this study, 20 consecutive narcoleptic patients diagnosed in Korea were studied at the genetic, clinical and pathophysiological level

and compared with 21 control subjects.

**Methods:** We selected 20 patients (mean age:  $28.2 \pm 13.0$ , 11 men and 9 women, BMI:  $23.9 \pm 3.4$ ) who were confirmed to have narcolepsy depending on the polysomnography and multiple sleep latency test (MSLT) as well as clinical history and symptoms at the St. Vincent's hospital and Korea university sleep disorders clinic. Any subjects co-morbid with other hypersomnic sleep disorders such as sleep apnea or periodic limb movements during sleep were excluded. All patients and 21 control did HLA typing for the presence of DQB1\*0602. Clinical variables were collected by semistructured interview for narcolepsy patients. Hypocretin (orexin) CSF studies were also performed in 6 cataplectic subjects. One control sample was collected

**Results:** 1) Average sleep latency was  $2.2 \pm 2.0$  minutes and average frequency of REM was  $3.2 \pm 1.5$  by MSLT. 2) Characteristic symptoms of narcolepsy were investigated as follows: excessive daytime sleepiness (100%), cataplexy (100%), sleep paralysis (60%), hypnagogic hallucination (70%) and disrupted nocturnal sleep (75%). 3) Prevalence of involved regions when cataplexy was developed were knee and leg (95%) and jaw (30%). Most triggering factors for cataplexy were laughing (80%) and joking (70%). 4) The positivity of HLA-DQB1\*0602 of patients and controls were 90%, 24% respectively ( $x^2 = 5.4$ , OR = 29,  $p < 0.05$ ). 5) DQB1\*0602 was more specific for narcolepsy than DR2. 6) DQB1\*0601 allele frequency was significantly decreased in narcoleptic patients ( $x^2 = 4.6$ , OR = 0,  $p < 0.05$ ). 7) All 6 narcolepsy subjects tested had undetectable hypocretin-1 level and control sample level was within the normal range (285 pg/ml).

**Conclusions:** High frequency HLA-DQB1\*0602 in Korean narcolepsy patients suggest that HLA-DQB1\*0602 could be a strong genetic marker in all ethnic groups. Hypocretin deficiency can be seen as also contributing to the development of narcolepsy in humans.

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496.K

**CSF HYPOCRETIN-1 (OREXIN-A) LEVELS IN NARCOLEPSY WITHOUT CATAPLEXY AND IDIOPATHIC HYPERSOMNIA.**

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**Introduction:** It has recently been reported that CSF hypocretin-1 (orexin-A) concentration in the majority of patients with narcolepsy-cataplexy was undetectably low (1). However, it is not known whether CSF hypocretin-1 is also altered in patients with narcolepsy without cataplexy and idiopathic hypersomnia (IHS). In this study, we measured CSF hypocretin-1 in these two other primary excessive daytime sleepiness (EDS) disorders.

**Methods:** In the current study, we measured CSF hypocretin-1 levels in 11 narcolepsy and 7 IHS Japanese patients. Narcoleptic patients were diagnosed by ICSD (2) and further divided into two groups (with cataplexy: n=7, and without cataplexy: n=4). IHS was defined as, EDS over 6 months, no cataplexy, shortened multiple sleep latency test (MSLT) with 0-1 sleep onset REM periods (SOREMs) and no other evident cause of EDS, such as sleep apnea, periodic leg movements and insufficient sleep syndrome.

**Results:** Six out of 7 narcolepsy-cataplexy patients had undetectable hypocretin-1 levels (Table 1-2). The hypocretin-1 level of one HLA DR2 negative narcolepsy-cataplexy subject was in the normal range (267 pg/ml). CSF hypocretin-1 levels in narcolepsy without cataplexy patients (296±41, [mean±SD] pg/ml) and IHS patients (265±50 pg/ml) were not significantly different from those in controls (280±33 pg/ml, n=15) previously reported (1). However, levels of two of the seven IHS patients were moderately low (189 and 198 pg/ml) and below the 95% confidence of the controls. Undetectable hypocretin-1 levels were also observed in 3 prepubertal narcolepsy-cataplexy cases, 6, 7 and 10 year-old subjects, whose duration of disease was 0.8, 0.2 and 1.5 years, respectively. On the other hand, the average of MSLT between 3 groups was almost same range in spite of the large differences of hypocretin-1 levels.

**Conclusions:** Our results in Japanese patients are in accordance with those of Caucasian subjects (1): most HLA positive narcolepsy-cataplexy patients have undetectable CSF hypocretin-1 levels, and a patient with HLA negative had a normal level. Furthermore, hypocretin deficiency is likely to occur in the early stages of the disease, since undetectable levels were observed in 3 prepubertal subjects, only few months after the onset of the disease. We also found that all four nar-

colepsy without cataplexy patients and five out of the seven IHS patients had normal hypocretin-1 levels. Since the ICSD criteria of diagnosis of narcolepsy had two standards, EDS without cataplexy accompanied by REM sleep-related symptoms and two or more SOREMs during an MSLT meets the narcolepsy criteria (2). However, Honda et al. described that a positive history of cataplexy associated with EDS was systematically required for the diagnosis of narcolepsy (3). Our results of hypocretin measures suggest that narcolepsy without cataplexy are not caused by the hypocretin ligand deficient and are etiologically different from narcolepsy-cataplexy. Our results also suggest that hypocretin-1 ligand deficiency is not involved in the majority of IHS cases. However, the roles of hypocretin neurotransmission in a subset of IHS should be further determined since about 30% of our IHS patients had moderately low Hypocretin-1 levels, and this patient group also shows obesity, as seen in patients with hypocretin deficient narcolepsy-cataplexy (1).

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497.K

**REGULATION OF OREXIN NEURONS BY PERIPHERAL NUTRITIONAL SIGNALS: ROLES OF LEPTIN, GHRELIN AND GLUCOSE**

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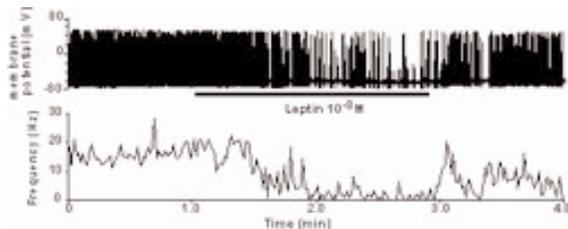
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**Introduction:** Orexin (hypocretin) mRNA is up-regulated during fasting in rats<sup>1</sup>, indicating that the orexin-expressing neurons are somehow sensing the animal's nutritional state. Furthermore, genetic ablation of orexin neurons in mice results in failure to increase ambulatory activity and wakefulness in response to food deprivation, an adaptive response observed robustly in wildtype mice (Beuckmann et al., companion abstract). Here we electrophysiologically examined isolated orexin neurons in order to understand the mechanism by which they monitor nutritional states. Because of the scarcity and diffuse distribution of orexin neurons as well as the lack of distinct morphological criteria, it is difficult to

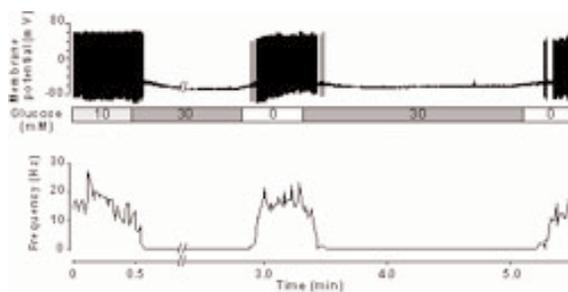
identify and directly examine the electrophysiological properties of orexin neurons. Therefore, we generated transgenic mouse lines in which orexin neurons are specifically labeled by enhanced green fluorescent protein (EGFP). We prepared EGFP-expressing neurons from the hypothalamus of these mice and subjected them to patch-clamp recordings.

**Methods:** We used a promoter segment of the human prepro-orexin gene to express EGFP specifically in orexin-containing neurons<sup>2</sup>. The LHA regions of orexin/EGFP mice were collected by punch biopsies and enzymatically dispersed. EGFP-expressing orexin neurons were identified by fluorescence microscopy and subsequently subjected to whole-cell patch-clamp recordings. To determine which extracellular factors can modulate the activity of orexin neurons, we applied several neurotransmitters and neuromodulators in superfused solution. After each recording, neuronal cytoplasmic were collected and subjected to reverse transcription-polymerase chain reaction (RT-PCR) analysis to confirm the presence of prepro-orexin mRNA.

**Table 1**



**Table 2**



**Results:** In current-clamp mode, EGFP-expressing orexin neurons had a resting potential of  $46.3 \pm 1.7$  mV and displayed high-frequency spontaneous action potentials ( $21.4 \pm 0.9$  Hz,  $n=20$ ) in physiological extracellular solution. All orexin neurons examined were strongly activated when glutamate was applied, and strongly inhibited when GABA was applied ( $n=10$ ). Leptin acutely inhibited 8 out of 10 EGFP-positive orexin neurons, causing hyperpolarization and decreased firing rates (Fig. 1). A high extracellular glucose concentration (30 mM) induced hyperpolarization and cessation of action potentials in EGFP-expressing orexin neurons. Conversely, a low extracellular glucose concentration (1 mM) induced depolarization and increased the frequency of action potential in

these neurons (Fig. 2). We observed that almost all orexin neurons examined showed glucose sensitivity (18/20 examined). Furthermore, ghrelin, a novel gastrointestinal peptide, activates EGFP-expressing orexin neurons when applied in superfused solution. We observed no appreciable changes of activity of orexin neurons in response to the following neurotransmitters: noradrenalin, serotonin, dopamine, histamine, acetylcholine, PGE<sub>2</sub>, melatonin, adenosine, vasopressin, NPY, alpha-melanocyte stimulating hormone (a-MSH), melanin-concentrating hormone (MCH).

**Conclusions:** This study demonstrates that the activity of isolated orexin neurons can be directly modulated by extracellular leptin, glucose and ghrelin. We speculate that in vivo orexin neurons may be activated directly by decreased plasma leptin and glucose levels, as well as by increased plasma ghrelin levels, all of which are reflections of reduced food availability to the organism. The resulting increase in orexinergic activity could then lead to increased wakefulness and exploratory activity, triggering increased food seeking and intake.

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**498.K**

**OREXINS ACTIVATE HISTAMINERGIC NEURONS IN THE TUBEROMAMMILLARY NUCLEUS VIA THE OX2S RECEPTOR**

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**Introduction:** Orexin neurons innervate almost all regions of the brain. Particularly dense projections are observed in monoaminergic nuclei, such as the noradrenergic locus coeruleus (LC), serotonergic raphe nucleus and histaminergic tuberomammillary nucleus (TMN). These aminergic nuclei have a crucial role in arousal control<sup>1</sup>. Recent studies have shown that the orexin system, especially orexin-OX2R interaction is important for in arousal control. Especially dense projection of orexin fiber to the TMN and abundant expression of OX2R in this region suggest that activation of TMN histaminergic neurons by orexins might be an important in arousal control. In the present study, therefore, we investigated the effects of orexins on the activity of histaminergic neurons prepared from the rat TMN. We further examined the significance of the histaminergic pathway in the orexin-induced arousal

response in rats.

**Methods:** Direct synaptic connection of TMN histaminergic neurons and orexin terminal was confirmed by double-labeled immunoelectron microscopy using anti orexin anti-serum and anti histamine decarboxylase (HDC) antibody. The TMN regions of Male Wistar rats were collected by punch biopsies and enzymatically dispersed. Thereafter, Neurons that showed the characteristics of morphologically and electrophysiologically histaminergic neurons; large size (30-40  $\mu\text{m}$ ) and multipolar type, a spontaneous firing rate of typically 2-5 Hz, a broad action potential with a shoulder on the falling phase and a long-lasting afterhyperpolarization, were selected for electrophysiological recording. At the end of each recording, the cytoplasm was collected and subjected to RT-PCR analysis to confirm HDC expression. For Simultaneous EEG and EMG recording, male wistar rats were chronically implanted with EEG/EMG electrodes. A cannula was also implanted in the third ventricle for continuous intracerebroventricular infusion.

**Results:** Immunoelectron microscopic studies revealed direct synaptic interaction between orexin-immunoreactive nerve terminals and histaminergic neurons in the TMN where the OX<sub>2</sub>R is abundantly expressed. Electrophysiological study revealed that orexin-A dose-dependently activate histaminergic neurons, which were freshly isolated from rats TMN region. Orexin A (30 nM) application increased spontaneous firing rate by 280% of the control rate (3.6 and 10.1 Hz, before and after orexin A application, respectively). Not only orexin A but also orexin B increased the firing rate of histaminergic neurons with similar potency. To further evaluate the physiological significance of activation of histaminergic pathways by orexins, we examined the effect of pyrilamine on orexin-induced arousal response in rats. Simultaneously recordings of electroencephalograph and electromyograph showed that intracerebroventricular infusion of orexin A (0.5 nmol/hr) significantly increased the awake state, while it decreased slow wave sleep and paradoxical sleep in the light phase. Central application of pyrilamine (10  $\mu\text{g/hr}$  or 30  $\mu\text{g/hr}$ ), an H<sub>1</sub>s receptor antagonist, significantly inhibited these responses with dose dependent manner. Figure 1: Orexin activated freshly isolated histaminergic neurons from the TMN. Whole-cell patch clamp recording under current clamp mode showing that spontaneous firing rates of histaminergic neurons were increased by application of orexin A (30 nM). Figure 2: An H<sub>1</sub>s receptor antagonist inhibited orexin A-induced wakefulness in the rat. The time spent awake per 1 hr is plotted (A). Orexin A was infused at a rate of 0.5 nmol/hr for 2 hr (11:00 A.M.-13:00 P.M.). Pylamine treatment was started 30 min before orexin A infusion. Horizontal solid bars indicate the duration of orexin A or pyrilamine infusion.

Figure 1

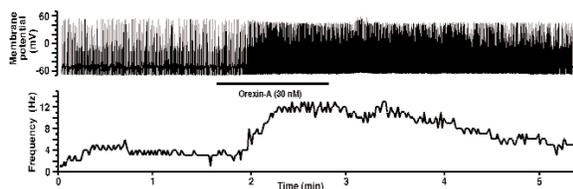
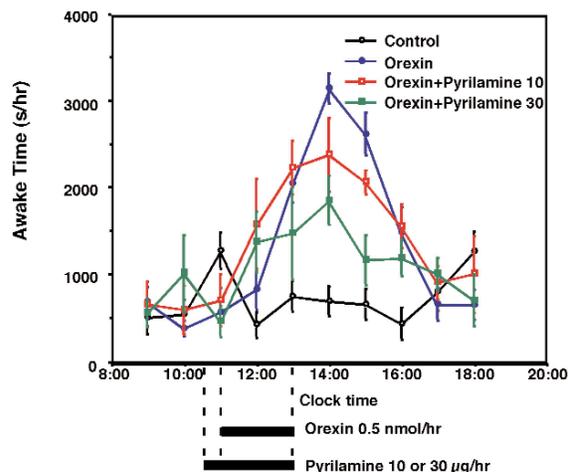


Figure 2



**Conclusions:** We found a direct synaptic connection between orexin neurons and histaminergic neurons in the TMN at the level of the electron microscopy. Orexins (orexin A and B) increased firing rates of isolated histaminergic neurons via OX<sub>2</sub>R. An H<sub>1</sub>s receptor antagonist inhibited orexin-induced wakefulness in conscious rats. These results strongly suggest that activation of histaminergic neurons by orexins might be important for modulation of the arousal.

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#### 499.K

##### EVALUATION OF A NEW TEST TO DIAGNOSE NARCOLEPSY. A PILOT STUDY.

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**Introduction:** Narcolepsy is a disease manifested by cataplexy, sleep paralysis, vivid dreams, hypnagogic hallucinations and excessive day time sleepiness. Multiple sleep latency test (MSLT) the standard test for diagnosing narcolepsy is time consuming, require overnight polysomnography and 4-5 daytime naps 2 hours apart. Cataplexy is present in 75-80% of narcoleptics and manifest clinically by brief episodes of hypotonia in one or more muscle groups precipitated by emotions such as laughter or anger. The aim of this study is to evaluate a new test for cataplexy as an indirect way to diagnose narcolepsy.

**Methods:** Patients were monitored continuously by an EEG, ECG, EOG and EMG of the chin and the neck and upper extremity muscles while watching a humorous 30-minute

video, 2 weeks after stopping all antiepileptic medications. Baseline DTR's were recorded and rechecked whenever the EMG showed hypotonia. 16 narcoleptic patients diagnosed by MSLT and 4 normal asymptomatic controls were studied. The test was positive if EMG hypotonia and clinical hyporeflexia with or without REM sleep in EEG were documented during laughing episodes.

**Results:** All subjects laughed to varying degrees while watching the video. None of the 4 normal subjects (controls) had a positive test. 12 of the 16 subjects with narcolepsy had a positive test. The test has a sensitivity and PPV of 83 % and a specificity and NPV of 50%. 2 of the 4 subjects with negative test had history of cataplexy. 2 of the 12 patients with positive test denied any history of cataplexy. 3 patients complained of headache, 4 patients had sleepiness, 2 had weakness and 3 patients did not notice any change during the test.

**Conclusions:** The cataplexy test we have described is a simple, less expensive and easily available, it could be used in diagnosing patients with suspected narcolepsy. Future larger studies are required to confirm the results of this study prior to using this test in the routine clinical practice.

## 500.L

### THE FLOYD-MEDLER SLEEP BELIEFS SCALE: FACTOR STRUCTURE AND SUB-SCALE RELIABILITY

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**Introduction:** Our purpose was to map out the full structure of healthy adults' sleep beliefs. It is widely accepted that the development of some forms of insomnia is due to mal-adaptive cognitions (1,2). The mental overactivity seen in insomniacs is typically in the form of faulty sleep beliefs. Such patterns of thinking may result in the exacerbation of sleep problems that were initially quite minor. Currently, there are two instruments being used to measure the attributional styles of individuals who already have insomnia (1,3). In contrast, our intention has been to develop a sleep belief scale for use with normal adults.

**Methods:** Subjects responded to public announcements to participate in a survey of sleep beliefs, knowledge, and practices. This convenience sample from the general population consisted of 865 adults of which 68% were female. The average age was 46.75 (S.D.=14.39) with a range of 16 to 90. Race composition was Caucasian 88%, African American 7%, and 5% "other".

**Results:** Principle Components Analysis (PCA) revealed a nine-dimension structure that accounted for 67% of the total variance in the 25-item Floyd-Medler Sleep Belief Scale. In order of extraction these dimensions were labeled (1) "Next-day Consequences", (2) "Health Consequences", (3) "Sleep Need", (4) "Psychological Consequences", (5) "Sleep Regularity", (6) "White Noise", (7) "Coping Strategies", (8) "Sleeping In", (9) and "Napping". Twelve items demonstrated factor loadings above .80, five more were above .70. The smallest loading was .47. A general belief in "consequences" of poor sleep was the only uni-dimensional section of the set of nine beliefs. The three sub-scales pertaining to conse-

quences included (a) "Next-day Consequences" (alpha=.80, 6 items), (b) "Health Consequences" (alpha=.72, 5 items), and (c) "Psychological Consequences" (alpha=.70, 2 items). When these 13 items were combined into a "Belief in Consequences" scale the alpha was .83. LISREL was used to ascertain the fit of our theoretical nine-dimension sleep beliefs model. The fit indices suggested that the nine-dimension model was sound after only slight modification: RMSEA=.04, NNFI=.92, GFI=.97, and CFI=.95. Inter-factor correlations were .23, .42, and .43 among the three "consequence" factors. Of the remaining six factors ten out of fifteen inter-factor correlations were less than .10.

**Conclusions:** Beliefs in consequences of poor sleep appears as a central component of healthy adults' beliefs about sleep. Low inter-factor correlations suggests that six factors are independent. This instrument has been shown to be structured and reliable for use in mapping sleep beliefs in the general population.

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## 501.L

### ARE INSOMNIACS POOR JUDGES OF TIME? RETROSPECTIVE AND PROSPECTIVE ESTIMATES OF TIME INTERVALS IN INSOMNIACS AND GOOD SLEEPERS

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**Introduction:** There are large discrepancies when comparing subjective and objective sleep parameters in insomniacs: underestimation of total sleep time, number and length of wake after sleep onset, and overestimation of sleep latency (1). It is unclear whether insomniacs have an impairment in time perception or if they misperceive their sleep state. Since clinicians often rely on subjective evaluations of sleep parameters, it is important to know whether insomniacs are capable of providing accurate estimates. This study compared time perception of insomniacs and good sleepers in sleep-related and sleep-unrelated settings. The main hypothesis was that insomniacs would overestimate time intervals to a greater extent than good sleepers, but that this difference would be displayed only in the sleep-related condition.

**Methods:** Thirty good sleepers (17 women, M = 23 years old) and thirty insomniacs (18 women, M = 26 years old) participated in this experiment. The inclusion criteria for the insomnia group were : (a) a subjective complaint of insomnia; (b) a

sleep latency over 30 minutes and/or more than 30 minutes of wake after sleep onset; (c) at least three episodes of insomnia per week; and (d) a duration of insomnia of at least one month. Time perception was measured with verbal estimations. Two paradigms were evaluated: retrospective (where the participant is unaware that he/she will have to estimate an interval until the interval is over), and prospective (where the participant is aware that he/she will have to produce an estimate). Four intervals were estimated: (a) a retrospective long interval (12.5 minutes); (b) a prospective short interval (35 seconds); (c) a prospective medium interval (3 minutes); and (d) a prospective long interval (12.5 minutes). The tasks were performed twice: in a sleep-unrelated condition (waiting in a bedroom) and a sleep-related condition (nap in the afternoon). Each estimate was transformed into a ratio of subjective evaluation over the objective duration.

Figure 1

Mean ratios of the 12.5 minutes retrospective judgement for good sleepers and insomniacs in both sleep-unrelated and sleep-related conditions.

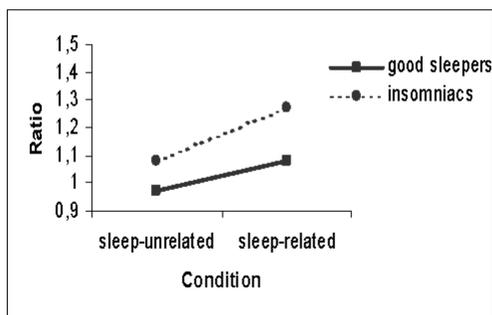
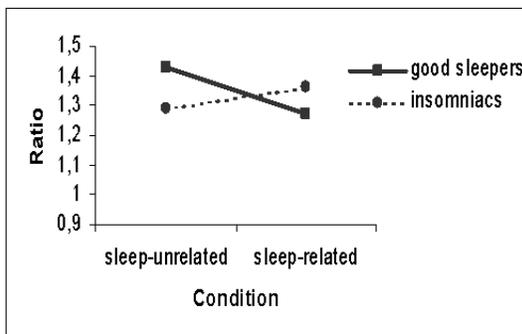


Figure 2

Mean ratios of the 12.5 minutes prospective judgement for good sleepers and insomniacs in both sleep-unrelated and sleep-related conditions.



**Results:** Four repeated measures ANOVAs were performed, one for each task. The results (see Figures 1 and 2) suggest that insomniacs are less accurate than good sleepers when estimat-

ing long intervals. This impairment is present in sleep-unrelated and sleep-related contexts when they estimate time retrospectively ( $p < .10$ ), but only in sleep-related situations when estimating time prospectively ( $p < .05$ ). Also, the results emphasize the importance of considering practice and order effects when evaluating time perception of short and medium intervals.

**Conclusions:** Insomniacs may overestimate their sleep latency because their time perception is inaccurate in sleep-related situations for prospective long intervals. These inaccurate estimates might result from a physiological and/or cognitive hyperarousal state that frequently characterizes insomniacs in sleep-related contexts. However, additional studies are needed to replicate these findings in a more naturalistic setting.

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**502.L**

**THE BEST OF BOTH: BRIEF HYPNOTIC USE TO ENHANCE BEHAVIORAL INSOMNIA THERAPY**

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**Introduction:** Chronic insomnia is a common and significant health problem. Fortunately, the poor sleep of insomniacs is improved by both pharmacological and behavioral treatments. These therapies, though, each have accompanying strengths and weaknesses. Pharmacotherapy works rapidly, but tolerance, dependence and loss of efficacy occur with extended use. Behavioral therapy is not fast-acting, but sleep improvements are quite durable. A combination treatment which takes advantage of the strengths of both pharmacological and behavioral therapy is a reasonable approach to treating insomnia. In spite of the compelling rationale for combining the treatments, empirical results have been disappointing. Recent findings have suggested that by adding pharmacotherapy to behavioral therapy, long-term treatment gains are diminished.(1) In previous research, medication was used as needed and continued throughout the course of behavioral treatment. A different approach to combining therapies is to restrict medication use to the early portion of behavioral therapy and not allow subjects to choose the nights that they use the medication. If hypnotic use is restricted to the first three weeks of treatment, we expect that poor sleep will rapidly improve and initial discomfort will be minimized. In addition, because the initial discomfort will be minimized, we expect that subjects who receive combination treatment will be better able to comply with cognitive-behavioral treatment regimen.

**Methods:** To test our hypotheses we recently conducted a blinded pilot study in which hypnotics were used in the first three weeks of the CBT protocol. Patients recruited to participate in this trial were adults (age range 33 to 63 yrs, mean=42.86, SD=10.2; F=4, M=3) who presented with mod-

erate to severe primary sleep-onset or sleep-maintenance insomnia. Subjects meeting study criteria were randomly assigned to one of 2 conditions, namely, zolpidem or no pill. Each subject in the enrolled protocol received a manualized-cognitive-behavioral therapy for insomnia.(2) Subjects in the zolpidem condition (ZCB) received 10 mg during Week 1, 5 mg Week 2 and 5 mg every other night during Week 3. This approach was chosen so that subjects would get the maximum therapeutic dose during Week 1 and then taper off the medication during the second two weeks. Subjects in the cognitive-behavioral treatment alone group (CBT) received no pills. In addition, subjects who were randomized to the zolpidem condition were not able to choose which nights to take their pills; instead, they were required to take the pill each night.

Figure 1

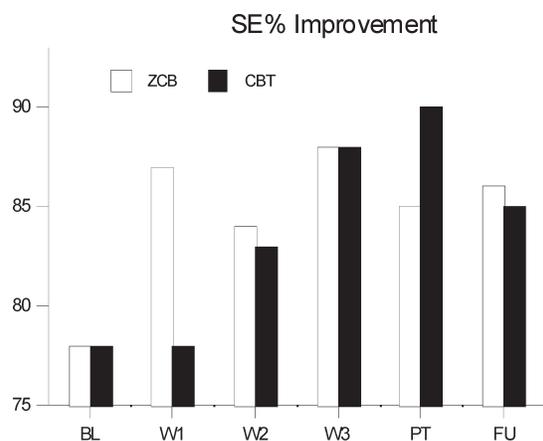
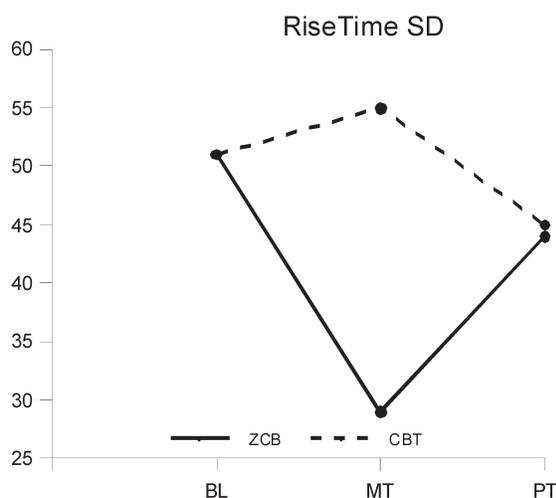


Figure 2



**Results:** Our pilot data suggest, as expected, that using zolpidem improved subjects sleep during the first few weeks of treatment (see Figure 1). Subjects in CBT became worse or

improved slowly during the first few weeks of treatment. The treatment effect sizes (mean difference/standard deviation) for sleep efficiency at W1, W2, W3, PT and FU were 1.03, 0.15, 0.02, -1.14, and 0.25, respectively. In addition, subjects who received zolpidem during the first three weeks had less variable sleep/wake schedules, suggesting that they were better able to comply with the TIB prescription (see Figure 2).

**Conclusions:** These preliminary data suggest that using zolpidem may more rapidly improve poor sleep during the first few weeks of behavioral treatment for insomnia than those receiving CBT alone. In addition, subjects who received zolpidem during the first three weeks had less variable sleep/wake schedules, suggesting that they were better able to comply with the TIB prescription. Larger clinical trials of brief hypnotic use during the initial stage of behavioral therapy are warranted.

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**503.L**

**THOUGHTS AT SLEEP ONSET IN GOOD AND POOR SLEEPERS**

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**Introduction:** Insomniacs commonly attribute their sleeping difficulties to intrusive cognitions. However, despite a growing interest in the cognitive model of insomnia, the type of thoughts experienced prior to sleep onset remains poorly documented and the relationship between cognitions and sleep quality poorly understood. To obtain a better understanding of the mechanism underlying the successful transition from wake to sleep we thought it instructive to compare thought content in-vivo at the time of sleep onset in good and poor sleepers.

**Methods:** Sixteen self-reported insomniacs [mean age (SD) = 44.1 (16.5)y] and 16 age-matched controls [44.9 (14.2)y] were recruited through advertisements in electronic and print media. According to 7-day sleep log, insomniacs were recruited if they reported SOL > 30min more than 3 times in a week and SE < 85%, and identified themselves as having sleep problem for at least 6 months. Good sleepers were recruited if they reported a mean SOL < 30min and a SE > 85%. To measure thought content, for three nights in their homes subjects used a voice-activated tape recorder to capture thoughts from lights out time to sleep onset. Two independent judges coded the transcripts using categories adapted from those first described by Wicklow & Espie (2000) [i.e. Rehearsing/planning, problem solving (e.g. work-related and social issues, etc); Sleep and its consequences (e.g. the desire for sleep, sleep expectancy, etc); Reflection on quality of thoughts (e.g. "thinking about

thinking”, mind buzzing, etc); Arousal status (e.g. feeling exhausted, experiencing sleepiness, etc); External noise (e.g. wind, traffic, etc); External environment (e.g. pet jumping onto bed, ambient temperature, etc); Autonomic experiences (e.g. headache, tension, restlessness, etc); and Procedural factors (e.g. what to say out loud, etc)]. They also rated the valence of thoughts as pleasant, unpleasant or neutral. To allow for any first night effects, results were calculated from nights 2 and 3 data. Where appropriate, independent t-tests and Chi-square tests were used to examine group differences. **Results:** Insomniacs compared to controls reported longer latencies to sleep onset [55.4 (54.0) vs 7.8 (4) min, respectively] and less efficient sleep [76.6 (15.8) vs 91.3 (3.7)%] (all  $p < .01$ ). The frequency distribution (and percentage) of thought categories are presented in table 1. Compared to controls, insomniacs reported a higher percentage of thoughts that were related to sleep and its consequences and a higher percentage of unpleasant thoughts (insomniacs vs controls; unpleasant 16% vs 8.1%, neutral 75.6% vs 73.3% and pleasant 8.3% vs 18.6%, respectively) (all  $p < .05$ ).

**Table 1**

Thought Category	Number and percentages of reported thoughts	
	Number of thoughts (%)	
	Poor sleepers	Good sleepers
Rehearsing/planning, problem solving	576 (62.2)	269 (61.7)
Sleep and its consequences	92 (9.9)	18 (4.1)
Reflection on quality of thoughts	24 (2.6)	44 (10.1)
Arousal status	30 (3.2)	15 (3.4)
External noise	51 (5.5)	20 (4.6)
External environment	46 (5.0)	25 (5.7)
Autonomic experiences	38 (4.1)	18 (4.1)
Procedural factors	69 (7.5)	27 (6.2)

**Conclusions:** Although insomniacs in general reported longer latencies to sleep onset and, hence, a greater number of thoughts, nevertheless, compared to good sleeping controls they reported a higher percentage of thoughts related to sleep and its consequences and a higher proportion of unpleasant thoughts. These findings support the role of negative affect and an increased pre-occupation with sleep and its consequences in the aetiology of sleep onset insomnia.

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**504.L**

**PUTATIVE MODELS OF PRIMARY INSOMNIA: A COMPARATIVE STUDY OF PRIMARY INSOMNIACS, DEPRESSED INSOMNIACS AND GOOD SLEEPERS**

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**Introduction:** Cognitive behavioural therapies (CBT) have been found to be effective in the treatment of chronic insomnia and interventions as diverse as relaxation, stimulus control treatment, sleep restriction, paradoxical intention and cognitive therapy have empirical support<sup>2</sup>. Each intervention is based on a presumed, specific pathway eg. stimulus control (conditioning). The aim of this study was to investigate evidence for or against the presence of such factors (eg. faulty conditioning, cognitive arousal) in untreated insomniac patients.

**Methods:** Eighteen primary insomniacs meeting DSM-IV and ICSD-R criteria, 18 depressed insomniacs satisfying DSM-IV criteria for depressive disorder and ICSD-R criteria for sleep disturbance associated with depression, and 18 good sleepers were recruited. The total sample comprised 35 women/ 19 men with a mean age of 40 years ( $p > .05$  between groups). Participants completed 5 nights of wrist actigraphic assessment of sleep, sleep diaries and a range of questionnaires relevant to underlying models of sleep disturbance.

**Results:** Multivariate analyses confirmed significant between group differences in actigraphically and subjectively-estimated sleep. Univariate analyses demonstrate that good sleepers generally slept better than both insomniac groups with actigraphic sleep revealing fewer between group differences (Table 1). Comparisons of putative models indicated that primary insomniacs exhibited some scores at an intermediate level relative to depressed insomniacs and controls (sleep hygiene, pre-sleep cognitive arousal, performance anxiety; Table 2). For other domains both insomniac groups differed from controls but not from each other (physiological arousal, mental overactivity, sleep anxiety, dysfunctional beliefs). No between group differences were observed on a measure of sleep-related stimulus control.

**Table 1**

Results from the one-way ANOVAs  
 ("group" = the independent variable, sleep variables = dependent variables).  
 \* represents  $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

	Control Group	Primary Insomniac Group	Depressed Insomniac Group	df	F	p	Post hoc (Scheffe)
Sleep Onset Latency (diary)	mean: 11.02 sd: 9.14	mean: 41.40 sd: 27.24	mean: 52.22 sd: 40.47	2, 51	9.99	0.000***	DI, PI>C
Wake time After Sleep Onset (diary)	mean: 4.72 sd: 5.04	mean: 60.75 sd: 49.48	mean: 55.64 sd: 70.28	2, 51	6.99	0.002**	DI, PI>C
Total Sleep Time (diary)	mean: 446.18 sd: 59.43	mean: 343.74 sd: 86.34	mean: 381.94 sd: 120.70	2, 51	5.66	0.006**	C>PI
Sleep Efficiency (diary)	mean: 95.87 sd: 3.01	mean: 77.63 sd: 11.68	mean: 75.79 sd: 18.31	2, 51	13.84	0.000***	C>PI, DI
Sleep Onset Latency (actigraph)	mean: 8.11 sd: 9.86	mean: 13.58 sd: 10.41	mean: 25.99 sd: 31.40	2, 51	3.81	0.03*	DI>C
Wake time After Sleep Onset (actigraph)	mean: 50.87 sd: 27.20	mean: 41.47 sd: 17.68	mean: 63.70 sd: 40.09	2, 51	2.53	0.09	N/A
Total Sleep Time (actigraph)	mean: 376.78 sd: 43.46	mean: 417.76 sd: 81.25	mean: 388.37 sd: 75.56	2, 51	1.70	0.19	N/A
Sleep Efficiency (actigraph)	mean: 86.81 sd: 5.36	mean: 87.38 sd: 4.90	mean: 80.06 sd: 12.97	2, 51	4.05	0.02*	PI>DI

**Table 2**

Results from one-way Anovas investigating the effect of "group" on each of the main measures.  
\* represents p<0.05, \*\*p<0.01, \*\*\*p<0.001

	Contr ol Group	Prima ry Insom niac Group	Depressed Insomniac Group	df	F	p	Post hoc (Scheffe) tests
Sleep Behaviour Self Rating Scale-Adapted	mean: 33.65 sd: 6.54	mean: 34.11 sd: 7.63	mean: 38.89 sd: 9.07	2, 50	2.44	0.10	N/A
Sleep Hygiene Awareness and Practice Scale	mean: 21.11 sd: 10.39	mean: 32.89 sd: 9.22	mean: 43.39 sd: 14.65	2, 51	16.45	0.00***	DI>PI>C
Pre-Sleep Arousal Scale (physiological subscale)	mean: 8.67 sd: 0.91	mean: 11.89 sd: 4.30	mean: 20.44 sd: 8.28	2, 51	22.79	0.00***	DI>PI>C
Pre-Sleep Arousal Scale (cognitive subscale)	mean: 14.00 sd: 3.80	mean: 24.94 sd: 8.19	mean: 30.83 sd: 4.29	2, 51	39.46	0.00***	DI>PI>C
Sleep Disturbance Questionnaire score	mean: 7.17 sd: 1.79	mean: 12.33 sd: 3.50	mean: 13.11 sd: 2.08	2, 51	28.50	0.00***	DI, PI>C
Sleep Anxiety Scale	mean: 9.17 sd: 1.62	mean: 17.61 sd: 3.63	mean: 18.82 sd: 2.51	2, 50	66.54	0.00***	DI, PI>C
Sleep Performance Anxiety Questionnaire	mean: 7.50 sd: 0.62	mean: 13.39 sd: 3.11	mean: 15.39 sd: 1.61	2, 51	71.79	0.00***	DI>PI>C
Dysfunctional Belief and Attitudes About Sleep Scale-10	mean: 30.07 sd: 13.71	mean: 47.73 sd: 15.92	mean: 54.85 sd: 21.88	2, 48	12.25	0.00***	DI, PI>C

**Conclusions:** In spite of 'stimulus control' being arguably the best supported intervention for insomnia, evidence from this study suggests that factors other than conditioning are implicated in the development and maintenance of insomnia, and in the therapeutic action of stimulus control treatment. Similarities between the insomniac sub-groups raises the possibility of a continuum of severity of (mainly cognitive) factors in primary insomnia and insomnia co-morbid with depression, rather than these being categorically different groups. It follows that this pathway may be amenable to CBT irrespective of the presence of depression.

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**505.L**

**INITIAL INSOMNIA AND PARADOXICAL INTENTION: AN EXPERIMENTAL INVESTIGATION OF PUTATIVE MECHANISMS USING SUBJECTIVE AND ACTIGRAPHIC MEASUREMENT OF SLEEP**

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**Introduction:** Paradoxical Intention (PI) is a "probably efficacious" treatment for initial insomnia (1). It is thought to operate by eliminating voluntary sleep effort, therefore minimising performance anxiety, an aroused state incompatible with sleep

(2). However, this model remains untested. Moreover, few studies have examined the effects of PI using objective sleep measures. A reliable and minimally intrusive objective sleep measure is the actigraph. There is recognition that movement is a good predictor of wakefulness, whilst lack of movement is a good predictor of sleep (3).

**Methods:** Following a seven night baseline, thirty-four initial insomniacs (mean age = 25.2 years) were randomly allocated to fourteen nights of PI, or to a control (no PI) condition. Objective (wrist actigraphy) and subjective (self-report) measures of sleep-onset latency (SOL) were collected, alongside a daily rating of sleep effort. Two measures of sleep anxiety were also recorded. Primary hypotheses were that insomniacs allocated to PI would, relative to controls, show a significant reduction in both objective and subjective SOL, a significant reduction in sleep performance anxiety, and a significant reduction in sleep effort.

**Table 1**

Condition	Objective SOL (mins)			Subjective SOL (mins)		
	B	Wk 1	Wk 2	B	Wk 1	Wk 2
Paradoxical Intention						
M	29.92	27.23	24.47	65.74	41.76	38.24
SD	17.16	15.06	17.20	33.97	19.62	25.28
Control						
M	26.62	25.19	25.03	54.67	58.82	55.33
SD	21.83	16.37	16.49	25.67	32.98	29.16

Mean and standard deviation Objective and subjective Sleep-Onset Latency at Baseline, Week One and Week Two.

**Table 2**

Condition	Sleep Effort			Sleep Anxiety					
	B	Wk 1	Wk 2	SAS		SPAQ			
	B	Wk 1	Wk 2	B	Wk 1	Wk 2	B	Wk 1	Wk 2
Paradoxical Intention									
M	2.33	1.11	1.10	16.18	13.59	12.29	15.41	12.53	11.41
SD	1.37	1.20	1.30	4.05	3.78	4.03	2.87	3.89	3.61
Control									
M	2.28	2.21	2.14	15.76	16.35	16.05	14.88	15.18	14.76
SD	1.44	1.12	1.28	3.83	3.12	3.60	2.71	2.43	2.51

Mean and standard deviation Sleep Effort and Sleep Anxiety (both scales) at Baseline, Week One and Week Two.

**Notes**

SAS = Sleep Anxiety Scale  
SPAQ = Sleep Performance Anxiety Questionnaire  
B = Baseline; Wk1 = Week One, Wk 2 = Week Two.

**Results:** Analysis of variance and simple main effects (critical p value = 0.017) demonstrated no significant objective SOL differences between PI and controls at either Treatment Week

(both  $p > 0.1$ ). However, a marginal trend for lower subjective SOL amongst insomniacs allocated to PI was observed at Weeks One ( $F[1,33] = 3.36, p = 0.076$ ) and Two ( $F[1,33] = 3.34, p = 0.077$ ) [Table 1]. Subjective SOL treatment effect size was “moderate” ( $d = 0.61$ ). Analysis also revealed a significant sleep anxiety reduction amongst PI participants at Week Two on both questionnaires ( $F[1,33] = 8.26, p = 0.007$ ), ( $F[1,33] = 9.89, p = 0.004$ ). A significant sleep effort reduction following PI was also observed at Week One ( $F[1,33] = 7.72, p = 0.009$ ), with a similar trend at Week Two ( $F[1,33] = 5.55, p = 0.025$ ) [Table 2].

**Conclusions:** The observation of reduced sleep anxiety and sleep effort following PI is consistent with the performance anxiety model of PI (2), and with recent models of ironic cognitive control. The failure to observe objective SOL reduction, despite significantly reduced subjective SOL and sleep anxiety, might relate to recent metacognitive models of anxiety, or to actigraphic measurement error. Together, results help determine putative mechanisms underlying PI, and have important implications for the clinical application of PI.

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## 506.L

### CARDIAC ACTIVATION IN ASSOCIATION WITH MICRO-AROUSALS IN INSOMNIACS WITH AND WITHOUT DEPRESSION

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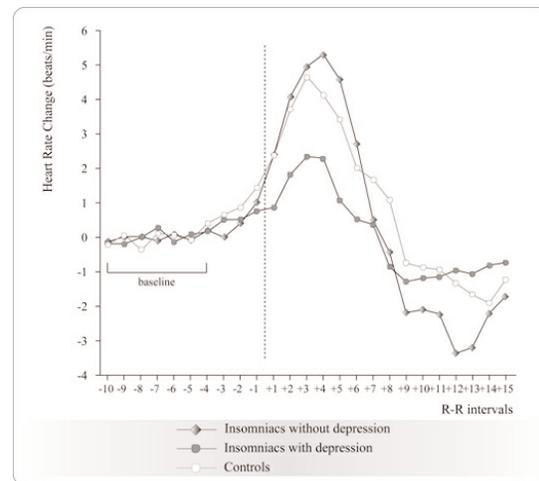
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**Introduction:** Micro-arousals (MA) are defined as abrupt shifts in EEG frequency, which may include theta, alpha and/or frequencies greater than 16Hz (ASDA, 1992). Recently, Sforza et al. (2000) found that MA were associated with a tachycardia followed by a bradycardia. Since hyperarousal was commonly reported in insomniac patients, the aim of the present study was to explore if the amplitude of cardiac variations associated with MA during sleep in insomniac patients with and without depression reflects a state of hyperarousal.

**Methods:** Fifteen patients who were evaluated for insomnia were divided into 2 groups according to the presence or absence of depression (8 insomniac without depression and 7 insomniacs with depression) and were compared to 8 controls matched for age and gender. None of the subjects were taking medication. MA were scored according to ASDA criteria. The R-R interval was calculated for 11 heartbeats before and 15 heartbeats after the onset of MA. The mean of the 7 R-R inter-

vals prior to MA (see figure) was considered as baseline and was subtracted from all R-R intervals. Values were then converted in beats per minute.

Figure 1



**Results:** No between-group difference was observed for mean MA index. The change in heart rate (HR) associated with MA was characterized by a tachycardia followed by a bradycardia and was observed in the 3 groups (see figure). However, the amplitude of both tachycardia and bradycardia was higher in insomniac patients without depression as compared with control subjects, but differences were only significant for bradycardia (bradycardia:  $p < 0.05$ ). Patients with depression tended to show a reduction in the amplitude of tachycardia in comparison with controls ( $p = 0.07$ ). No difference was found in the amplitude of bradycardia between depression and control groups. Finally, differences in HR associated with MA were found between insomniacs with and without depression. Insomniacs with depression showed a reduction in the amplitude of both tachycardia ( $p < 0.001$ ) and bradycardia ( $p < 0.001$ ) compared to insomniacs without depression.

**Conclusions:** As in previous studies, these results showed that cardiac change associated with MA is characterized by a tachycardia followed by a bradycardia in all groups. Insomniacs with depression tended to show a reduction in the HR changes associated with MA, whereas insomniacs without depression showed an increase in the amplitude of these changes. The absence of significant results in the amplitude of tachycardia in insomniac groups in comparison with controls can be explained by the important age range in our study. Our results support the state of hyperarousal reported in insomniac subjects. The reduction in HR found in insomniac patients with depression parallels the attenuation of HR changes associated with movement during sleep in depressed patients found in another study (Lahmeyer & Bellur, 1987). The results obtained in this study suggest that different therapeutic approaches should probably be used in the treatment of insomnia depending on the presence or absence of depression.

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**507.L**

**MORNINGNESS-EVENINGNESS IN OLDER INSOMNIACS**

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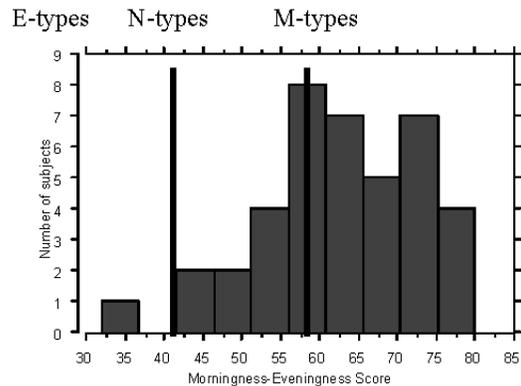
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**Introduction:** The poor sleep connected with older age is widely believed to be associated with a phase advance of circadian rhythms. A tendency to greater morningness is thought to reflect this phase advance. Recently, Carrier et al. (1) have documented this trend in middle-aged subjects using the Horne-Ostberg Morningness-Eveningness Questionnaire (HOMEQ) (2). We expected that the trend to greater morningness with greater age would continue in our group of older insomniacs who had a higher average age than those in Carrier et al. (1). In the present report, we hypothesized that with increasing age our subjects would exhibit greater tendencies to morningness and that this tendency would be associated with poorer sleep

**Methods:** Subjects were 40 older, (mean age = 64.1 + 7 yrs) participants in an ongoing study of behavioral treatments for insomnia in older adults. Data collected were 2 weeks of sleep logs, 1 week of actigraphy and self-ratings on the HOMEQ. We analyzed the correlation of age, lights out time, morning wake time, total sleep time, sleep latency, wake time after sleep onset, and sleep efficiency with scores on the HOMEQ. We also compared our findings with earlier ones of Carrier et al. (1).

**Results:** We found no significant correlations between age and tendencies to morningness. With one exception (one woman who was mostly evening type) all our subjects were either morning, mostly morning, or neither types on the HOMEQ (fig.1). The tendency to morningness was strongly related to earlier wakeup time ( $r = -.65, p < .0001$ ) but there were no other significant relations between HOMEQ score and sleep parameters either as measured by sleep log or actigraphy. Our subjects' age distribution was 35% in their fifties, 45%, sixties; and 20%, seventies compared with Carrier et al.'s age distribution of 36% in their twenties; 34%, thirties; 30% who were in the forty-fifty-nine age range. Our subjects age distribution was higher than Carrier and her colleagues. With only a slight overlap in the 50-59 age range. In Table one we compare the chronotype distribution between the two studies.

**Figure 1**



**Histogram Of HOMEQ Chronotypes In Sample Of Older Insomniacs**

**Table 1**

Chronotype	Carrier et al. MornEve Score (% of sample)	Current study MornEve Score (% of sample)
Moderately Evening	2/110 (1.8 %)	1/40 (2.5 %)
Neither	39/110 (35.5 %)	11/40 (27.5 %)
Moderately Morning	47/110 (42.7 %)	17/40 (42.5 %)
Definite Morning	22/110 (20.0 %)	11/40 (27.5 %)

**Comparison of Chronotype Distribution (Carrier et al. and Current Sample)**

**Conclusions:** We did not find the expected association between increasing age and morningness. Conclusions are limited by the fact that our sample size is small and all participants are applicants for a treatments for insomnia study. It is interesting, however, that our subjects who had a higher mean age than those of Carrier et al.(1) had a very similar chronotype distribution. Both samples could be characterized as moderately morning types. These findings suggest that change to greater morningness occurs during later middle age and may be relatively stable thereafter. The finding of the earlier wake up times associated with greater morningness was expected but failure to find associations of chronotype with other sleep variables was unexpected. It may be that because all our subjects suffered from insomnia there was not much variability in their sleep parameters. Comments: Longitudinal studies that follow subjects from adolescence through older age would be required to decide definitively the influence of aging on morningness/eveningness.

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508.L

COGNITIVE-BEHAVIOURAL-THERAPY FOR INSOMNIA FOLLOWING TRAUMATIC BRAIN INJURY: A CASE STUDY

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**Introduction:** Among the residual sequelae of traumatic brain injury (TBI), sleep disturbances have received very little attention despite the fact that they are reported by a large number of patients (1). For individuals with TBI, problems falling asleep or maintaining sleep can exacerbate other symptoms such as pain, cognitive deficits, fatigue, or irritability. Insomnia can thus significantly compromise the rehabilitation process and complicate social re-integration (e.g., return to work). Systematic studies evaluating treatment options for post-TBI insomnia are extremely rare and limited to pharmacological agents. Because patients with TBI are faced with an amalgam of emotional and environmental stressors, psychological factors such as emotional arousal or maladaptive habits probably play a very important role in producing, exacerbating, or maintaining insomnia after TBI. Psychological treatment options for insomnia should thereby be promising. The objective of the present study was to adapt a cognitive-behavioural therapy (CBT) for insomnia (2) to a TBI population. We present the first of a series of case studies aimed at testing the efficacy of CBT with mild to moderate TBI patients.

**Methods:** The patient is a 38 year-old man having sustained moderate TBI in August 2000 following a motor vehicle accident. The medical history prior to the accident is unremarkable. Apart from increased fatigability and mild pain to the left knee, his major complaint related to difficulties initiating sleep, and more importantly, in maintaining it. These problems appeared shortly after the trauma and persisted despite pharmacotherapeutic interventions. The patient completed 5 nights (3 pre, and 2 post-treatment) of polysomnography (PSG), as well as subjective measures of sleep and psychopathology. He also completed a daily sleep diary throughout 5 weeks of baseline and 8 weeks of CBT. Treatment was based on a manual including Stimulus Control, Sleep Restriction, Sleep Hygiene Education and Cognitive Therapy (2). Adaptation of this intervention for TBI consisted of (a) providing information on physiological, psychological and environmental factors contributing to insomnia after a TBI, (b) adapting treatment material for possible cognitive limitations, (c) including fatigue management skills training, (d) discussing issues related to return to work and acceptance of a newly acquired vulnerability to insomnia because of TBI.

**Results:** The diary data showed important reductions in sleep onset latency, wake after sleep onset, and number of awakenings with CBT implementation. Sleep efficiency increased substantially (57.6% to 84.8%) but total sleep time was only slightly increased. PSG data indicated decreases in total wake time (63.2 to 26.3 minutes) and in the number of awakenings

(21 to 7.5).

Figure 1

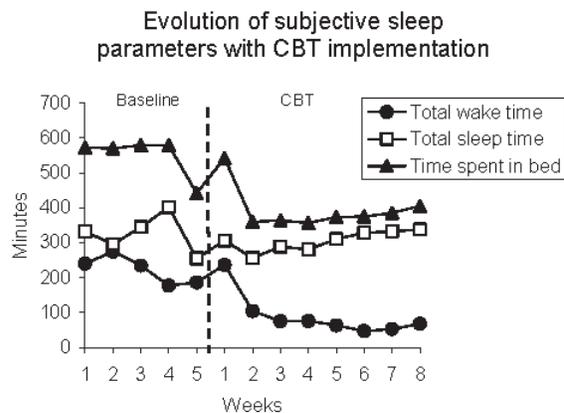
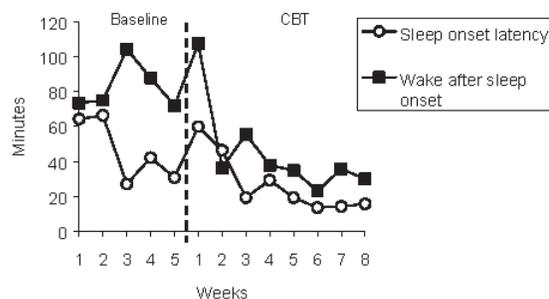


Figure 2



**Conclusions:** These preliminary results suggest that sleep disturbances following TBI can be successfully alleviated with a psychological intervention. This study thereby represents the first attempt to demonstrate that CBT for post-TBI insomnia is a promising therapeutic avenue deserving more scientific and clinical attention.

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Research supported by the Fonds de Recherche en Santé du Québec.

## 509.L

## SELF-REPORTED SLEEP IN MENOPAUSAL WOMEN CORRELATES WITH SYMPTOMS MORE THAN WITH OBJECTIVELY-RECORDED SLEEP

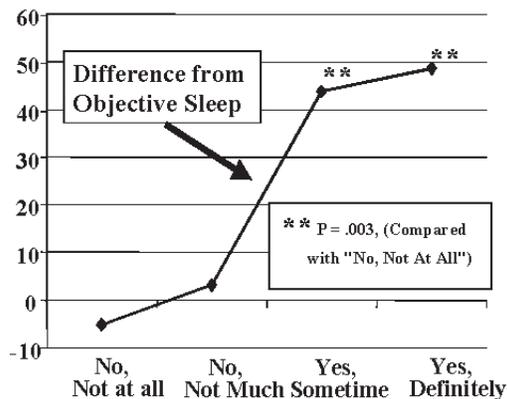
Regestein QR,<sup>1</sup> Friebely J,<sup>1</sup> Shifren JL,<sup>1</sup> Scharf MB,<sup>2</sup> Wiita B,<sup>3</sup> Carver J,<sup>4</sup> Schiff I<sup>4</sup>

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**Introduction:** Almost half of menopausal women report disturbed sleep (Shaver & Zenk, 2000), but this is often not confirmed by objective sleep measures (Mendelson et al, 1986). We explored how their sleep self-reports related to psychological symptoms, cognitive status, FSH levels and objective sleep measures.

**Methods:** Using drug baseline trial data from 88 healthy postmenopausal women complaining of vasomotor symptoms but not taking replacement estrogen, we tested whether 7-day averaged St. Mary's sleep questionnaire responses predicted scores on the Women's Health Questionnaire (WHQ), the Hyperarousal scale, computerized cognitive tests, measures of FSH and 7-day averaged actigraphic sleep.

Figure 1



**Results:** Average self-reported sleep was slightly disturbed. Sleep questionnaire scores predicted WHQ symptoms and cognitive test performance more than objective sleep measures. Most strongly predicted WHQ symptoms were tiredness, clumsiness and difficulty concentrating. Most frequently predicted were irritability, worry about growing old, decreased feelings of well being and night sweats. Women with reported sleep latencies longer than the median overestimated their objective sleep latencies by 30 minutes, but the rest underestimated theirs by 15 minutes ( $p < .0001$ ). Women whose self-reported total sleep was longer or shorter than the median, respectively, underestimated objective sleep times by 9 and 71 minutes ( $p < .0001$ ). The figure shows the effect of an insomnia complaint. High Hyperarousal scores predicted underestimation of objective sleep in self-reports. Higher than median FSH levels were associated with longer self-reported sleep

onset times ( $p < .01$ ).

**Conclusions:** Self-reported sleep predicts measures of psychological symptoms and cognitive function more than objective sleep. Self-reported disturbed sleep may signal problems independent from sleepiness, such as negative affect, attention problems, or fatigue.

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Research supported by Johnson & Johnson Corp.

## 510.L

## NEUROIMAGING OF NREM SLEEP IN PRIMARY INSOMNIA: A TC-99-HMPAO SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY STUDY

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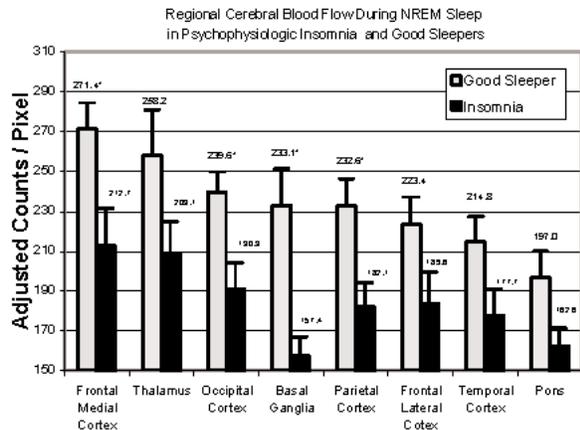
**Introduction:** At the neurobiologic level, the pathophysiology of primary insomnia (PI) is poorly understood. Accordingly, neuroimaging may be useful in the effort to identify sleep-related CNS abnormalities in this sleep disorder. The present study was undertaken to: 1) demonstrate feasibility of capturing tomographs during sleep in patients with sleep initiation and maintenance problems and 2) acquire data to suggest what brain regions might be functionally dysregulated during the sleep of patients with Primary Insomnia as compared to good sleeper controls.

**Methods:** Nine females, 5 with chronic psychophysiological insomnia and 4 healthy good sleepers (mean age=36, SD=12, range=27-55) were studied polysomnographically for three nights. Groups were screened for medical/psychiatric history, substance use and were matched on age, body mass index, and education. Night1 screened for other sleep disorders. Night2 was an accommodation night. On Night3, 25mCi of TC-99HMPAO was administered via an IV line, 10-minutes after the 1st K-Complex or sleep spindle and when 5 minutes of continuous sleep was achieved. Subjects were awakened 10 minutes after the injection of the radiopharmaceutical and scanned. The two-minute HMPAO uptake period was coregistered with PSG data. A semiquantitative index of regional cerebral blood flow [(rCBF) counts/pixel] was calculated using ROI arithmetic with standard neuroanatomic templates.

**Results:** All 9 subjects were judged to be in NREM during the entire 2-minute uptake window (slow wave sleep: Insomnia = 70%, Control = 56%,  $p = .64$ ). Contrary to expectation, patients with insomnia had a pattern of hypoperfusion across all 8 pre-selected regions of interest, with particular deactivation in the basal ganglia ( $p = .006$ ). See Figure1. The frontal medial, occipital, and parietal cortices also showed significant decreases in blood flow compared to good sleepers ( $p < .05$ ).

Subjects with insomnia had decreased activity in the basal ganglia relative to the frontal lateral cortex, frontal medial cortex, thalamus, occipital and parietal cortices ( $p < .05$ ).

Figure 1



**Conclusions:** This study demonstrated the feasibility of undertaking neuroimaging procedures to study the sleeping brain in patients with Primary Insomnia. The preliminary results suggest that PI may be associated with abnormal CNS activity during NREM sleep that is particularly linked to basal ganglia function. One possible interpretation of the hypoperfusion findings is that they reflect the effects of chronic sleep debt and therefore represent an early and perhaps short-lived homeostatic response to sleep loss. While the results seemingly contradict hyperarousal theories of insomnia, it should be noted that they reflect only a brief snap shot of activity, approximately 15 minutes after sleep onset. It is possible that arousal mechanisms are temporarily suppressed once sleep is successfully initiated and are later reactivated. Future investigations are needed to obtain multiple scans across the sleep-wake continuum.

Research supported by a Salzman Award, University of Rochester Department of Psychiatry (MTS), a General Clinical Research Center Grant (5M01-RR 00044: National Center for Research Resources, NIH), and MH 35931 (DEG).

511.L

**DIM LIGHT MELATONIN ONSET ESTIMATION IN ELDERLY INDIVIDUALS WITH AND WITHOUT DIFFICULTY INITIATING OR MAINTAINING SLEEP**

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**Introduction:** As part of our ongoing case control study of risk factors for insomnia among elderly, community residing, cognitively intact, non-depressed individuals, dim light melatonin offset (DLMO) [1] and melatonin net area under the

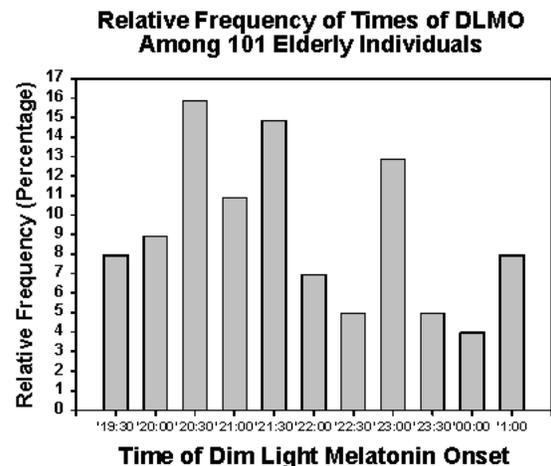
curve (AUC) are being used to assess whether altered circadian phase and/or altered melatonin levels are risk factors for insomnia. The current sample for DLMO assessment includes 77 insomnia cases (28.4% male) and 43 controls (42.1% male). Mean (SD, range) ages among cases and controls are 72.0 (4.8, 64 to 85) years and 73.2 (6.1, 65 to 87) years, respectively.

**Methods:** Serum melatonin (assessed by Melatonin Direct I-125 RIA, IBL Laboratories, Germany) was collected every 0.5 hr from 18:00 to 24:00, at 1:00, 2:00, 3:00, and 4:00, and then every 0.5 hr until 8:00. DLMO times were determined using 3 algorithms including the 1st time in which melatonin concentration: 1) exceeded 100% of baseline [2] (mean over 18:00, 18:30, and 19:00); 2) exceeded 10 pg/ml in absolute value [2] while the mean of the next 3 observations also exceeded 10 pg/ml; and 3) was more than 100% larger than the mean of the preceding 3 values. An objective consensus DLMO was determined using these criteria as follows: 1) if all were identical, DLMO was set equal to this value; 2) if two were equal and the third differed or was missing, then DLMO was set equal to the common value; 3) if all three were non-missing but unequal and the extremes differed by no more than one hour, DLMO was set to the middle value; and 4) if one value was missing and remaining two values differed by no more than ½ hour, DLMO was set to the earlier value. If there was no objective consensus, then blinded adjudication was performed with the objective of determining the time when there was a “sustained detectable melatonin level”[3]. DLMO phase angles were used in analyses and then back transformed to describe the findings.

Table 1

Status	Cases (N=77)	Controls (N=43)	Median Melatonin AUC
Objective consensus	42 (54.6%)	33 (76.7%)	426.8
Adjudication	19 (24.7%)	7 (16.3%)	154.2
Non-identifiable	16 (20.8%)	3 (7.0%)	6.6

Figure 1



**Results:** The table summarizes case-control differences in DLMO identification status distributions ( $df=2$ ,  $p=0.041$ ). Non-identification resulted from lack of sustained increase in melatonin levels as reflected in median AUC values. Significantly more insomnia cases (20.8% vs. 7.0%,  $p=0.048$ ) had inadequate sustained elevation in melatonin for DLMO identification. Among 61 cases and 40 controls with DLMO determinations, the mean (SD) phase angle values were 0.60 (0.39) and 0.58 (0.44) degrees, respectively. Since cases and controls did not differ with regard to mean DLMO phase, the pooled distribution of DLMO times is presented in the figure.

**Conclusions:** Among elderly with and without reports of difficulty maintaining and/or initiating sleep, circadian phase distributions, when estimable by DLMO, were indistinguishable. Yet, there was an appreciable subgroup of elderly with insomnia (20.8%) who had no clear melatonin secretory profile relative to controls (7.0%). This suggests that absence of melatonin secretion might be a risk factor for insomnia in a subset of elderly. Analyses are underway to determine if the severity of insomnia was worse in subjects with no apparent melatonin signal.

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**Research supported by R01 AG-14155, P50 HL-60287, and M01 RR-00040**

**512.M**

**LET THE SLEEP FAIRY TAKE YOUR CHILD FROM A TO ZZZZZ'S**

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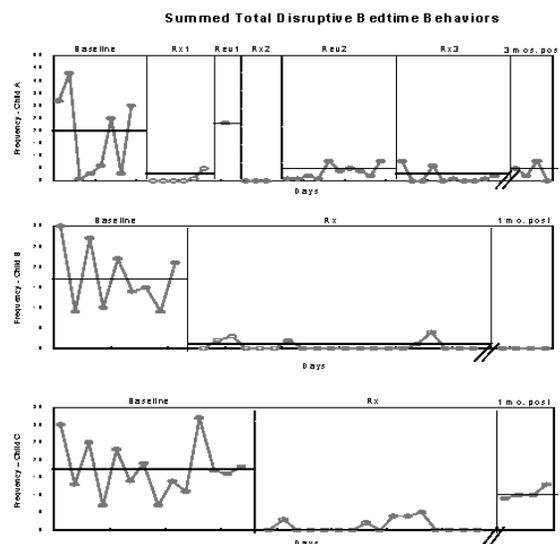
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- (2) Girls and Boys Town, USA,
- (3) Behave'n Day Center, Inc.,

**Introduction:** Problems with settling and night waking are the most frequently encountered sleep problems in young children. Recent reviews conclude that effective treatment options are available, however, those interventions with the highest efficacy (e.g., unmodified ignoring, sedative medication) tend to have the lowest treatment acceptability by parents.<sup>s1,2s</sup> The current study evaluates the efficacy of a "child-friendly" intervention that involves reading a pre-bedtime story about the "Sleep Fairy," who leaves a small reward under the child's pillow for demonstrating appropriate bedtime behavior.

**Methods:** Participants included three children (2.5, 5, and 7 yrs.) who were physician-referred and met criteria previously established for disturbed sleep.<sup>s3s</sup> The intervention consisted simply of having the parent read the *Sleep Fairy* book to the child prior to bedtime. The "Sleep Fairy" then provided a small reward under the child's pillow contingent upon demonstrat-

ing appropriate bedtime behavior and remaining in bed until morning. The primary dependent measures were derived from parent-completed diaries of disruptive bedtime behavior and sleep (sleep onset latency, number and duration of awakenings, total sleep time). Disruptive bedtime behavior was recorded any time the child engaged in stalling, noncompliance, vocal protests, tantruming, complaining, aggressive behavior, or leaving the bedroom without permission. A within-subjects ABAB (A, baseline; B, intervention) reversal design was used for participant A. An additional reversal phase occurred incidentally for participant A when a babysitter put the child to bed without intervention (see Figure 1). A multiple baseline across subjects design was used for participants B and C.

**Figure 1**



**Table 1**

Mean Sleep Latency in Minutes

Participant	Pre-	Post-	Difference
A	55.9 min	32.8 min	23.12 min.
B	41.1 min	29.1 min	11.99 min.
C	48.9 min	27.5 min	21.43 min.
Total	50.1 min.	30.4 min.	19.70 min.

**Results:** The *Sleep Fairy* successfully reduced disruptive bedtime behaviors for all three children. Experimental control is indicated by the contrast between data rates and trends between baseline and intervention phases (see Figure 1). The magnitude of change, represented by the change in mean rates of

problem behavior, is readily evident for the three participants. Improvements in bedtime behavior were accompanied by shorter sleep latencies for all three participants, with a mean reduction of nearly 20 minutes (see Table 1). One participant (C) obtained 33 minutes per night of additional sleep time during treatment compared to baseline. One-month follow-up data indicated that treatment effects were well-maintained for two participants, while the third participant exhibited a mild increase in bedtime behavior problems.

**Conclusions:** These data support the utility of a novel, "child-friendly" intervention to reduce disruptive bedtime behaviors and night-time awakenings in three clinically-referred children. Because this study employed only three children, our results await replication within a large-group, randomized study. Limitations notwithstanding, the "Sleep Fairy" appears to possess potential as an effective, positive approach for treating young children who present with bedtime struggles and night-waking.

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### 513.M

#### EATING IN HER SLEEP: A BEHAVIORAL SLEEP INTERVENTION CASE STUDY

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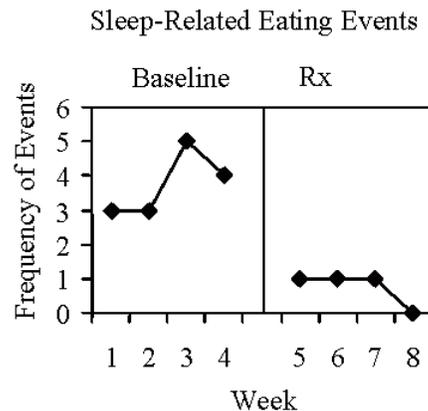
(1) Munroe-Meyer Institute and Dept. Pediatrics, University of Nebraska Medical Center,

**Introduction:** Sleep-related eating is a disorder characterized by episodes of uncontrolled, nightly eating of high calorie foods that occur after sleep onset. Patients eat foods not normally consumed, and often have little or no recall for the event. <sup>s1s</sup> Sleep-related eating disorder is more common among females, and adolescent onset is common. Sleep-related eating has been associated with sleep disorders, primarily partial arousal parasomnias, eating disorders, and major life stressors. <sup>s2s</sup> Schenck describes a pharmacologic (dopamnergic combined with an opiate or clonazepam) treatment protocol that has proven effective in a number of patients. <sup>s2s</sup> Schneck added that sleep hygiene and sleep-wake schedules should be attended to. The purpose of this case study was to evaluate a behavioral treatment approach for sleep-related eating.

**Methods:** A 16-year-old diabetic Caucasian female was referred by her physician to a Behavioral Pediatric Sleep Clinic for nightly sleep-related eating episodes that began abruptly 16 months prior. The sleep-related eating posed serious medical health risks due to her diabetes. The patient reported a history of borderline anorexia shortly before the onset of her sleep-related eating behavior. Parent report of the nighttime eating episodes were consistent with the clinical characteristics of sleep-related eating (e.g., unremitting, driven episodes

of nightly eating following an initial period of sleep, amnesia for the event, consuming high calorie foods, agitation if eating was prevented). <sup>s3s</sup> Parents maintained a daily sleep diary to record sleep onset, total sleep time, and sleep-related eating events. Parents completed separate diaries to assess reliability. In keeping with behavioral treatment of partial arousal parasomnias, the goal was to increase the patient's total sleep time, regulate her sleep-wake schedule, and insure her safety. Specific recommendations targeted sleep hygiene (i.e., limiting TV in bedroom, restricting caffeine), safety (access to "safe" foods, motion detector, guide back to bed) and her sleep-wake schedule.

Figure 1



**Results:** Pre-treatment sleep diaries indicated that the patient averaged 6.9 hours total sleep time, more than 2 hours below published developmental norms. Post-treatment diaries revealed the patient increased her total sleep time to 7.8 hours. Frequency of sleep-related eating events showed an immediate reduction from 3.75 per week to 0.75 per week. A reversal design to establish methodological control of treatment effects was considered, however, the medical risk associated with the patient's sleep-related eating precluded withdrawal of treatment.

**Conclusions:** The results of this study should be interpreted with caution as they represent an uncontrolled, single case study. These data suggest that sleep-related eating may be a variant of partial arousal parasomnia for which behavioral sleep interventions are a promising alternative. By increasing this patient's total sleep time through practical behavioral recommendations, rapid and clinically impressive reductions were attained in the frequency of sleep-related eating events.

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## 514.M

## MMPI PROFILES OF SLEEPWALKERS AND CONTROLS

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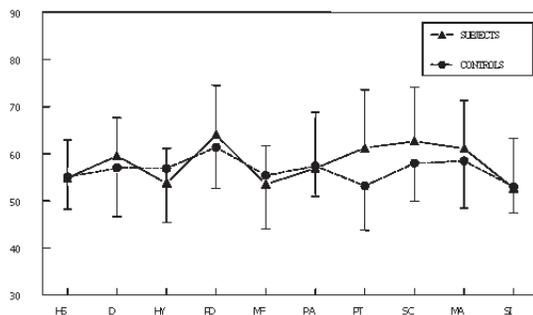
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**Introduction:** Sleepwalking is considered a disorder of arousal in which there occurs a physiological dysfunction in the neural regulation of generalized cortical activation. Some authors view the presence of somnambulism as a sign of marked psychopathology. Clinical reports have shown that the adult onset of sleepwalking in adults is sometimes linked to a major psychological event (1). Attempts to assess the personality of sleepwalkers using psychometric instruments such as the Minnesota Multiphasic Personality Inventory (MMPI) have yielded mixed results. The goal of the present study was designed to assess the personality of this population by an analysis of responses and profiles on the MMPI.

**Methods:** Ten sleepwalkers (3 males, 7 females, mean age: 25.1, SD:4.09) and 10 sex and age-matched controls (mean ages: 25.2, SD: 3.55) were investigated as part of a sleep deprivation study detailed elsewhere (2). All participants were in good physical health, did not suffer from other sleep disorders, and none had a history of neurological or major psychiatric (e.g., schizophrenia) disorders. During their visit in the sleep lab, subjects completed the French version of the MMPI, form R (Institut de recherche psychologiques, Montréal, Québec). Group comparisons of the MMPI data were performed using t-tests for independent samples.

**Results:** Figure 1 illustrates the mean MMPI profiles obtained from the both groups. Due to missing data from one sleepwalker, analyses were performed on 10 controls and 9 patients. T-tests for independent samples revealed no significant group differences on any of the clinical scales. Five patients and 5 controls had at least one clinical scale higher than the normal limit ( $50 \pm 20$  t-score) with 75 being the highest score obtained. There was no consistency in the elevation patterns observed across subjects.

Figure 1



**Conclusions:** Our results are consistent with those from other studies (3) showing that a majority of patients do not have a DSM-based Axis I psychiatric disorder nor do they necessari-

ly present with highly deviant personality profiles. However, sleepwalkers are not a homogenous group. Comparisons among specific subgroups of somnambulistic patients (e.g., childhood onset versus adult onset, with versus without violent behavioural manifestations) may provide a clearer understanding of this issue.

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**Research supported by the Canadian Institutes of Health Research and the « Fonds de la Recherche en Santé du Québec ».**

## 515.N

## MOOD AND ANXIETY DISORDERS IN PATIENTS WITH RESTLESS LEGS SYNDROME

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**Introduction:** Increased anxiety and depression scores in restless legs syndrome (RLS) patients have been described repeatedly. However, no data are available on the prevalence of mood and anxiety disorders in these patients.

**Methods:** We contacted 397 RLS patients. All participants were questioned with the sections for depressive and anxiety disorders of the M-CIDI/DIA-X and a RLS questionnaire on the clinical characteristics and severity of RLS. The control subjects were selected from a population with one or more somatic disorders but no neurological disorder investigated within the Bundes-Gesundheitssurvey 1998 (BGS).

**Results:** 238 patients (mean age 63 years, range 12-89, SEM±12.5; 58.4% female and 41.6% male) participated in the study. 12-month prevalence rates were 4.6% for panic disorder, 5.5% for generalized anxiety disorder (GAD) and 14.3% for specific phobia. 5.9% fulfilled criteria for a mood disorder due to a general medical condition. Compared to the control group, RLS patients had an increased 12-month prevalence rate for panic disorder (OR=3.03; 95% CI=1.22-7.50), GAD (OR=2.42; 95% CI=1.14-5.14), specific phobia (OR=2.82; CI=1.74-4.56) and mood disorder due to a general medical condition (OR=10.91; CI=4.48-26.60). The lifetime prevalence rates were 8.4% for panic disorder, 19.8% for major depression, and 9.2% for a mood disorder due to a general medical condition. Compared to the control group, RLS

patients have an increased lifetime prevalence rate for panic disorder (OR=2.79; CI=1.43-5.43), major depression (OR=1.58; CI=1.05-2.38) and mood disorder due to a general medical condition (OR=6.53; CI=2.94-14.54).

**Conclusions:** This study demonstrates that RLS patients are at increased risk for panic disorder, generalized anxiety disorder, specific phobia, major depression and mood disorder due to a general medical condition. Because we choose a control group with one or more somatic disorders it is unlikely that the simple fact of suffering of a somatic disorder accounts for the increased risk for specific mood and anxiety disorders. RLS patients have no increased risk for panic attacks only, which may be explained by sleep disturbances, but an increased risk for panic disorder. This increased risk is constant in 12-month and lifetime prevalences. Prevalence rates for specific phobia are not only increased for specific situations like narrow spaces and the impossibility to move, a crucial situation for a RLS patient with the urge to move, but also elevated for the animal type. The comorbidity of RLS with anxiety and depressive disorders is of clinical relevance because it is known that antidepressants may aggravate RLS. Our results raise the question on the relationship of RLS and anxiety and mood disorders, especially as these disorders show familial aggregation.

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## 516.N

### CORRELATES OF SLEEPINESS IN PATIENTS WITH PARKINSON'S DISEASE

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**Introduction:** Daytime sleepiness is commonly reported in patients with Parkinson's disease (PD). The cause of sleepiness in this population is unknown and might be due to medication effects, CNS dysfunction or sleep disorders. To understand the cause of sleepiness in these patients, we recruited consecutive patients from a movement disorders clinic at a tertiary care hospital for evaluation of PD as well as evaluation of sleep.

**Methods:** Patients being seen in the Movement Disorders Clinic completed a questionnaire in the waiting room prior to their appointment. Of those agreeing to participate and not on antidepressants or sedative-hypnotics, 20 out of 44 gave consent. Clinical information including Epworth Sleepiness Scale (ESS), Hoehn and Yahr, United Parkinson's Disease Rating Scale (UPDRS), and current medication was collected prior to polysomnography.

**Table 1**

	ESS < 10 (n=10)	ESS > 10 (n=10)
Age	60.5 (14.3)	66 (8.04)
Gender	8 males, 2 female	7 males, 3 female
BMI	23.7 (5.6)	28.9 (5.8)
Hoehn & Yahr	2.25	2.4
UPDRS-motor	23.9 (10.5)	28.2 (7.3)
Pergolide Equivalents	1.7	1.8
L-dopa daily dose (mg)	418.8 (234.4)	638.9 (284)
TST minutes	355.8 (76.5)	300.5 (90.9)
SE percentage	76.7 (16.1)	63.9 (19.7)
SOL minutes	11.5 (15.4)	6.2 (5.0)
AHI*	6.2 (6.8)	21.4 (22.1)
PLMI	21.5 (29.1)	18.8 (25.2)
Arousal index	26.8 (14.0)	41.9 (28.1)

Reported as means ( $\pm$ SD) for clinical and sleep variables

\*p=0.05, t-test

**Results:** To analyze factors contributing to reported daytime sleepiness, subjects were divided into two groups based on ESS score. A score greater than 10 indicates subjective sleepiness. Sleep quantity and quality is reduced in the high ESS group as expected due to more severe sleep disordered breathing. However, these differences are not statistically significant due to small sample size.

**Conclusions:** Patients with ESS greater than 10 demonstrated a higher AHI than those with ESS less than 10. There were no differences in severity of underlying PD, but the dose of L-dopa was higher in the ESS > 10 group. Primary sleep disorders should be strongly considered in PD patients with daytime sleepiness. Complaints of persistent daytime sleepiness may warrant further evaluation with overnight polysomnography.

## 517.N

### UNINTENDED SLEEP EPISODES IN PARKINSON'S DISEASE PATIENTS RECEIVING DOPAMINERGIC AGENTS

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**Introduction:** Unintended sleep episodes (SEs) have been reported in the Parkinson's disease (PD) population taking dopamine agonists (DAs).<sup>1</sup> The present study was undertaken to determine whether patients reporting "sleep attacks" (ie, SEs) and taking DAs are (a) sleepy during the day and (b) sleepier than PD patients not reporting SEs.

**Methods:** This is an observational study in which 24 patients (5 women, 19 men) who received DAs for idiopathic PD and who had sleepiness as evidenced by abnormal Significant Other Epworth Sleepiness Scale (SOESS) scores of >10 com-

pleted a 2-day sleep-wake evaluation. Patients were dichotomized into 2 groups: those with SEs (SE+, n = 16) and those without SEs (SE-, n = 8). Patients underwent 2 consecutive nights of polysomnography followed by multiple sleep testing (MSLT).

**Results:** The overall frequency of pathological sleepiness (MSLT <5) was 42% (10/24). No significant differences were observed between the SE+ and SE- groups in mean level of sleepiness, frequency of pathological sleepiness, frequency of naps with stage 2 sleep (p>0.10), or frequency of REM naps. Interestingly, there was no relation between the level of sleepiness and nocturnal sleep parameters, or specific DAs.

**Conclusions:** We conclude that SEs occur in PD patients with a history of excessive daytime sleepiness and are not simply the result of insufficient sleep or the effects of any DAs. Further studies are needed to assess the contribution of other drug effects, disease progression, and other as yet unidentified factors in the etiology of SEs among PD patients.

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## 518.N

### RESTLESS LEGS SYNDROME AMONG BLOOD DONORS

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**Introduction:** Restless legs syndrome (RLS) is known to be a major cause of sleep disturbance. In a recent Swedish survey, the prevalence of RLS was estimated to be 5.8% among males and 11.4% among women (1, 2). Blood donors may experience sideropenia and iron deficiency is known to be a substantial contributor to secondary RLS. This study investigates the prevalence of RLS among blood donors.

**Methods:** Nine hundred forty-six consecutive voluntary blood donors (males: 618, women: 328) aged 18-64 years, who visited Avesta Hospital, Sweden, during a 10 months period, responded to a questionnaire that included questions about sleep habits and symptoms of sleepiness. The four symptom questions determined by The International Restless Legs Syndrome Study Group as minimal diagnostic criteria for RLS were included as well as the Epworth Sleepiness Scale (ESS). Frequency of blood donation was recorded and intake of iron tablets was assessed. Red blood distribution with (RDW), an estimation of the average distribution of the diameter of the red blood cell was recorded as well as hemoglobin count. The value of RDW increases in relation to sideropenia. Statistical analyses were performed using Student's t-test and Fisher's

exact test

**Results:** According to the response to the questionnaire, 91(14,7%), of the male blood donors and 81 (24,7%), of the female blood donors were affected by RLS. The mean values of the scores on the ESS in both the male and female RLS-sufferers was higher than in those not affected by RLS ( 9,7 vs 7,7, p<0.001 and 8,8 vs 7,2, p<0,003). The RLS-sufferers were more affected by problems with initiating sleep (p<0.0001), maintaining sleep (p<0.0001) and they were less often refreshed upon awakening (p<0.001). Night sleep less than 6 hours, was also more often reported among the RLS-sufferers (p<0.01). Reported RLS vs non-RLS was equal among both men and women in relation to frequency of blood donation and intake of iron during the last 12 months. The mean RDW was equal statistically among the male blood donors irrespective of RLS-status. The mean RDW among the female blood donors with RLS was higher (13,3 vs 13,1, p<0.03)

**Conclusions:** This study shows that among Swedish blood donors, RLS is much more common than in the general Swedish population. The study also shows that insufficient sleep and daytime sleepiness are more common among those suffering from RLS. It is hypothesized, that sideropenia among female blood donors may cause this high RLS-frequency. However, it is puzzling why RLS is also more prevalent among male blood donors.

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## 519.N

### SPECTRAL ANALYSIS OF HIDDEN EEG AROUSAL ACTIVITY IN PERIODIC LEG MOVEMENTS IN SLEEP WITHOUT MICROAROUSAL

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**Introduction:** Periodic leg movements in sleep (PLMS) might be subdivided based upon whether or not they are associated with visible EEG microarousals (MA). MA is being considered to be responsible for the nonrestorative sleep and daytime fatigue. The American Sleep Disorders Association (ASDA)'s scoring rules for MA based on the visual analysis of the EEG changes suggest that they should last more than 3 seconds (1). However, it has been suggested that the visual analysis may not detect some changes in EEG activity. We aimed at measuring changes in EEG spectra during PLMS without MA in order to better understand the arousing response of PLMS.

**Methods:** Ten drug-free patients (three men and seven women) diagnosed as PLMS by polysomnography were stud-

ied. Spectral analysis of the EEG was performed in each patient on 30 episodes of PLMS without MA chosen randomly across the night in stage 2 non-REM sleep. We applied more strict criteria for MA compared to the ASDA criteria by defining it as a return to alpha and theta frequency lasting at least 1 second (2).

**Results:** The mean PLMS index was 16.7  $\pm$  10.0. The mean PLMS duration was 1.3  $\pm$  0.7 seconds. Comparison of 4-second EEG activity each before and after the onset of PLMS without MA using independent t-test showed that the movements were associated with significant increase of the relative activity in delta band ( $p=0.000$ ) and significant decrease of the activity in alpha ( $p=0.01$ ) and sigma ( $p=0.000$ ) bands. No significant decrease in the theta ( $p=0.05$ ), beta ( $p=0.129$ ), and gamma ( $p=0.062$ ) bands was found.

**Conclusions:** We found that PLMS without MA was associated EEG change characterized by increase in delta frequency band. This finding seems to be compatible with the hypothesis of an integrative hierarchy of arousal responses(2). Considering that our patients had lower PLMS index and shorter PLMS duration than those of the previous study(2), we suggest that even less severe form of PLMS without MA could induce neurophysiologic change. And it might be potentially of clinical significance.

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**520.N**

**THE PREVALENCE OF RESTLESS LEGS SYNDROME IS THE SAME IN REMEDIAL PRIMARY SCHOOLS WHEN COMPARED TO MAINSTREAM SCHOOLS.**

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**Introduction:** Periodic limb movement disorder (PLMD) has been found to be relatively common in children with Attention deficit Disorder (ADD) when compared to children without ADD<sup>1</sup>. Restless Legs Syndrome (RLS) is a commonly associated disorder in patients with PLMD. We investigated the presence of symptoms suggestive of RLS in primary school children as a possible marker for PLMD and subsequent learning difficulties.

**Methods:** A detailed questionnaire was completed by parents of children attending one mainstream school (n=925) and three remedial schools (n=253).

**Results:** In the mainstream school 10.5% of the children complained of "strange feelings in their legs before going to sleep". The corresponding figure in the remedial schools was 10.7%. There were no gender or ethnic differences within the schools between the children with RLS and those without symptoms. A positive family history of restless legs or PLMS

was doubled in those children who had RLS compared to those children without symptoms. Ethnic and gender differences between schools were confounded by the differing overall composition of the student body in each school. The incidence of ADD was higher in the RLS symptom group when compared to the children with no symptoms in both the mainstream and remedial schools. There was no difference in the overall incidence of general learning problems between the two groups.

**Conclusions:** We report on a 10% incidence of restless legs-like symptoms in children at primary school, which is not increased in the remedial school population. A diagnosis of ADD is, however, more likely in the children with RLS at the mainstream and remedial schools. The children in the remedial schools are thus a subset of the normal population of children and are not a group necessarily at high risk for restless legs syndrome.

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**521.N**

**PRELIMINARY RESULTS OF A FAMILY STUDY OF RLS: ALMOST ALL FAMILIES OF IDIOPATHIC RLS PATIENTS ARE POSITIVE FOR RLS AND FREQUENCY OF RLS IN RELATIVES INFLUENCED BY AGE OF RLS ONSET IN PROBANDS**

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**Introduction:** It has long been noted that the restless legs syndrome shows a strong clinical suggestion of familial aggregation. Recently, a linkage to chromosome 12 has been reported using a model of recessive inheritance (1). However, this linkage appears unlikely to provide a suitable model for most inherited forms of this disorder. The recessive model requires a very high prevalence of the RLS allele in the population (probably >20% frequency) to achieve the generally estimated overall prevalence of the condition (3 to 8%). This finding also conflicts with a recent report (2) that families with a mean age of onset of 31 or less show statistical support for a dominant inheritance model.

**Methods:** Consecutive patients seen at the Johns Hopkins Bayview Medical Center Sleep and Neurology clinics with a diagnosis of RLS were invited to participate in a family study. Those participating agreed to be interviewed for medical history and to provide contact information for all first and second degree relatives. These relatives were then contacted to provide background medical data and to be interviewed by a blinded expert clinician (WH) who determined RLS diagnosis on the basis of a validated telephone diagnostic interview (3). Proband were also requested to find a community associate without RLS who might be similarly interviewed and whose first degree relatives would also be contacted, interviewed, and diagnosed. Diagnoses included both definite and probable RLS, depending on features of the disease presentation.

**Results:** 24 families have now been analysed, 21 of whom

have an RLS proband. Family aggregation was noted with 18 of 21 RLS proband families having at least one affected first degree relative member compared to only 1 of 3 control proband families. The prevalence of RLS (definite or probable) in first and second degree relatives of RLS proband families was 47% and 39% respectively. This compared to a prevalence of 14% in control proband families. Considering only definite RLS, the respective percentages were 33% and 25% for RLS families and 0% for control families. RLS prevalence in family members increased with decreasing age of onset of the proband's disorder (53% for proband onset under 45, 30% for onset over 45). 55% of the children of RLS probands were positive (43% of those under 45, 65% of those over 45).

**Conclusions:** A very high percentage of RLS relatives appear also to have RLS. In families with a single affected parent, the proportion of affected children is higher than expected using a recessive model of inheritance. More family members were affected in families whose probands had an earlier age of onset. We conclude that RLS is a strongly familial disorder, especially for patients with an earlier age of onset. The inherited nature of the condition remains to be proven as well as the specific genetic mechanisms, but a dominant, co-dominant, or multifactorial model might well fit the overall data of this study.

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## 522.N

### FREQUENCY OF REM SLEEP BEHAVIOR DISORDER AND REM SLEEP WITHOUT ATONIA IN PARKINSON'S DISEASE

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**Introduction:** The reported prevalence of REM sleep behavior disorder (RBD) in Parkinson's disease (PD) varies from 15 to 47%,<sup>(1,2)</sup> but this estimation was based on sleep questionnaires without polysomnographic (PSG) recordings or on

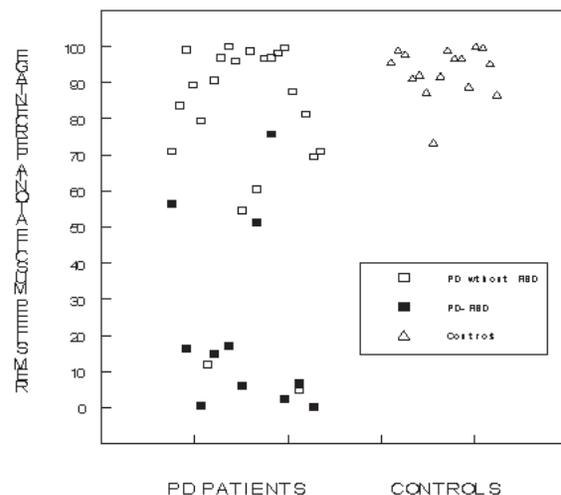
sleep laboratory studies of a selected group of PD patients all complaining of sleep disturbance. No study has estimated the prevalence of RBD using PSG recordings or analyzed in details the characteristics of REM sleep muscle atonia in a large group of unselected PD patients. The aim of the present study was to determine the prevalence of RBD in patients with PD using both clinical history and PSG recordings and to further study REM sleep muscle atonia in PD.

**Methods:** Thirty-three consecutive PD patients (21 men, 12 women; mean age, 62.9 ± 11.8 years; mean disease duration, 5.9 ± 4.4 years; mean Hoehn and Yahr stage, 1.9 ± 0.8) and 16 healthy controls without clinical evidence of sleep disturbance (10 men, 6 women; mean age, 62.31 ± 6.9 years) were studied in a sleep laboratory for one night. Twenty-seven PD patients were treated with dopaminergic drugs, 1 was drug-free for three months and 5 had never been treated for PD. Each had a structured clinical interview and a sleep laboratory study. PSG recordings included EEG, EOG, chin EMG and infrared video monitoring to detect movements during REM sleep. REM sleep was scored using a method<sup>(3)</sup> which allows the scoring of REM sleep without atonia (RSWA). Between-group comparison for the percentage of time spent with muscle atonia was done by a Mann-Whitney U-test.

**Results:** Eleven of 33 (33%; 10 men, 1 woman) PD patients met the diagnostic criteria of RBD based on PSG recordings. In half of these PD patients, the presence of RBD would have been undetected based on clinical interviews alone. Moreover, PD patients showed a decreased percentage of time spent with muscle atonia during REM sleep in comparison to healthy controls (60.1% vs 93.2% p = 0.003). In fact, 19 of 33 (58%) PD patients and only 1 of 16 (6%) control subjects had increased tonic EMG activity during REM sleep (figure 1). A significant subgroup of PD patients (24%) had RSWA but did not present behavioral manifestations of RBD.

Figure 1

Distribution of REM sleep atonia percentage in PD patients and control subjects.



**Conclusions:** Our findings show a high prevalence of RBD and RSWA in PD and indicate the importance of performing

PSG recordings for detecting RBD in these patients. Several PD patients had RSWA without a clinical history of problematic sleep behaviors or REM sleep behavioral manifestations in the laboratory. This subgroup of patients may represent a preclinical form of RBD associated with PD.

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**523.O**

**THE PREVALENCE OF SLEEP COMPLAINTS IN PATIENTS WITH HEADACHES**

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**Introduction:** The complex relationship of sleep deprivation and body pain raises questions as to sleep complaints in other pain syndromes such as headache. The goal of this study is to evaluate the prevalence of sleep complaints in patients with headaches and the association of sleep complaints to severity and/or frequency of headaches.

**Methods:** Patients seen at the University of North Carolina Hospital Headache Clinic, with a chief complaint of headache, were asked to complete a questionnaire including the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), and the MIDAS Pain Scale. Results were tabulated and analyzed for statistical significance using an analysis of variance procedure.

**Results:** A total of 36 patient questionnaires were completed, including 32 women and 4 men with ages ranging from 18-71 years. The mean ESS score was 6.9 (st.dev. 4.6), and the mean SSS score was 2 (st.dev. 0.8). Seven (19.4%) patients had an ESS score of >10, and nine (25%) patients had an SSS score of >2. An Analysis of Variance with the independent variable of Frequency of Pain (headaches in at least 45 out of 90 days) and the dependent variable of the Stanford Sleepiness Scale was completed. There was a trend for increased sleepiness in those subjects with more frequent pain ( $F(1, 30)=3.00; p<.10$ ; Frequent ( $n=16$ ) = 2.25; Less Frequent ( $n=16$ ) = 1.75). Less of a trend was noted for the Epworth Sleepiness Scale in the same model of Frequency of Pain ( $F(1, 30)=1.91; p<.18$ . Frequent = 8.44; Less Frequent = 6.25). Interestingly, no significant differences in Sleepiness as measured by the ESS and SSS were noted in models assessing Average Severity of Pain.

**Conclusions:** Sleep complaints are common among patients with headaches. The results of this study reveal a trend toward increased sleep complaints in patients with an increased frequency of headaches. This study raises a question of the cause and effect relationship between headache and sleep complaints: Do frequent headaches affect the quality of sleep leading to increasing sleep complaints, or does poor sleep lead to increasing frequency of headaches? Further evaluation is

needed to determine 1) if certain types of headaches are associated with increased prevalence of sleep complaints, 2) if there is an increased risk of sleep disorders (via polysomnography) in patients with headaches, and 3) if there are stereotypical behaviors in patients with headaches that increase risk for sleep complaints.

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**524.O**

**CSF HYPOCRETIN-1 (OREXIN-A) CONCENTRATION OF PATIENTS WITH NIEMANN-PICK TYPE C DISEASE.**

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**Introduction:** Niemann-Pick type C disease (NPD) is an autosomal recessive lipodosis characterized by hepatosplenomegaly, vertical supranuclearophthalmoplegia, progressive ataxia, dystonia, dementia and also cataplexy (1,2). Since hypocretin deficiency has been shown to be involved in pathogenesis of narcolepsy-cataplexy both in animals and human, it is important to know whether this is also observed in NPD (3). CSF hypocretin concentration was measured in the two cases with NPD, one case cataplexy, and the other did not. Cerebrospinal fluid (CSF) hypocretin-1 concentration was moderately decreased (142 pg/ml) in the patient who had cataplexy, but was normal (299 pg/ml) in the case who never complained of sleepiness or cataplexy.

**Methods:** Hypocretin-1 in CSF was measured using radioimmunoassay kits (Phoenix Pharmaceuticals, Mountain View, CA) as previously reported (3). Intra-assay variability was 4.3% and the detection limit was 40 pg/ml. Either patients or families gave informed consent for the lumbar puncture.

**Results:** Case 1: A 3-year-old boy, was admitted to our hospital for detailed investigation. At 2 months old, he developed jaundice and hepatosplenomegaly and it was thought to be due to hypoplasia of intrahepatic bile duct. Hepatosplenomegaly lasted after that. At 2 years old, he could walk about several meters, but his development was stopped thereafter. Since the age of 2 years 4 months, intention tremor had been observed. Three months later, dysphagia had been observed. At 3 years old, he could not stand on her feet even by hanging on something around him. Niemann-Pick cells were found in his bone marrow. He was diagnosed NPD disease by biochemical cell investigation. Since 2 years 4 months old, laughing and exciting provoked sudden loss of muscle tone. It was thought to be cataplexy. The CSF hypocretin-1 levels were 178 pg/ml and 142 pg/ml at the age of 4 and 5 years old, respectively. The

symptom of cataplexy was slightly worsened in this one year. Case 2: A 2-year-old girl was admitted to our hospital for detailed investigation. There had been hepatosplenomegaly and slight liver dysfunction since her birth. Since the age of 1 year 3 months, intention tremor of upper limbs had been observed. Seven months later, ataxic gait had been observed. Since 3 years old, she had not been able to sit by herself. Many Niemann-pick cells were found in her bone marrow. She was finally diagnosed NPD disease by gene analysis. She died at 4 years 8 months old. She had neither excessive daytime sleepiness nor cataplexy for her life. The hypocretin-1 concentration in the CSF was 299 pg/ml, when she was 3 years old.

**Conclusions:** Patients with narcolepsy-cataplexy are reported to have low CSF hypocretin-1 levels (3). In our patients, one with cataplexy also had low CSF hypocretin-1 level and others without cataplexy did not. However our cases with NPD did not show excessive daytime sleepiness, which is an essential symptom of narcolepsy-cataplexy. So low hypocretin-1 in the CSF may also be involved in the pathogenesis of cataplexy in NPD. Further studies are needed to decide why a decrease concentration of hypocretin-1 occurs in patients with NPD, as this is critical for understanding the pathogenesis of cataplexy.

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## 525.O

**SLOW WAVE SLEEP (SWS) AND REM SLEEP DISTRIBUTION IN PATIENTS WITH PARKINSON'S DISEASE**  
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**Introduction:** REM sleep disruption is an indicator of desynchronization of the circadian pacemaker. This has been reported previously in elderly population. High prevalence of sleep/wake cycle disruption has been noted in the patients with Parkinson's disease. The aim of the present study was to investigate the distribution of REM sleep (regulated by circadian mechanisms) and SWS (regulated by homeostatic mechanisms) in Parkinson's patients throughout the night. We hypothesized that patients with Parkinson's disease would have aberrant circadian rhythms of REM distribution in different sleep cycles and normal distribution of deep sleep across the night.

**Methods:** Forty-eight consecutive patients (32 males, aged 65.6±8.7 and 16 females, aged 66.2±8.9) with an established diagnosis of Parkinson's disease were investigated in the study. A single scorer blindly reviewed the polysomnographic

findings according to standardized criteria. The duration of REM sleep and slow wave sleep episodes in each sleep cycle was calculated. Statistical analysis was performed using general linear procedure (SPSS for Windows).

**Results:** Data were derived from the analysis of five sleep cycles. Compared to the epidemiological normative data, overall amount of SWS was reduced. There was statistically significant decrease of SWS duration from the first to the subsequent sleep cycles ( $F=9.1$   $p=0.0001$ ). The highest amount of SWS was observed during the first half of the night. Percentage of REM sleep did not significantly differ from cycle to cycle. The study showed a flattened distribution of REM sleep throughout the night ( $F=0.86$ ;  $p=0.46$ ).

**Conclusions:** The initial hypothesis was confirmed in this study. REM sleep had an abnormal pattern of distribution in different sleep cycles indicating disruption of the circadian oscillator in the group of Parkinson's patients. Although decreased amount of slow wave sleep was observed, the regulating mechanisms of slow wave sleep distribution remained intact.

## 526.O

**REM SLEEP ATONIA IN PARKINSON'S DISEASE**

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**Introduction:** High prevalence of REM Sleep Behavior Disorder (RBD) has been reported in the patients with Parkinson's disease. One of the most common polysomnographic features of RBD is excessive augmentation of chin electromyographic tone (EMG). The aim of this study was to investigate the prevalence and distribution of augmentation of chin muscle tone in REM sleep of Parkinson's patients in different sleep cycle.

**Methods:** Forty-eight consecutive patients (32 males, aged 65.6±8.7 and 16 females, aged 66.2±8.9) who were diagnosed with Parkinson's disease participated in this study. A single scorer blindly reviewed polysomnographic findings according to standardized criteria. The duration of REM sleep episodes and duration of REM sleep with augmented chin muscle tone in each sleep cycle was calculated. Ratios between these two parameters obtained for each sleep cycle were used for the analysis.

**Results:** Episodes of REM sleep with augmented muscle tone were observed in 44 out of 48 patients with Parkinson's disease. The repeated measure procedure showed a high proportion of REM sleep with partial or complete loss of atonia in Parkinson's patients (ranging from 61 to 71% in different sleep cycles). The peak amount of augmented muscle tone was found in the 3rd REM episode and the nadir was in the 4th REM episode ( $71.5±0.33$  vs.  $61.9±0.38$ ;  $p<.05$ ).

**Conclusions:** REM sleep disruption is extremely common in the patients with Parkinson's disease resulting in high prevalence of nightmares and violent behavior observed in this clinical entity.

**527.O**

**CSF HYPOCRETIN LEVELS IN NEUROLOGIC AND PSYCHIATRIC CONDITIONS**

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**Introduction:** Two previous studies measuring CSF hypocretin (Hcrt) in patients with neurological illness [1,2] and one series reporting on CSF Hcrt levels across gender and generation [3] have found that CSF Hcrt did not differ significantly between neurological disease and normal controls. The low levels of CSF Hcrt found in some patients with subarachnoid haemorrhage (SAH), acoustic schwannoma, and head trauma and a small subgroup of patients with Guillain Barre Syndrome who have undetectable levels remains to be explained as does the role, if any, of hypocretin in neurological and psychiatric disorders.[1]

**Methods:** CSF was collected from 194 patients, 61 males and 133 females, with a variety of neurological diagnoses and including 15 control samples collected during epidural procedures from women in early labour. CSF hypocretin-1 was measured in crude CSF samples (no extraction procedure) (100 µl, duplicate) using a commercially available radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals Inc.). Intra-assay variability was 3.6% and the detection limit was 40 pg/ml. Samples were drawn from patients aged 15 to 80 years (mean age 42 ± 14 years) after obtaining informed consent for the lumbar puncture. Statistical analysis was made by using one-way ANOVA and Fisher's PLSD, and Fisher's exact probability test.

**Results:** Hcrt was detectable in all the specimens tested. The mean Hcrt for the entire sample (n = 194) was 176 ± 53 pg/ml (mean ± SD; range: 44-302 pg/ml). There was no significant difference between males (167 ± 55 pg/ml; range: 44-302 pg/ml) and females (180 ± 57 pg/ml; range: 57-291). Hypocretin levels in the crude CSF of 15 healthy controls were found to be 224 ± 39pg/ml (range 145-283pg/ml) in keeping with previously reported data on control values for CSF Hcrt.[2,3] Patients with Multiple Sclerosis (MS) (n = 44; mean CSF Hcrt ± SD 164 ± 49 pg/ml; range: 71-258 pg/ml) were found within the control range, again similar to previously published data.[2] A group of patients (n = 30) fulfilling the DSM IV criteria for Conversion Disorder had CSF Hcrt levels within the control range (187 ± 39 pg/ml; range: 120-280pg/ml). CSF samples of patients with Benign Intracranial Hypertension (BIH) (n = 33; CSF Hcrt 193 ± 53pg/ml; range: 90-290pg/ml), Normal Pressure Hydrocephalus (NPH)(n = 10; Mean CSF Hcrt 174 ± 58pg/ml; range: 53-247pg/ml), infections (i.e. meningitis and encephalitis) (n = 11) and Degenerative diseases including Alzheimer's disease (n=10) all scored within the control range. At the time of abstract submission, we are currently analysing samples from patients with Guillain Barre

Syndrome, CIDP and other polyneuropathies.

**Conclusions:** CSF Hcrt levels in patients with neurological diseases such as MS, BIH, NPH, Alzheimer's and CNS infections were within the control range, as were levels from patients with Conversion disorders. The finding that low levels of CSF Hcrt are present in some patients in all of the groups analysed suggests that low Hcrt levels may reflect generalized CNS or hypothalamic dysfunction. The finding that Hcrt was detectable in all specimens tested provides further evidence that undetectable Hcrt in CSF is highly specific for narcolepsy.

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**528.O**

**A STUDY TO LOOK FOR THE INCIDENCE OF RESTLESS LEGS SYNDROME IN PATIENTS WITH PARKINSON'S DISEASE**

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**Introduction:** Sleep related disturbances are common in Parkinson's disease(P.D), which includes insomnia, excessive daytime sleepiness, and REM behavior disorder etc. This study is done to look for presence of symptoms of Restless Legs Syndrome(RLS) in patients with P.D. RLS is a disorder, characterized by unpleasant leg sensations at bedtime that interfere with sleep onset and disrupt sleep.

**Methods:** This is a randomized study done by sending questionnaires regarding RLS to established patients with diagnosis of P.D. from our Neurology Clinic. We asked following questions about RLS.(1)1) Do you have unpleasant sensations like creeping, crawling, or uncomfortable, difficult to describe feelings in your legs or arms combined with a motor restlessness and an urge to move?2) Do you have motor restlessness as seen in activities such as floor pacing, tossing and turning in bed and rubbing in legs?3) Do these symptoms occur only at rest or are they worse at rest (i.e. lying, sitting) and does moving improve them.4) Are these symptoms worse in the evening or at night compared with morning?5) Do these sensations interfere with sleep at its onset or returning to sleep?6) Do you have daytime fatigue/sleepiness?7) Does your bed partner report that your legs or arm jerk during sleep.

**Results:** A total of 30 patients with diagnosis of PD were contacted and 26 replied our questionnaire. This was also followed by a telephone interview. Patients demographics. (n=26)Age, range in years 37-85 Sex Male /female 12/14 Duration of P.D.in yrs 2-20 On levodopa 26/26On DA agonists 7/26On selegine 2/26Diabetes. 5/26Peripheral neuropathy 3/26(One diabetic and other idiopathic)OSA. 1/26Kidney Disease. 0/26 Anemia. 0/26 The following

results were obtained from questionnaires:1) In our small study 10/26(38.46%) patients fulfill the minimal criteria necessary to make a diagnosis of RLS. (Positive reply on Question No.1 to 3 and presence of symptoms at evening/night are necessary to make a diagnosis of RLS)(1)2) 19/26(73.07%) patients have at least one characteristic necessary to meet the minimal criteria to make a diagnosis of RLS.3) 21/26(80.76%) patients reported to have daytime fatigue/sleepiness.

**Conclusions:** Based on our small study, RLS is quite common (38.46%) in patients with P.D. Majority of patients (73.07%) had at least one characteristic symptom necessary to make a diagnosis of RLS(1). We also conclude that daytime fatigue/sleepiness is quite common (80.76%) in patients with P.D.

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## 529.O

### MULTIPLE SCLEROSIS AND SLEEP: A DESCRIPTIVE STUDY

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**Introduction:** Fatigue is a well-known complication of multiple sclerosis (MS), but sleep disturbance in MS is less clearly understood. Previous studies have investigated MS and narcolepsy (1), circadian rhythm disturbance (2), and periodic limb movements (3). The current study utilized a questionnaire to examine the range and extent of sleep problems in MS.

**Methods:** 101 outpatients with clinically definite MS were given questionnaires, with ninety-six completed. Questionnaires included Epworth Sleepiness Scale, demographics, and general sleep, periodic limb movement, restless legs, insomnia, apnea, and MS questions. Answers were rated on a one to five scale, from "never" to "always," and a total sleep score tallied. Patients also circled a description of "sleepy" "fatigued" or "alert" and were queried about depression and alcohol consumption.

**Results:** The study consisted of 76 women and 19 men with a mean age of 44.5, mean expanded disability status scale (EDSS) of 3.38 and mean MS duration of five years. Sixty-five percent were relapsing remitting, 22% secondary progressive and 6% primary progressive. Sixty-three percent lived independently, 18% cared for by the family, and 2% in a nursing home. Self-description was "alert" for 36%, "fatigued" for 52%, "sleepy" for 10% (with two percent both "fatigued" and "sleepy.") The mean Epworth score was 7.03 (SD 4.6), with no correlation found between self-description and Epworth score (Chi-square.) The mean total sleep score (out of a total possible of 95 points) was 40.9 (SD 11.2) with a range of 16 to 73. Sixty-nine percent of patients had sleep problems at least sometimes. Sixty-one percent reported no sleep problems before MS, 18% complained of spasms frequently or always, and 66% had nocturia at least sometimes. Insomnia was reported frequently or always for 21%. Twenty-four percent reported snoring; 12.5% noted a choking sensation during the

night, and 5% were witnessed to have actual apnea spells frequently or always. Twelve percent agreed to a "creepy feeling" in their legs and 19% of partners noted kicking at night frequently or always. Fourteen percent named young children, 15% snoring partners, and 3% pain as other sleep problems. The Epworth Sleepiness Scale correlated with total sleep score and several subsets of questions, but not with EDSS. EDSS correlated strongly with age, and weakly with MS duration, but not with total sleep scores or other subsets. (Pearson)

**Conclusions:** This questionnaire confirms the overwhelming presence of sleep disturbance in MS patients. Reported concerns included problems with general sleep, insomnia, possible obstructive sleep apnea, and MS issues. Epworth Sleepiness Scale was in the mildly elevated range. Future studies will include polysomnograms to validate the questionnaire.

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## 530.O

### PREVALENCE AND CLINICAL SIGNIFICANCE OF SLEEP APNEA DURING THE FIRST NIGHT AFTER CEREBRAL INFARCTION

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**Introduction:** Previous studies showed a high frequency of sleep apnea (SA) in patients with recent stroke, but the prevalence and clinical significance of SA during the first night after cerebral infarction is unknown. The objectives of our study were to determine the prevalence of SA during the first night after hemispheric ischemic stroke, and its influence on clinical presentation, course and functional outcome at six months.

**Methods:** The first night after cerebral infarction onset, 50 patients underwent polysomnography(PSG) followed by oxymetry during the next 24 hours. Neurological severity and early worsening were assessed by the Scandinavian Stroke Scale, and outcome by the Barthel Index. MRI was performed within the first week after cerebral infarction. Patients were evaluated on admission, on the third day, at discharge, and at one, three and six months.

**Results:** There were 30 men and 20 women with a mean age of 66.8 ± 9.5 years. Latency between stroke onset and PSG was 11.6 ± 5.3 hours. Thirty-one (62%) subjects had SA (apnea-hypopnea index (AHI) >10. Of these, 23 (46%) had an AHI >20, and 21 (42%) an AHI >25. Sleep-related stroke onset occurred in 24 (48%) patients, and was only predicted by an AHI >25 on logistic regression analysis. SA was related to early neurological worsening and oxyhemoglobin desaturations but not with sleep history previous to stroke onset, infarct

topography and size, neurological severity and functional outcome. Early neurological worsening was found in 15 (30%) patients, and logistic regression analysis identified SA and serum glucose as its independent predictors. Conclusions: SA is frequent during the first night after cerebral infarction (62%), and is associated with early neurological worsening but not with functional outcome at six months. Cerebral infarction onset during sleep is associated with the presence of moderate-severe SA (AHI >25).

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### 531.P

#### PRESENCE OF DELTA WAVES IN REM SLEEP DURING POLYSOMNOGRAPHY AS A SIGN OF ACUTE HYPOGLYCEMIC ENCEPHALOPATHY.

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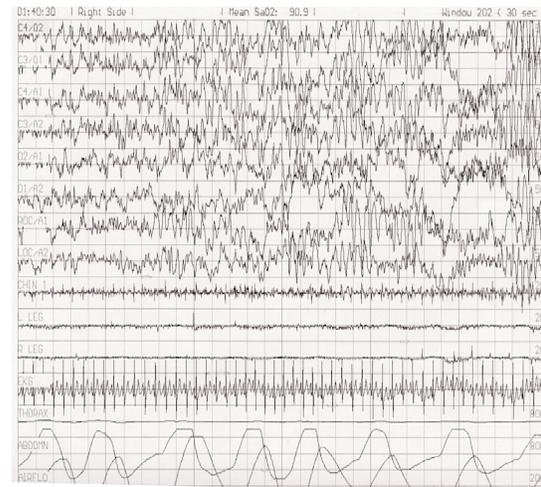
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**Introduction:** REM sleep is characterized by low voltage mixed frequency wave forms, in contrast Delta waves are high voltage low frequency waves. Slowing of EEG during metabolic encephalopathy including hypoglycemic encephalopathy had been reported in the literature. To our knowledge, the presence of delta wave during REM sleep as a sign of metabolic encephalopathy had never been reported.

**Methods:** A33 year old female, type one Diabetic patient on insulin therapy, admitted to the sleep lab. For nocturnal Polysomnography to evaluate excessive daytime sleepiness, fatigue and loud snoring. Patient had a sleep latency of 3 minutes, REM latency of 37 minutes. During REM sleep, patient noted to have frequent Delta waves with their characteristic low frequency and high voltage. During this stage patient wake up complaining of being hot, was very confused and diaphoretic. Oxygen saturation at that point was 97% and Heart rate was 124. Shortly patient became agitated then unresponsive. Patient was taken to the emergency department. In the ER the patient blood sugar was 12. One amp. of D50 was given and patient woke up immediately. Patient was observed for 4 hours in the ER and Discharged home in a stable condition.

**Results:** The whole sleep study lasted only 80 minutes, 54 minutes of sleep. Obstructive sleep apnea with RDI of 33 was documented. REM sleep lasted only 9 minutes. Repeat sleep study one week later-after nocturnal insulin dose was reduced by primary care physician- confirmed the obstructive sleep apnea disorder which was corrected with CPAP of 11 cm water pressure. No delta waves were noted in REM sleep during this repeat study.

Figure 1



**Conclusions:** Presence of delta waves during REM sleep indicated severe hypoglycemic episode in our patient. Slowing of EEG secondary to metabolic encephalopathy is well known. Presence of Delta waves with its slow frequency during REM sleep with its fast mixed - frequency, reflects the same phenomena, which indicated slowing in the metabolic rate in the brain.

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### 532.P

#### THE RELATIONSHIP BETWEEN FATIGUE AND OBJECTIVELY MEASURED SLEEP AND RHYTHMS IN BREAST CANCER

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**Introduction:** Fatigue is one of the most common and long-lasting complaints of cancer patients undergoing chemotherapy. It has been associated with several causal factors, including physical (e.g. pain), biochemical (e.g. anemia), and psychological (e.g. depression) components. However, it remains unclear whether a relationship exists between fatigue and objective sleep quality and quantity or the sleep/wake circadian rhythms cycle in this population.

**Methods:** Sixteen women (mean age 51.63 yrs, SD 9.75, range 34-68 yrs) diagnosed with stage I-IIIa breast cancer and treated with adjuvant or neoadjuvant anthracycline-based

chemotherapy participated. Each completed the Multidimensional Fatigue Symptom Inventory (MFSI)1 and wore an Actillum (Ambulatory Monitoring, Inc., Ardsley, NY) for 72 consecutive hours before the start of chemotherapy and again during weeks 1-3 of cycle 1. The MFSI contains 5 subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor) and was specifically designed to assess the multi-faceted nature of fatigue in cancer patients.

**Results:** Correlations were computed between objective sleep variables (TST, WASO, and number of awakenings), circadian rhythms variables (acrophase, amplitude, and mesor) and the five subscales of the MFSI. **Sleep:** Significant negative correlations between objective measurements of sleep and fatigue were only present at baseline, prior to chemotherapy, with increased general, physical and mental fatigue subscales associated with decreased TST (range -.59 to -.63;  $p=0.020-0.040$ ). There were no significant relationships between sleep variables and MFSI fatigue scales during cycle 1 weeks 1-3. **Circadian Rhythms:** There were no significant correlations between any of the MFSI scales and the circadian rhythms variables at baseline or week 1 (acute reaction phase). However, during week 2 (nadir of blood count phase), 4 out of 5 scales (general, emotional, physical, mental) significantly correlated with the mesor of the rhythm (range of -.56 to -.73;  $p=0.004-0.047$ ) indicating that increased fatigue was related to a decreased mean of the rhythm. By week 3 (recovery phase), only general and mental scales still correlated with the mesor (range -.62 to -.6373;  $p=0.030-0.032$ ). There were no other significant relationships between circadian rhythms variables and MFSI fatigue scales.

**Conclusions:** These data suggest that reports of fatigue were related to decreased sleep quantity and associated with lower mean activity rhythms, particularly prior to the start of chemotherapy and during the physiologically most sensitive phase of the chemotherapy treatment, when blood counts were at their lowest point. As the patients progressed to the recovery phase, the relationships between sleep, rhythms and fatigue became weaker. We have shown that subjective reports of sleep in this population suggest a similar relationship, with the strongest association between fatigue and subjective sleep occurring during the nadir of the blood counts and a weakening of this relationship during the recovery from chemotherapy phase2. As we collect more data, we will be able to further explore the complex relationships between sleep, circadian rhythms and fatigue in this population.

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### 533.P

#### SUBJECTIVE REPORTS OF FATIGUE AND SLEEP IN BREAST CANCER

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**Introduction:** Women with breast cancer report great difficulty with fatigue and many also report poor sleep. However, little is known about the relationships between fatigue and self-reports of sleep quality or quantity. We examined the association between self-reports of fatigue and sleep in 16 women with breast cancer being treated with chemotherapy.

**Methods:** 16 women (mean age 51.63 years, SD 9.75; range 34-68 years) who were recently diagnosed with stage I-III breast cancer and scheduled to receive 4 cycles of adjuvant or neoadjuvant anthracycline-based chemotherapy were included. As part of a larger study, each completed the Multidimensional Fatigue Symptom Inventory (MFSI)1 and the Pittsburgh Sleep Quality Index (PSQI)2 before the start of chemotherapy (baseline week 0), during week 1 (acute reaction to chemotherapy), week 2 (nadir of blood counts), and week 3 (recovery phase) of cycle 1, before cycle 4, and during weeks 1-3 of cycle 4.

**Results:** Correlations were calculated between the PSQI and the 5 subscales (general, emotional, physical, mental, and vigor) of the MFSI. During cycle 1 week 0, there were no significant correlations between any of the scales. During cycle 1 week 1, (chemotherapy week) the physical subscale correlated significantly with the PSQI ( $r$  of .73,  $p$  equal to 0.005) indicating that increased physical fatigue was associated with poor sleep. However by cycle 1 week 2, all 5 subscales correlated significantly with the PSQI (range of .58 to -.59,  $p$  equal to 0.005 to 0.039) suggesting that all aspects of fatigue were associated with poor sleep. By cycle 1 week 3, correlations were no longer significant. For cycle 4 week 0, significant correlations were again found for the physical, mental, and vigor subscales: range of -.88 to .79 ( $p$  equal to 0.004 to 0.04), at cycle 4 week 1 for the emotional, mental, and vigor subscales: range of -.77 to .80 ( $p$  equal to 0.002 to 0.035), and at cycle 4 week 2 for the emotional subscale:  $r=.77$  ( $p$  equal to 0.01). There were no significant correlations during cycle 4 week 3.

**Conclusions:** These data suggest a relationship between self-reports of poor sleep and fatigue. This was most apparent in cycle 1 week 2, during the nadir of blood counts. The relationship began to express itself during week 1 in the form of physical fatigue and grew to include general, emotional, and mental fatigue, as well as decreased vigor. By week 3 of the first cycle of chemotherapy (recovery phase), sleep quality and fatigue no longer showed a relationship. A similar pattern was seen in cycle 4. This suggests that as the course of chemotherapy progresses, reports of fatigue and reports of poor sleep become more strongly associated.

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### 534.P

#### NOCTURNAL SLEEP PATTERNS AND THEIR RELATIONSHIP TO SERUM CYTOKINE LEVELS IN ALLERGIC AND NON-ALLERGIC SUBJECTS

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**Introduction:** Patients with allergic symptoms frequently complain of disrupted sleep and daytime drowsiness with increased nasal symptoms upon awakening. Recent research demonstrates that cytokines have a physiological role in regulating sleep and may also have a role in atopic allergic response. The major purpose of this pilot study was to determine if there are common immunological mediators in sleep and allergy. The specific objectives were (1) to compare the nocturnal sleep patterns of allergic and non-allergic subjects and (2) to determine the relationship between nocturnal sleep patterns and serum cytokine levels.

**Methods:** Eight subjects participated in the study; 4 without allergies and 4 with perennial allergies as confirmed by RAST testing. Each group consisted of 1 male and 3 females. Subjects ranged in age from 20-41 years. Mean age of the non-allergic group was 27 ( $\pm 6.4$ ) years and mean age of the allergic group was 29 ( $\pm 8.4$ ) years. Objective sleep measures included sleep architecture and sleep continuity measures as recorded by all-night polysomnography. Serum cytokine measures included IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-10, IL-12, IL-1ra, TNF and INF  $\gamma$ . Cytokines were measured by high sensitivity ELISA analysis of serum specimens. All subjects were initially screened and a full Human Subjects Consent was obtained. Beck Depression Inventory was completed and RAST blood tests were conducted. Each subject then slept for two consecutive nights in a sleep laboratory. Night one was for adaptation. During night two, polysomnographic data and cytokine data were obtained. Subjects were prepared for polysomnographic recordings following internationally-accepted electrode placement procedures. Signals were continuously recorded on a Compumedics Sleep Analysis System. Subjects were prepared for blood draws by inserting a long indwelling catheter from which 1.5 ml blood per assay were collected 15 minutes prior to sleep onset, during first SWS episode in first half of SPT, during first REM episode in second half of SPT, within 5 minutes after final awakening, and one hour following final awakening.

**Results:** Allergic subjects spent less time in Stage 1 Sleep and less time in REM sleep compared to non-allergic subjects. They also had a shorter sleep latency and longer REM latency than non-allergic subjects. Three cytokines were consistently higher in allergic subjects compared to non-allergic subjects: IL-1 $\beta$ , IL-4, and IL-10. Three cytokines were consistently

higher in non-allergic subjects compared to allergic subjects; IL-1ra, IL-2, and IL-12. Sleep latency and time spent in Sleep Stage 1 significantly ( $p \leq .05$ ) correlated with IL-1ra, IL-2, and IL-12. REM latency significantly correlated with IL-1 $\beta$ , IL-4, and IL-10 and time spent in REM sleep negatively correlated with IL-1 $\beta$ , IL-4, and IL-10.

**Conclusions:** Allergic subjects demonstrate a shorter sleep latency and spend less time in lighter Stage 1 Sleep than non-allergic subjects. They also exhibit an increased REM latency and decreased time in REM sleep. Two clusters of cytokines were found: an allergy-inhibitory group that was positively associated with sleep latency and time spent in Sleep Stage 1 and a pro-allergy group that was positively associated with REM latency and negatively associated with time spent in REM sleep.

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### 535.P

#### PAROXYSMAL NOCTURNAL DYSPNEA (PND) AS A PREDICTOR FOR SLEEP DISORDERS IN PATIENTS WITH CONGESTIVE HEART FAILURE

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**Introduction:** Sleep disorders are clinical entities with great health and socioeconomic impact. Sleepiness and sleeplessness are not only a sign of disease but also a negative influence on quality of life. The purpose was to survey patients with CHF for a range of sleep complaints and to evaluate the correlation among these, PND and cardiac status.

**Methods:** The Cleveland Sleep Habits Survey was provided to consecutive new patients evaluated at a heart failure clinic from February 2000 to March 2001. The research staff gathered clinical information such as sex, race, age; height and weight; and clinical information that included cardiac diagnosis, ejection fraction, functional classification (NYHA Class), co-morbid conditions and presence of paroxysmal nocturnal dyspnea (PND). The instrument is designed as a patient self-report tool to help in the medical decision making for sleep testing. It incorporates the Berlin Questionnaire, providing a high pre-test probability for sleep apnea, with additional questions to address symptoms of insomnia, leg jerks during sleep, strange sensations at legs, drop attacks or weakness during wakefulness and using of drugs or alcohol to promote sleep. Scoring of these questions was performed as to possible risk of a sleep disorder based upon the presence of persistent symptoms (3-4 times a week or more) and sleepiness (as assessed on the Berlin questionnaire) for restless leg syndrome and narcolepsy.

**Results:** Data were available for 146 patients. 54% were males. The mean age (SD) was 58.3  $\pm$  14.8 years; BMI, 29.0  $\pm$  7.8 kg/m<sup>2</sup>; and ejection fraction, 27.8  $\pm$  15.7%. Based upon criteria (1), 50% were at "high risk" for obstructive sleep apnea syndrome (OSAHS). Moreover, 28.3% reported symptoms suggesting insomnia, and 3.4% for narcolepsy or restless leg syndrome. 18.7% met criteria for risk for 2 or more disorders.

2.1% reported drowsy driving at least 1-2 times a week. There were correlations between the complaint of PND and sleepiness. Also patients with PND have a higher risk of complaining of insomnia and to have risk for more than one sleep disorder. Respondents were also most likely to report snoring and to meet criteria for OSAS if they have a lower ejection fraction. We also found that patients in NYHA class III and IV were more likely to complain of insomnia than those in NYHA class I and II. (See table).The odds ratio (confidence interval) of complaining of sleepiness or insomnia if the patient states having PND was 2.33 (1.2-4.7) and 2.71 (1.3-5.7) respectively.

Table 1

Correlation among Sleep Disorders and Clinical markers for Congestive Heart Failure

	NYHA Class		History of PND		Ejection Fraction	
	Paroxo	Puake	Paroxo	Puake	Paroxo	Puake
OSAS Risk	.057	.497	.147	.077	.166	.045*
Snoring	.019	.820	.132	.113	.180	.030*
Sleepiness	.112	.178	.221	.007**	.047	.574
Obesity and/or hypertension	.152	.067	.080	.340	.153	.066
Insomnia Risk	.171	.039*	.233	.005**	.048	.570
Narcolepsy Risk	.019	.820	.097	.245	.123	.139
RLS Risk	.114	.169	.097	.245	.027	.748
Number of Sleep disorders categories	.091	.274	.277	.001**	.105	.205

\*p < 0.05, \*\*p < 0.005, NYHA=New York Heart Association functional class; PND=paroxysmal nocturnal dyspnea; OSAS=Obstructive Sleep Apnea Syndrome; RLS=Restless Leg Syndrome

**Conclusions:** There is a high prevalence of sleep complaints in patients with CHF. Half of them have a high pre-test probability for OSAS, independent of gender and functional status. PND and NYHA III/IV are associated with primary symptoms of sleepiness or insufficient sleep and may be a starting point for a sleep history or a search for a sleep disorder.

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**536.P**

**SLEEP COMPLAINTS IN THE PREGNANCY**

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**Introduction:** It's not well known why do animals and particularly humans sleep. The main explanation refers to restoration of vital energy, but this concept seems not enough for such complex function. This process is fundamental for organisms

since tiredness in general precedes sleep and it is followed by wellbeing sensation. The sleep disorders cause impairment to the daily functioning from cognitive to organic aspect. Women show, during their entire existence, physical, emotional and social variations that account for sleep disturbs, and the pregnancy-puerperal cycle represents a crucial period. The pregnancy can be divided in three periods, with specific features for each one. The study of sleep disturbs during the pregnancy may bring some insights for the understanding of these findings. The main goal of this research is to check the frequency of sleep disorders during the three trimesters of pregnancy in comparison to the pre-gestational period.

**Methods:** Ninety pregnant women were seen at Obstetrician Center in São Paulo, Brazil. We got thirty patients in each trimester. The age range from 14 to 43 years. Two of the authors applied personally a Sleep Questionnaire (adapted from Bruni et al, 1996). Independent variables: insomnia, excessive daytime somnolence(EDS), parasomnias, respiratory disturbance (RD) and periodic legs movements of sleep (PLMS).The data were analyzed by Confidence Intervals with significance level at 5%.

**Results:** Except for Parasomnia, all sleep parameters increased from pre-gestational period to the first trimester. When statistically analysed the increase in PLMS was not significant, all the others were. The analyse of second and third trimesters showed persistent differences in relation to prior state and were significant statistically, except for Parasomnia. The results will be viewed in the next three tables:

Table 1

Sleep complaints found during and before pregnancy in 90 women.

Pregnant 1	Insomnia	RD	Parasomnia	EDS	PLMS
Before	3(10%)	6(20%)	12(40%)	3(10%)	18(60%)
1 <sup>st</sup> trimester	21(70%)	27(90%)	8(27%)	24(80%)	20(67%)
Pregnant 2					
Before	5(17%)	8(27%)	8(27%)	4(13%)	12(40%)
1 <sup>st</sup> trimester	18(60%)	24(80%)	3(10%)	21(70%)	18(60%)
2 <sup>nd</sup> trimester	20(67%)	25(83%)	3(10%)	22(73%)	18(60%)
Pregnant 3					
Before	3(10%)	6(20%)	6(20%)	2(7%)	12(40%)
1 <sup>st</sup> trimester	17(57%)	22(73%)	4(13%)	19(70%)	17(57%)
2 <sup>nd</sup> trimester	20(67%)	25(83%)	5(17%)	21(70%)	17(57%)
3 <sup>rd</sup> trimester	23(77%)	24(80%)	5(17%)	22(73%)	18(60%)

**Conclusions:** There is an important increase of sleep complaints during the pregnancy in comparison to the pre-gestational period no matter what trimester is considered. The sleep complaints are sustained high in all pregnancy trimesters. Parasomnia was the only parameter not significant.

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**537.P**

**BEHAVIORAL INSOMNIA THERAPY FOR PATIENTS WITH FIBROMYALGIA**

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**Introduction:** Fibromyalgia (FM) is a prevalent, debilitating, and poorly understood condition that contributes to impaired occupational/social functioning and increased health care utilization among affected individuals. The vast majority of FM patients complain of unrelenting sleep disturbances (delayed onset, extended awakenings and/ or nonrestorative sleep) which only serve to exacerbate their other presenting symptoms including generalized pain, fatigue, malaise and global diurnal dysfunction. Whereas various pharmacotherapies have shown some efficacy in reducing sleep disturbances among a subset of these patients, a substantial proportion of those with FM-related sleep complaints fail to respond to such treatments. Our clinical observations suggest that factors common among other insomnia subtypes such as conditioned arousal at bedtime, erratic sleep-wake schedules and spending too much time in bed likely perpetuate the sleep problems of these medication-refractory FM patients. Thus, nonpharmacologic interventions which directly address these psychophysiological and behavioral perpetuating mechanisms are likely needed to remedy the sleep difficulties of these patients.

**Methods:** We designed a randomized clinical trial to test the effect of behavioral insomnia therapy on subjective and objective sleep disturbances among FM patients who do not show sleep improvements with conventional pharmacotherapy. Prior to randomization to treatment, subjects were comprehensively screened for psychiatric, medical (other than FM) and sleep disorders. In addition subjects were required to have an average of 60 minutes of total wake time (TWT) during the week prior to their lab visit. Subjects were diagnosed with FM by a collaborating rheumatologist using tenderpoint criteria. Subjects were then assigned to one of three conditions: standard care (SC), sleep hygiene (SH), and cognitive-behavioral therapy (CB). Subjects in SC receive ongoing standard medical care for fibromyalgia, but no behavioral intervention. Subjects in SH receive sleep related information and recommendations for reducing caffeine and alcohol, engaging in moderate exercise, and making sure their sleep environment is comfortable. Subjects in CB receive sleep related information as well as stimulus control and sleep restriction therapies. All therapy took place over 6 weeks.

**Results:** Our preliminary results from 24 randomized subjects (23 female, Mean age=48) indicate significant treatment-by-time interactions from sleep logs for wake after sleep onset

(WASO,  $p < .05$ , see Figure 1) and trends for TWT ( $p < .06$ ) and sleep efficiency (SE%,  $p < .06$ , see Figure 2). WASO was reduced by 53% for CBT, 2% for SH and 28% for SC. TWT was reduced by 44% for CBT, 5% for SH and 22% for SC. SE% was improved by 10% for CBT, 1% for SH and 4% for SC. There was a significant reduction in WASO, TWT and SE% for those receiving CBT but not for other groups.

Figure 1

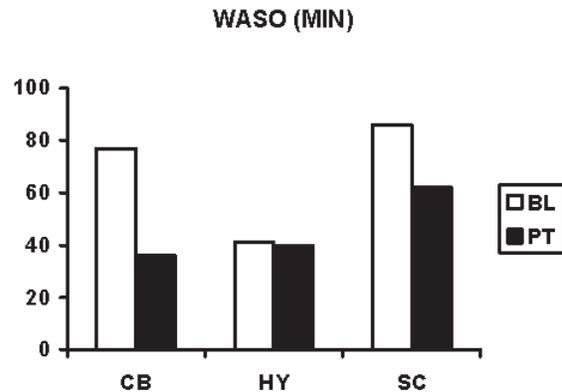
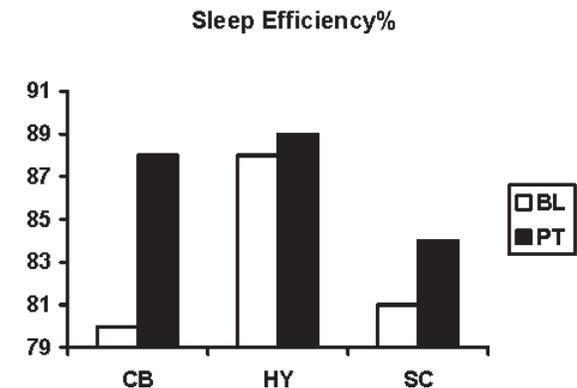


Figure 2



**Conclusions:** The results provide preliminary evidence that stimulus control and sleep restriction therapies can improve the sleep of individuals suffering from fibromyalgia.

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**538.P**

**WRITTEN EMOTIONAL DISCLOSURE IN FIBROMYALGIA: EFFECTS ON SLEEP QUALITY AND FATIGUE**

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**Introduction:** Privately writing for several days about stress-

ful life events has been shown to improve health status in student and community samples, and several studies have found benefits among patients with rheumatoid arthritis or asthma. People with Fibromyalgia Syndrome (FMS) often have fatigue and sleep complaints, and FMS is associated with increased stressful life events, but the effects of written disclosure have not been examined in this group, nor has sleep quality been examined as an outcome in any study of written disclosure.

**Methods:** We assessed subjective sleep quality (a 4-item scale assessing the previous night's sleep quality, degree to which sleep was restorative, upon waking level of alertness, and ability to concentrate), fatigue (Fatigue Severity Scale), and negative affect (PANAS-X) on 72 adults with FMS (70 women; 67 Caucasian; mean age = 50.3 years). They were then randomly assigned to 1 of 2 groups: Written Disclosure, which wrote privately for 4 days at home, 15-20 minutes per day about stressful life events; or Neutral, Control Writing (how they manage their time). Patients' sleep, fatigue, and NA were reassessed 1 month and 3 months after writing.

**Results:** Mixed model repeated-measures analyses (between 2 groups, within 2 assessment times: baseline and 1 or 3-month) were conducted on the 3 measures. Group X Time interactions showed that compared with controls, the written disclosure had significant improvements in sleep quality at both 1 month ( $p = .01$ ) and 3 months ( $p = .008$ ). Fatigue was reduced among written disclosure subjects at 1-month ( $p < .05$ ), although not at 3 months ( $p = .28$ ). Interestingly, these effects were not due to differential mood changes; indeed, negative affectivity decreased in both groups ( $p = .02$ ).

**Conclusions:** We conclude that written disclosure about stress improves subjective sleep quality and fatigue, even though negative affect worsens or remains unchanged, suggesting that written disclosure differentially influences functional versus mood complaints in people with FMS.

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### 539.P

#### SERIAL ASSESSMENT OF DAYTIME SOMNOLENCE IN PREGNANT WOMEN WITH THE EPWORTH SLEEPINESS SCALE

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**Introduction:** Most pregnant women report changes in sleep over the course of pregnancy. Previous studies have described daytime sleepiness in the first trimester, despite a concomitant increase in total sleep time. During the second trimester, sleep may normalize in many women. The third trimester may be characterized by frequent nighttime awakenings, diminished daytime alertness and worsening insomnia. In a previous study in which women completed the Epworth Sleepiness Scale

(ESS) during the second or third trimester of pregnancy, there was no significant difference in ESS scores of pregnant women compared to non-pregnant controls. However, given the reported increase in daytime somnolence of the first trimester, ESS scores may be highest during early pregnancy and decrease later in gestation. We administered the Epworth Sleepiness Scale to a cohort of women serially during pregnancy to assess whether ESS scores decreased in late pregnancy compared to early pregnancy.

**Methods:** We recruited 79 women presenting to our institution for prenatal care, whose pregnancy was not more advanced than 14 0/7 gestational weeks (i.e., first trimester), estimated by the date of the last menstrual period. Subjects completed the ESS at study entry and at 28-29 and 34-35 weeks of pregnancy. The ESS was also administered within 48 hours after delivery; subjects were asked to recall their level of sleepiness in the month before delivery. On each occasion, subjects were also asked to estimate their average daily sleep time in the past week, including naps. ESS scores from the time points in late pregnancy and post-delivery were compared to first trimester ESS scores using unpaired t-tests.

**Results:** Results are summarized in Table 1. The mean age of these subjects was  $22.91 \pm 0.57$  years. The first trimester mean ESS score was  $8.05 \pm 4.04$ . Sixty-two subjects completed the ESS at 28-29 weeks of pregnancy, with a mean ESS score of  $9.32 \pm 3.95$ , significantly higher than the first trimester ESS score. Thirty-eight subjects have completed the ESS at 34-35 gestational weeks. Their mean ESS score was  $10.00 \pm 4.22$ , also significantly higher than the first trimester ESS score. Finally, 16 subjects have delivered and completed a final ESS. These subjects had a mean ESS score of  $9.56 \pm 3.91$ , which was not significantly higher than in the first trimester. In the first trimester, subjects reported a mean 24-hour sleep time of  $10.01 \pm 3.29$  hours. This was not significantly different from self-reported daily sleep time at any of the other measured time points.

Table 1

	ESS Score	No. Subjects (%)	Total Sleep Time (hrs)
First trimester	$8.05 \pm 4.04$	79 (100)	$10.01 \pm 3.29$
28-29 wks gestation	$9.32 \pm 3.95$ $p = 0.03$	62 (78.4)	$9.56 \pm 3.20$ $p = 0.43$
34-35 wks gestation	$10.00 \pm 4.22$ $p = 0.008$	38 (48.1)	$9.48 \pm 2.94$ $p = 0.43$
Post-delivery	$9.56 \pm 3.91$ $p = 0.09$	16 (20.3)	$8.58 \pm 3.57$ $p = 0.17$

**Conclusions:** Increased daytime sleepiness in pregnancy has previously been described in the first trimester. However, in this cohort of young pregnant women, scores on the Epworth Sleepiness Scale were significantly higher at 2 third trimester points (28-29 and 34-35 weeks of gestation) than in the first trimester. Although worsening insomnia has been described with advancing gestation, in this cohort self-reported average

daily sleep time was not significantly different throughout pregnancy. Potential contributors to increased daytime somnolence include sleep fragmentation and symptoms of sleep-disordered breathing, both of which appear to worsen over the course of pregnancy. Hormonal factors including high levels of estrogen and progesterone may also promote hypersomnia.

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**540.Q**

**UNUSUAL REM PATTERN IN NEAR-DEATH TRAUMA SURVIVORS**

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**Introduction:** Approximately one out of every three individuals that survives a life-threatening trauma reports a profound spiritual experience, often called a near-death experience, which is characterized by dissociative events like autoscopia, depersonalization, time distortions, and intense positive emotions. Such experiences are almost always followed by dramatic long-term personality changes including hyperspirituality, decreased interest in monetary or material interests, reduced fear of death, and changes in social preferences, job and priorities (Greyson, 1983). Alternatively, post-traumatic stress disorder (PTSD) is a primarily negative response to trauma that is characterized by heightened fear, anxiety and considerable distress and impairment. PTSD has been found to have certain PSG correlates, including more frequent arousals, less SWS, and NREM nightmares. Similarly, other psychological disorders such as endogenous depression and schizophrenia have characteristic sleep patterns. In order to determine if this unusually positive response to trauma and its accompanying personality changes are associated with specific PSG correlates, we compared trauma survivors to age matched controls on a number of measures, including sleep/EEG, epilepsy and PTSD assessments.

**Methods:** Trauma survivors met criteria for the study by surviving a life-threatening situation that required emergency hospitalization and resuscitation efforts. In addition, they reported a significant number of components of the typical near-death experience (Greyson, 1985) during the trauma. Age and gender-matched controls had no history of sleep problems, a sleep efficiency of at least 60% on the test night, and no history of trauma, including serious illness or accident, physical/sexual abuse, assault, rape or combat experience. All subjects (n=40, 16 male, 24 female, ranging in age from 25 to 71yrs) underwent an overnight EEG/video recording with 27 channels, and completed the following questionnaires: Dissociative Experiences Scale, the Mississippi Scale, the Personal Philosophy Inventory, and a brief dream inventory.

**Results:** Preliminary results indicate that near-death trauma

survivors had significantly fewer REM periods and significantly longer REM latency than controls ( $p<.05$ ). The trauma group also tended to spend less time asleep and have a lower sleep efficiency ( $p<.1$ ), although sleep onset latency, time in stage 1 and number of awakenings were similar in both groups. No clinically significant seizure activity was found in near-death trauma survivors, although they reported significantly more complex partial epileptic and temporal lobe symptoms than controls. The PTSD assessment revealed that the near-death trauma group scored significantly higher than controls on the Dissociative Experiences Scale but not on the Mississippi Scale.

**Conclusions:** Near-death trauma survivors had significantly fewer REM periods and longer REM latency than controls. This pattern may be sufficiently distinct from the patterns associated with depression (i.e. shortened REM latency) and PTSD (i.e. more arousals, that it may represent a sleep pattern uniquely associated with this atypically positive response to a life-threatening trauma. Dissociation appears to be highly characteristic of this response and may be an important factor associated with this sleep pattern.

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**541.Q**

**THE SLEEP OF STABLE BIPOLAR OUTPATIENTS: A NATURALISTIC STUDY USING ACTIGRAPHY**

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**Introduction:** Studies have suggested that sleep abnormalities are stable and persist during remission of bipolar and unipolar depressive disorders (1,2). However, reliance on polysomnography confines measurement to one or two nights in a sleep laboratory. This study compared remitted bipolar subjects with controls on actigraphic and subjective sleep parameters in a naturalistic (home) setting over five consecutive nights.

**Methods:** Nineteen subjects (8 M, 11 F) fulfilling DSM-IV criteria for bipolar disorder who were currently euthymic were age (mean = 47 yr.) and sex matched with 19 controls. Sleep parameters were estimated using wrist actigraphs. Sleep diaries and mood ratings were completed for the same period. Sleep data were averaged within subjects across nights, and raw score standard deviations were also calculated as a measure of night-to-night variability.

**Results:** Multivariate analyses of variance yielded significant group differences for both actigraphic [ $F(4,33)=3.80, p=.012$ ] and subjective measures [ $F(4,31)=3.18, p=.027$ ]. Univariate analyses identified reliable differences in sleep onset latency (subjective), sleep duration (subjective), and variability of sleep duration and night wake time (actigraphic). Bipolar subjects slept longer, report longer onset latencies, and displayed greater variability across nights (Table 1). The best predictive logistic regression model combined sleep variability (actigraphy), two subjective variables (sleep duration, sleep latency) and a rating of mood to correctly identify 79% of bipolar sub-

jects and 90% of controls [ $c2(4) = 23.7$ ;  $p < .001$ ].

**Table 1**

Variable	Bipolar Mean(SD)	Control Mean(SD)	df	F	p
Actigraphy Mean					
TST	434.2 (91.7)	387.5(53.0)	37	3.69	.063
SOL	19.5(22.1)	8.0(6.9)	37	3.66	.064
SE	83.0(9.2)	86.9(3.6)	37	3.04	.090
WASO	59.0(26.0)	49.2(17.5)	37	1.83	.184
Actigraphy SD					
TST	70.0(39.6)	44.8(24.6)	37	5.53	.024*
SOL	21.4(28.7)	8.8(12.2)	37	3.27	.079
SE	6.6(6.3)	4.3(2.3)	37	.936	.340
WASO	23.6(15.1)	15.4(8.1)	37	4.33	.045*
Diary mean					
TST	473.5(112.9)	411.7(56.1)	35	4.19	.048*
SOL	40.9(45.3)	17.3(11.0)	35	9.01	.005**
SE	85.7(8.7)	89.3(10.3)	35	1.32	.258
WASO	38.8(40.8)	30.2(51.0)	35	.362	.552
Diary SD					
TST	91.9(63.2)	55.6(31.8)	35	5.19	.029*
SOL	31.2(54.9)	11.6(13.5)	35	4.86	.034*
SE	12.5(8.4)	6.9(5.4)	35	6.23	.018*
WASO	37.2(39.2)	20.8(25.3)	35	1.00	.324

Means and standard deviations of bipolar and control groups on actigraphic and subjective sleep parameters (averaged and night-tonight variability), and results of univariate analyses [TST = total sleep time (min.); SOL = sleep-onset latency (min.); SE = sleep efficiency (%); WASO = wake-time after sleep-onset (min.)  
\*  $p < .05$ ; \*\*  $p < .01$

**Conclusions:** The study suggests that the sleep of bipolar outpatients does not normalise during euthymic periods. Sleep variables continue to contribute to the prediction of such mood disorder.

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**542.Q**

**MANAGEMENT OF COSLEEPING IN CHILDREN AND PREADOLESCENT WITH PSYCHIATRIC DISORDERS - ONE YEAR FOLLOW-UP STUDY**

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**Introduction:** Cosleeping, the practice of parents and children sleeping together in body contact for all the night, is quite common in families with young children, mainly suffering from sleep disorders. Since no studies have investigated cosleeping in school-aged children with psychiatric disorders, we decided to study this practice and the effect of behavioral methods in the management of sleep in this population.

**Methods:** Out of all children attending the psychiatric outpatient clinic for school aged children of our Department, we selected a sample of 43 regular bedsharers (for at least one year) aged 5,10-12,7 yr (mean age 9,2 yr; 27 M,17 F), (34 with

anxiety disorders, 6 with conduct disorders, 3 with ADHD, based on DSM IV criteria). To assess baseline behavior and sleep related problems parents completed Child Behavior Checklist (CBCL 4/18) and Children’s Sleep Habits Questionnaire (Owens, 2000) that yields both a total and 8 subscales scores, reflecting key sleep domains. Higher score are indicative of more disturbed sleep. Furthermore current child’s sleep problems and nighttime behavior were investigated. Baseline sleep variables, CSHQ and CBCL scores were compared with those obtained by a control group of 213 controls (mean age 8.7 yrs). Parents were given instructions about management of child’s sleep and asked to complete a diary of child’s sleep for all the behavioral treatment period. All children were followed over a period of one year. Then parents completed again the CSHQ.

**Results:** Ten per cent of children with psychiatric disorders reported cosleeping for at least two years; on the contrary the prevalence of regular bedsharing in the control sample was only of 1.5%. In our sample children started cosleeping at a mean age of 3.7 yr. Furthermore, 33% complained of sleep onset insomnia, 5% of nightmares and 3% of enuresis. T-test for independent sample results at baseline of the comparison between cosleepers and control group were reported in the table. One year after treatment evaluation carried on 25/43 cases (drop out 40%) showed that 28 % coslept sometimes with parents and 72% of cases did not cosleep anymore and this habit disappeared, on average, after three months of treatment. T-test for dependent sample showed an overall improvement of all sleep scores after one year behavioral treatment (total score 57 vs 39;  $p < .001$ ). Particularly, bedtime resistance (15 vs 7  $p < .001$ ), night wakings ( 6.2 vs 3.9;  $p < .001$ ) and sleep anxiety showed strongest improvement.

**Table 1**

VARIABLES	CONTR	COSL	P
Sleep latency (min)	10	30	<.001
Bedtime (hh.mm)	21.40	22.20	<.001
Risetime (hh.mm)	7.15	7.15	Ns
Sleep length (min)	570	525	<.001
CBCL Total score	50,4	65	<.001
CBCL Externalizing	49,2	58,7	<.001
CBCL Internalizing	51,9	66,3	<.001
CSHQ Total Score	43,5	56,8	<.001
1. Bedtime Resistance	7.3	15.4	<.001
2. Sleep Onset Delay	1.1	1.9	<.01
3. Sleep Duration	3.3	4.1	<.01
4. Sleep Anxiety	4.5	10.6	<.001
5. Night Wakings	3.1	5.1	<.001
6. Parasomnias	8.2	8.0	Ns
7. Breath problems	3.4	3.2	Ns
8. Sleepiness	14.5	13.4	Ns

**Conclusions:** Results of our study pointed out a high incidence of regular and long lasting cosleeping in children with psychiatric disorders, mainly in those suffering from anxiety disorders. Follow up results showed a significant improvement of sleep hygiene and problems after behavioral treatment. Therefore, results of our study suggest that behavioral therapy may represent a valid and simple strategy in the management of cosleeping and sleep problems in children with

psychiatric disorders.

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**543.Q**

**AUTOBIOGRAPHIC MEMORY AND ITS ASSOCIATION WITH REM SLEEP IN PATIENTS WITH MDD AND GOOD SLEEPER CONTROLS**

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**Introduction:** Patients with Major Depressive Disorder (MDD) show both increased REM sleep activation and an increased tendency for the recollection of negative life events (1). Since it has been hypothesized that REM sleep subserves a memory consolidation function, it follows that increased REM sleep activation may be associated with the memory distortions observed in MDD. This possibility was tested, in a preliminary way, by evaluating the association between REM sleep and autobiographical memory in patients with MDD (n=5) and in Healthy Good Sleepers (HGS; n= 7).

**Methods:** Groups were matched for age, sex and body mass. The sample was 75% female and the mean age was 41.0 ( $\pm$  9.78). All subjects spent at least two nights in the laboratory and completed an Autobiographical Memory Questionnaire (AMQ) on the first in-lab night. This instrument requires subjects to recall up to 10 significant life events and to rate each event as either positive or negative. PSG measures included 2 EOGs, 6 EEGs and a submental EMG. Electrophysiologic signals were acquired digitally using Stellate Harmonie™ software and experienced scorers scored all records. The primary memory measures for the present analysis were number of negative (NE) and positive events (PE) and number of negative (NE5) and positive events (PE5) listed within the first five items. The sleep architecture measures were REM latency, REM time and REM percent. Groups were compared on the AMQ measures using t-tests. The association between REM sleep and the AMQ measures was assessed using within group correlations.

**Results:** The groups significantly differed on the AMQ measures. In comparison to controls, subjects with MDD recalled significantly more negative events (MDD NE = 2.8 vs. HGS NE = 0.8,  $p < 0.05$ ) and recalled them preferentially (MDD NE5 = 2.0 vs. HGS NE5 = 0.6,  $p < 0.01$ ). Subjects with MDD also recalled less positive events within the first five items (MDD PE5 = 3.0 vs. HGS PE5 = 4.4,  $p < 0.01$ ). Within group correlations revealed that the MDD subjects showed a negative relationship between REM latency and NE and NE5 ( $r = -.51$ [NE],  $r = -.62$ [NE5]) and a positive correlation between the NE measures and REM time ( $r = .24$ [NE],  $r = .43$ [NE5]) and REM percent ( $r = .31$ [NE5]). For controls, an opposite pattern was observed and the correlations were of a lesser magnitude (range  $r = -.41$  to  $r = .23$ ). The correlational effects, although suggestive, await replication and significance testing in an appropriately large sample.

**Conclusions:** Our results support the finding that subjects

with MDD have a bias towards negative memory recollection. Our data also lend support to the possibility that REM sleep abnormalities may be related to depression functionally, i.e., that excessive activation of the REM system may lead to the preferential consolidation of negative affect related memory.

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**544.Q**

**TEMPORAL DISTRIBUTION OF PHASIC EVENTS IN PATIENTS WITH MAJOR DEPRESSION & PRIMARY INSOMNIA AND IN GOOD SLEEPER CONTROLS**

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**Introduction:** To our knowledge, there has never been a formal assessment of the temporal ordering of K-Complexes and Spindles. In this study, the temporal patterning of K-Complexes and Spindles were assessed to determine whether these events mirror ontogenic/phylogenetic sequencing or if their occurrence follows a pattern that might be expected based on their physiological correlates (K-Complexes being associated with arousal and Spindles with the genesis of slow wave sleep).

**Methods:** Three groups (n=20 per group) were evaluated: Primary Insomnia, Major Depression, Good Sleeper Controls (no history of psychiatric/sleep disorders). Groups were matched for age, sex, and body mass. The sample was 66% female and the mean age was 37.5 ( $\pm$  10.7). Subjects spent at least two nights in the sleep laboratory. PSGs included 2 EOGs, 6-10 EEGs and a submental EMG. Digital acquisition was governed by Stellate Harmonie™ software and accomplished by a BSMI 519 AD board. All records were scored in 30 second epochs and phasic events were assessed visually according to Rechtschaffen and Kales criteria. Latency to phasic events were measured from initial sleep onset (30 seconds any stage sleep). Statistical analyses included a contingency analysis to assess the relative frequency of the phasic events by group and a One-Way ANOVA was used to determine whether the latencies to the phasic events differed by group.

**Results:** K-Complexes occurred first, regardless of group status, in 85% of subjects (90% for Controls, 75% for MDDs and 90% for PIs). The average latency to the occurrence of the first K-Complex was about 3 minutes (X=161.8 seconds). The groups were not found to differ on either the rate of occurrence of initial K-Complexes or the latency to these events. Although not significant, it should be noted that the MDD subjects exhibited a 2.5x increase in the initial occurrence of Spindles (10%[GS & PI] vs 25%[MDD]).

**Conclusions:** The finding that K-Complexes reliably precede Spindles suggests that the temporal patterning of these events do not "recapitulate" either ontogeny or phylogeny. Instead, it seems likely that physiologic considerations determine the sequencing of K-complexes and Spindles. That is, K-Com-

plexes are likely to occur first because of the increased probability of arousals during shallow sleep. Similarly, Spindles may be more likely to occur second because of their association with cortical synchronization and the genesis of slow wave sleep. Finally, although the 2.5x increase in the occurrence of spindles in the MDD group did not distinguish this group from the others, it may be of interest to evaluate whether MDD subjects that exhibit this pattern are the same subjects that show either slow wave sleep deficits or preservation of this stage of sleep.

**545.Q**

**ALEXITHYMIA AND SLEEP DISORDER SYMPTOMS**

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**Introduction:** The personality construct of alexithymia involves the following core features: difficulty identifying and describing feelings, difficulty distinguishing between feelings and bodily sensations of emotional arousal, constricted imaginal processes, and an externally oriented cognitive style<sup>1</sup>. Previous research has suggested that alexithymia may be related to poor sleep quality<sup>2</sup>. The present study examined the relationship between alexithymia and symptoms related to a broad range of sleep disorders in an adult community-based sample. **Methods:** The 20-item Toronto Alexithymia Scale (TAS-20)<sup>1</sup> and the 65-item Sleep Problems Inventory (SPI)<sup>3</sup> were completed by 661 adults (180 men and 481 women). The mean age for the sample was 23.45 (Sd = 6.22) years. The SPI (developed to assess symptoms associated with common sleep disorders) has 5 sleep disorder scales: nightmares; circadian rhythm, sleepwalking, insomnia, and excessive sleepiness. The SPI also has two sleep hygiene scales that assess problems associated with substance abuse and disrupted routines. Using cut-off scores for the TAS-20, 67 individuals (20 men and 47 women) were identified who scored in the alexithymia range. These individuals were matched (on age and gender) with 67 individuals scoring in the non-alexithymia range.

**Table 1**

SPI Scale	Alexithymic		Non-alexithymic	
	Mean	SD	Mean	SD
Sleep Hygiene				
1. substance abuse	12.19	5.07	11.69	3.85
2. disrupted routines	23.97	4.73	22.88	4.75
Sleep Disorder				
1. nightmares	19.92	8.96	14.87	5.08*
2. circadian rhythm	17.60	5.00	15.99	4.78
3. sleepwalking	14.22	5.18	11.98	2.91*
4. insomnia	20.85	5.93	15.30	4.48*
5. excessive sleepiness	23.58	6.30	18.19	5.19*

\* p < .007 (Bonferroni correction).

**Results:** Table 1 presents means and standard deviations for the two groups (alexithymic and non-alexithymic individuals) on the various SPI scales. The two groups did not differ significantly on the two sleep hygiene scales or the circadian rhythm scale (p > .05). However, the alexithymic group scored significantly higher than the non-alexithymic group on the nightmares (t = 4.02, df = 132, p < .001), sleepwalking (t = 3.09, df = 132, p = .002), insomnia (t = 6.12, df = 132, p < .001), and excessive sleepiness (t = 5.40, df = 132, p < .001) scales.

**Conclusions:** The findings of the present study suggest that alexithymia is associated with subjective reports of excessive sleepiness, insomnia, sleepwalking, and nightmares.

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**546.Q**

**DISTINCTION BETWEEN DEPRESSION AND VITAL EXHAUSTION IN SLEEP-DISORDERED BREATHING**

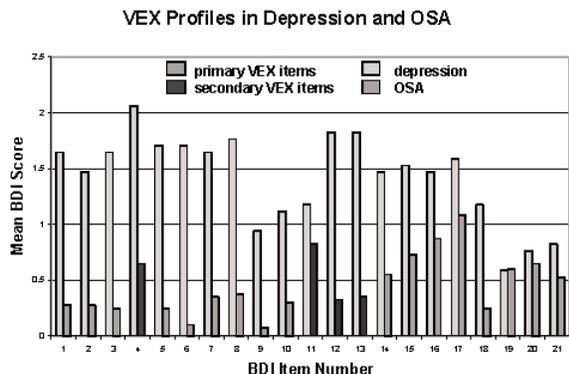
Giray N,<sup>1</sup> Castriotta RJ,<sup>1</sup> Hirshkowitz M,<sup>2</sup> Allen T,<sup>1</sup> Swann A<sup>3</sup>

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**Introduction:** Vital Exhaustion (VEX) is a related but distinct concept from sleepiness and depression. The definition of VEX is based on research concerning predictors of cardiac illness in a large cohort study (Van Diest et al, 1991). VEX consists of two subscales of the Beck Depression Inventory (BDI): Primary and Secondary VEX Scales. Primary VEX includes work inhibition (#15), sleep disturbance (#16), fatigability (#17), and decreased libido (#21); Secondary VEX includes general dissatisfaction (#4), irritability (#11), loss of social interest (#12), and problems making decisions (#13). In patients with VEX, primary affective components of depression (sadness, hopelessness or guilt) are typically not present. The concept of VEX has been explored in patient groups with several different sleep disorders, including Obstructive Sleep Apnea (OSA), Upper Airway Resistance Syndrome (UARS), narcolepsy, Periodic Limb Movement Disorder (PLMD), Primary Snoring and REM-OSA (Gokcebay et al 1999, Giray et

al 2000). These studies revealed that patients with sleep-disordered breathing showed elevated VEX profiles despite varying levels of disease severity and daytime sleepiness. Patients with narcolepsy and PLMD differed in their VEX profiles from the groups with sleep-disordered breathing. In the present study, Major Depressive Disorder (MDD)-related VEX profiles are compared to those of subjects with sleep-disordered breathing. **Methods:** Seventeen subjects recruited for a depression study who met criteria for MDD were evaluated with structured clinical interview and psychometric tests. The subjects were screened for comorbid sleep disorders by clinical assessment, sleep diaries, sleep disorders screening questionnaire (Sleep Quality Profile), Epworth Sleepiness Scale (ESS) and BDI. The subjects did not undergo PSG evaluation. The mean age of the subjects was  $32.5 \pm 9$ , (7M and 10F). Their VEX profiles are compared to subjects with sleep-disordered breathing. **Results:** As expected, subjects with MDD had higher overall scores on BDI and scored especially higher on affective items, such as sadness, hopelessness and guilt. Daytime sleepiness as measured by ESS was variable. The VEX profiles of subjects with MDD were different than those of subjects with sleep-disordered breathing (Fig.1).

Figure 1



**Conclusions:** In clinical practice, it is important to differentiate VEX masquerading as depression in patients with sleep-disordered breathing. One important clue may be the VEX profiles. When VEX is recognized, consideration should be given to underlying causes, such as sleep-disordered breathing, heart disease and other medical conditions. This study provides further evidence that VEX, sleepiness and depression are related but distinct phenomena.

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**547.R**

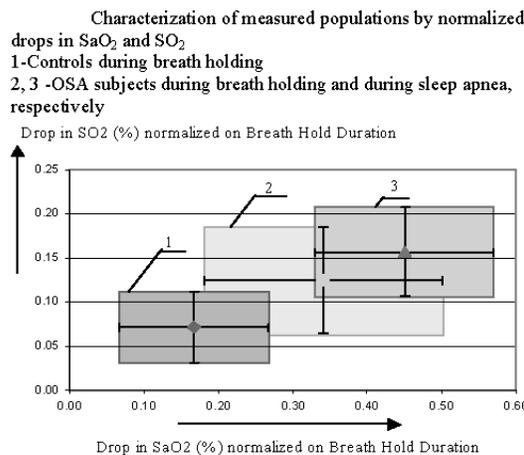
**OBSTRUCTIVE SLEEP APNEA: EVALUATION OF BRAIN OXYGENATION AND HEMODYNAMICS BY NEAR-INFRARED SPECTROSCOPY**

Michalos A,<sup>1,2</sup> Safonova LP,<sup>1,2</sup> Wolf U,<sup>1</sup> Wolf M,<sup>1</sup> Choi JH,<sup>1</sup> Gupta R,<sup>1</sup> Mantulin WW,<sup>1</sup> Hueber DM,<sup>1</sup> Barbieri B<sup>2</sup> Gratton E  
 (1) Laboratory for Fluorescence Dynamics, Department of Physics, University of Illinois at Urbana-Champaign, (2) ISS, Inc. Champaign, Illinois,

**Introduction:** Obstructive sleep apnea (OSA) is a potentially lethal disease, which leads to hypoxia and hypoxemia. Chronic, recurrent hypoxia during sleep may cause brain injury. Neuropsychological and cognitive deficits, as well as cerebrovascular accidents, including fatal strokes are not uncommon (1). Conventional polysomnography does not provide information on brain oxygenation, an important parameter in subjects with preexisting cardiovascular pathology. Near-infrared spectroscopy (NIRS), a safe, non-invasive, portable, bedside method, provides real-time transcranial measurements of changes in cerebral oxygenation and hemodynamics. These characteristics make NIRS the ideal tool to study physiological and pathological processes of the brain, in research and clinical settings (2).

**Methods:** Thirteen males and eight females (age 22-74 years) participated in the study. Eight were OSA sufferers. Thirteen individuals constituted the control group. One control subject had family history OSA. All OSA subjects and six controls were snorers. Two OSA subjects had severe hypertension and asthma. Arterial blood oxygen saturation (SaO2) and heart rate (HR) were monitored via pulse oximetry, and the breathing rate with a respiratory strain gauge. The NIRS parameters, such as oxy- (O2Hb), deoxy- (HHb), and total hemoglobin (tHb) concentrations, as well as tissue hemoglobin oxygen saturation (SO2) were monitored by a frequency-domain tissue oximeter (OxiplexTS, ISS Inc., Champaign, IL).

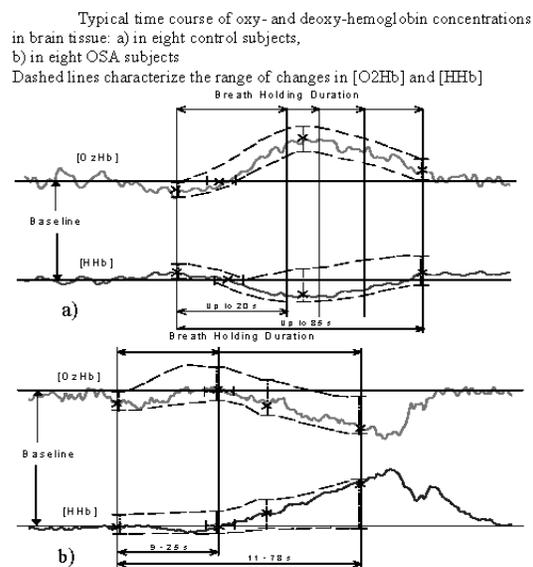
Figure 1



**Results:** We applied NIRS during voluntary breath holding and during daytime napping. Observed changes in SaO<sub>2</sub> and

SO<sub>2</sub> were significantly smaller ( $p \leq 0.025$ ) for controls during breath holding than those in SaO<sub>2</sub> and SO<sub>2</sub> recorded in the OSA group during breath holding and spontaneous sleep apnea events (Fig. 1). Higher levels of arterial and brain deoxygenation were observed for OSA subjects during napping. Different dynamics of O<sub>2</sub>Hb, HHb, and tHb concentrations and SO<sub>2</sub> were detected for control and OSA groups during voluntary hypoxia. We observed that the response to simple breath holding exercises, registered by NIRS, is sufficient to discriminate OSA subjects from healthy controls. The amplitude of the hemodynamic response to hypoxia was significantly larger than the amplitude of the baseline fluctuations in both control and OSA groups (Fig. 2). This response was altered in OSA subjects with a cardiovascular medical history (Fig. 2b).

**Figure 2.**



**Conclusions:** From these measurements we can assume that, in healthy individuals with obstructive sleep apnea, there is a protective cerebrovascular response to hypoxia which is likely to prevent eventual brain injury during apnea. In subjects with preexistent cardiovascular pathology, this protective mechanism may be defective. An adequate response may not fulfill the oxygen demands of the brain. Thus, the recurrent hypoxic insult, during sleep, may contribute to the risk for cerebrovascular morbidity. NIRS may be a valuable tool for early detection of cerebral hemodynamic abnormalities in obstructive sleep apnea. Quantitative measurements of oxygenation by NIRS may complement polysomnography for the prevention of hypoxic damage.

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27(4):801-15

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**548.R**

**EFFECT OF MOTIVATION ON THE EPWORTH SLEEPINESS SCALE SCORE**

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**Introduction:** The Epworth Sleepiness Scale (ESS) is a commonly used measure of subjective daytime sleepiness. It asks patients how likely they are to fall asleep in various situations. However, numerous patients within our clinical laboratory have indicated that their ability to doze off is dependent upon several factors within those situations, one of which is their level of motivation. The ESS does not specify any level of motivation for each of its conditions. Therefore we chose to explore if defining the motivational component would make a change to the overall ESS score.

**Methods:** To determine the effect of motivation on ESS scores, 50 consecutive patients presenting for sleep studies completed 3 questionnaires. They were first given the ESS (original) and then in random order 2 versions which we adapted to either include or exclude a motivational component. The motivational ESS (ESS M+) asked patients "if you tried to resist sleep or if you tried to stay awake, how likely are you to doze off in the following situations?". The non-motivational ESS (ESS M-) asked patients "if you did not try to stay awake or if you let yourself fall asleep, how likely are you to doze off in the following situations?" A repeated measures analysis of variance was performed using the SAS Mixed Procedure with one between subjects factor, gender, and one within subjects factor, ESS situation.

**Results:** The least squares means were 13.1 for the ESS M-, 10.0 for the ESS , and 8.8 for the ESS M+. The ESS M- was significantly different than the other two measures ( $p < 0.0001$ ). The average of the three questionnaire scores was higher for women than men, 12.5 v 8.7 ( $p = 0.01$ ) but there was no significant interaction between gender and the 3 questionnaire scenarios. Age did not influence these findings.

**Conclusions:** ESS scores may be significantly different depending on whether the respondent interprets the scenarios to be with or without motivation. With the multiple sleep latency test (MSLT), the degree of motivation is clarified to the subject by words such as "let yourself fall asleep". If the ESS score is being used to measure sleepiness similar to the way in which the MSLT is interpreted, then consideration should be given to clarifying the expected degree of motivation for the ESS.

## 549.R

## NONLINEAR ANALYSIS OF TRANSIENT AROUSAL IN ADULT SLEEP EEG

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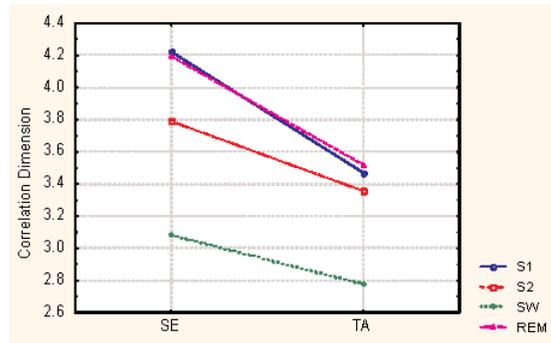
**Introduction:** Recent advances in neural network modeling and the relatively new mathematics and techniques of nonlinear dynamic systems theory have offered additional knowledge of the intrinsic properties of the neural networks responsible for the EEG phenomena. These neural networks underlying the EEG act as essential nonlinear elements that possess both static and dynamics nonlinearities that are voltage dependent.<sup>1</sup> Current methods of transient arousal (TA) identification and analysis are subjective interpretations of the frequency and amplitude variations in scalp electrical potentials. The identification of TA does not take into account the underlying brain events or neural networks that produce these potentials or whether TA events are independent of the ongoing brain activity during sleep. The goal of this study was to conduct a preliminary analysis of TA EEG events using a nonlinear dynamic correlate, specifically, correlation dimension (D2). D2 is a representative measure of the geometrical complexity of the EEG time series. Further, D2 was used to search for differences between sleep stage epoch2 and TA event complexity.

**Methods:** EEG (C4-A1) data for 20 healthy male (N=13) and female (N=7) subjects, between 25 and 46 years of age provided the arousal information. Subjects were free of known neurologic, medical conditions or medications that could alter EEG characteristics, such as hypertensives and/or stimulants on nocturnal polysomnography and had an apnea/hypopnea index (AHI)  $\leq 5.0$ , a periodic limb movements in sleep (PLMS) index  $\leq 2$ , and total sleep time (TST) was  $> 300$  minutes. TAs were extracted using ASDA criteria.<sup>3</sup> TAs, together with 10 typical 30-second epochs from each stage of sleep were analyzed using the tools of deterministic chaos theory. D2 was calculated for each TA event and all sleep stage epochs; the TA events had variable time series lengths from 3 to 15 seconds. These time series were entered into the nonlinear analytical model that yielded numerical and graphical representations of the EEG.

**Results:** The plots of D2 TA (TA) and 30-second sleep stage epoch (SE) means are seen in Figure 1. Differences in sleep stages and between SE and TA were tested with analysis of variance. No significant differences exist between arousal values in stages S1, S2 and REM, but did for stage 3+4 (SW) ( $p < 0.001$ ). However, only 5% of the arousal in this study was found in SW sleep. A comparison of sleep stage (S1, S2, SW and REM), state (SE and TA) and the nonlinear parameter (D2) were also done. The D2 showed a significant difference between states (TA and SE) for all sleep stages except SW. This indicates that the arousal complexity is in the range of 3.3–3.6 and does not vary greatly except for SW sleep.

Figure 1

D2 means for 30-second sleep state epoch (SE) and transient arousal (TA) events by sleep stage.



**Conclusions:** This research suggests that TA may be brain activity that is independent of sleep stage. Because of the low number of arousals found in stages 3+4, one might argue that the mean D2 value of SW sleep arousal should not be trusted. Indeed, if SW sleep TAs were removed from this study, then TA values would be independent of sleep stage. Further investigation should continue to determine if D2 results are indicative of changes in the conditions of a single neural network or if SE and TA signals are the result of independent, competing networks.

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## 550.R

## THE IMPACT OF BED FIRMNESS ON SLEEP

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**Introduction:** The impact of bed firmness on sleep quality is controversial and there is only limited data reporting the effects of sleeping surfaces on sleep. Young people sleep well regardless the sleeping conditions, while sleep in adults seems to be affected by the sleeping surfaces - in a survey from the USA 7 % of the subjects reported sleep problems related to uncomfortable mattresses (1). Many bed manufacturers present unfounded claims about "sleep-improved" qualities of their bed. The aim of the study was to investigate whether it is possible to record any influence of bed firmness on sleep quality.

**Methods:** Subjects, Sixteen healthy adult men, professionally active, having regular working hours and without sleep disorders, EDS or allergy were selected for the study. Their age ranged from 35 to 65 years. Experimental protocol. The study was a double blind, crossover design. Three beds, with different controlled firmness, were tested. The beds had the same physical appearance although one of them was thicker than the others. The subjects were investigated at home, first sleeping in their habitual bed for 3 days. Thereafter they slept 2 weeks in each test bed. The investigation period for each man was 7 weeks. Three subjects was investigated simultaneously. Sleep estimation a) Subjective measures The subjects kept a sleep diary during the whole investigation period. They reported everyday their sleepiness on analogue visual scales and Karolinska Sleepiness scale (KSS). Subjective estimates of sleep quality were measured using various questionnaires. b) Objective measures 1) Actigraphy was started at the beginning of the investigation, one week before the first test bed. Recording was continued uninterrupted during the 7 weeks trial period. 2) The 3 first nights of the investigation, while the subject slept in his own bed, night sleep was recorded using a sensor pad and a pulse oximeter connected to a solid state recording device. The same type of recording was also done the 3 first and the 3 last nights of each test bed. 3) Complete standard polysomnography – together with the sensor pad was done in the middle of each period for each test bed. Analysis was computer-assisted.

**Results:** Significant changes in sleep quality were observed related to bed firmness. The results showed a prevailing preference for one of the beds tested – the most flexible, with however strong individual differences. The effects were seen on both the subjective ratings and all types of recordings, however, subjective ratings were less consistent and did not always corroborate the objective measures. The overall results observed in the actigraph corresponded to the results of the other more sophisticated recording methods. Changing bed required many nights of adaptation, depending on the type of the bed.

**Conclusions:** The group studied was small. Nonetheless the results showed that it is possible to record changes in sleep quality when changing sleeping surfaces. The study extended to about a year. The effects of changes in the environmental factors, especially seasonal variation were not studied. This investigation shows that it is possible to estimate the effect of bed firmness on sleep. The choice of a firm or soft sleeping surface can differ for every subject. There is an adaptation period to a new sleeping surface.

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## 551.R

### CONFIRMATORY FACTOR ANALYSIS OF THE SLEEP PROBLEMS INVENTORY (SPI)

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**Introduction:** The Sleep Problems Inventory (SPI) is a 65-item self-report instrument that was developed to assess symptoms associated with common sleep disorders 1,2. The SPI has 5 sleep disorder scales: Nightmares (10 items), circadian rhythm (7 items), sleepwalking (11 items), insomnia (8 items), and excessive sleepiness (10 items). The SPI also has sleep hygiene scales that assess problems associated with substance abuse (7 items) and disrupted routine (9 items). The SPI was developed using a series of exploratory and confirmatory factor analyses with several different community based adult samples 1,2. The present study sought to cross-validate the factor structure for the SPI using a sample of adults that were referred to a sleep center for assessment of possible sleep disorder using nocturnal polysomnogram.

**Methods:** The sample consisted of 240 adults (141 men and 99 women) who were consecutive referrals to the Oshawa Clinic Center for Sleep Medicine (Oshawa, Ontario, Canada). The mean age for the sample was 47.51 (SD=13.57) years. Participants completed the SPI prior to their initial overnight sleep study.

**Results:** The 5-factor model of the sleep disorder scales and the 2-factor model of the sleep hygiene scales was tested using confirmatory factor analysis (CFA). The following criteria were used to evaluate goodness of fit: GFI>.85, AGFI>.80, RMS<.10. The 5-factor model for the 46 sleep disorder items was found to have good fit to the data (GFI=.88, AGFI=.87, RMS=.09). The parameter estimates for the sleep disorder items were moderate to high. The ranges were .44-.83 for nightmares, .32-.85 for circadian rhythm, .30-.68 for sleepwalking, .47-.75 for insomnia, and .30-.68 for excessive sleepiness. The 2-factor model for the 16 sleep hygiene items was found to have excellent fit to the data (GFI=.93, AGFI=.91, RMS=.09). The parameter estimates for the sleep hygiene items were moderate to high. The ranges were .40-.84 for substance abuse and .35-.78 for disrupted routine.

**Conclusions:** The results of the confirmatory factor analysis with the sleep clinic sample suggests that the factor structure of the SPI can be satisfactorily cross-validated with adults who were reporting current sleep problems. Our findings suggest that the SPI has sufficient psychometric properties to warrant additional research. Future research will examine whether the SPI can discriminate between patients that do, and do not receive a sleep disorder diagnosis.

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ders. Poster presentation at the annual meeting of the American Psychological Association, San Francisco, California, August, 2001.

**Research supported by an Ontario Graduate Scholarship to the first author and research grants to the second author from the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Ontario Government's Premier's Research Excellence Award (PREA) program.**

**552.R**

**STABILITY OF ACTIGRAPHIC SLEEP MEASURES AMONG OLDER ADULTS: A COMMUNITY-BASED STUDY**

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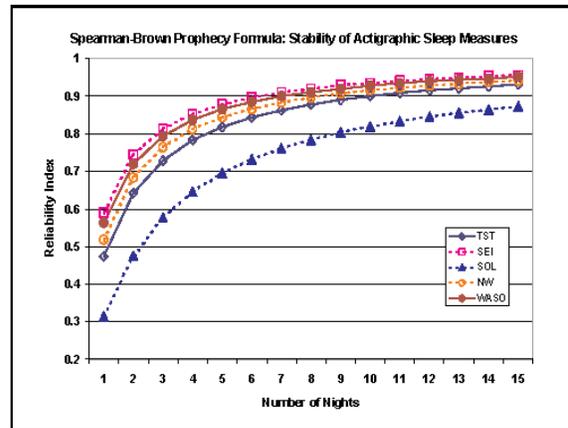
**Introduction:** Research has shown that home recordings may be advantageous to characterize sleep patterns since individuals can be continuously monitored comfortably for extended periods. Longitudinal studies have shown that sleep at home may be quite variable, particularly among individuals experiencing sleep disturbances.<sup>1</sup> An important home study demonstrated that a week of recording was necessary to achieve stability in older adults, even when polysomnography, the gold standard, was used.<sup>2</sup> Many studies now use actigraphy for home recording, as it proves a more cost-effective and less burdensome methodology. However, whether actigraphy yields stable sleep measures has not been systematically ascertained. This study sought to examine the stability of actigraphic sleep measures among community-residing older adults.

**Methods:** Data were collected from 390 postmenopausal women (mean age = 67.71±7.87) that participated in the Women's Health Initiative study. The sample included Non-Hispanic White = 72%, Hispanic = 14%, Black = 9%, and Other = 5%. Home sleep patterns of women were continuously recorded for 7 days with Actillum recorders (AMI, NY). The Actillum is a wrist-like device that incorporates a piezoelectric sensor (sensitivity >= 0.003 g), which measures bidirectional uniaxial accelerations. In this study, we used the MAXACT activity quantification modality. MAXACT integrates the largest acceleration over 10 seconds within each minute; this then was stored in memory until transferred to a PC. Activity data were recorded every minute, and volunteers maintained usual daily routines including work, intimacy, exercise, and bedtimes. Actigraphic data were analyzed with an optimized sleep-scoring algorithm.<sup>3</sup> Derived sleep parameters were total sleep time (TST), sleep onset latency (SOL), sleep efficiency index (SEI), wake after sleep onset (WASO), and number of awakenings (NW).

**Results:** The first analysis determined the intraclass correlation coefficient (ICC) for each of the five actigraphic sleep measures (i.e., TST, SOL, SEI, WASO, and NW) using a one-

way random model of the intraclass correlation procedure (SPSS 10.0). The average ICC values obtained for each sleep measure were then used to estimate the number of nights necessary to reach adequate stability, using the standard 80% criterion. The estimates were derived using the Spearman-Brown Prophecy Formula subroutine, executed with MATLAB. As seen in the figure, except for SOL 3-4 nights were necessary to reach adequate stability; for SOL, eight nights of recording would be necessary.

**Figure 1**



**Conclusions:** Results of this study demonstrated that several nights are necessary to obtain reliable sleep estimates with actigraphy. Of interest, in our study TST, SEI, WASO, and NW required an average of 3-4 nights to reach adequate stability. This is comparable to a previous report suggesting that five nights of home polysomnographic recordings were needed to reach adequate stability among older volunteers with or without insomnia.<sup>2</sup> However, in both studies, longer recordings would be necessary to reach stability for SOL; based on our data, 8 nights would be needed, whereas 10 nights would be necessary according to the previous report. Perhaps volunteers in our study may have been characterized by less sleep disturbances than those in the previous study. It is also important to note that some sleep measures among older adults may be more stable relative to younger volunteers. Indeed, a study investigating reliability of TST among adolescents found that 7 nights of actigraphic recordings were needed for adequate stability, whereas for SEI, 3 nights were necessary. This suggests that sleep length among adolescents may be more variable than among older adults, who may tend to maintain regular sleep schedules.

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### 553.R

#### COMPARISON OF DIGITAL INFRARED THERMAL IMAGING WITH CONTACT THERMOMETRY: PILOT DATA

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**Introduction:** It is generally accepted that sleep propensity is associated with thermoregulatory behavior. In laboratory studies however, assessment of skin surface temperatures generally requires attachment of thermistors that can limit subjects' movement and comfort. During sleep, this may confound the results by delaying sleep initiation or increasing wake after sleep onset. One way of eliminating this potential confound is by using a non-invasive digital infrared thermal imaging (DITI) system. The aim of this study was to compare temperature data from a new DITI system against a contact thermometry system already in use in our sleep laboratory.

**Methods:** At the time of submission, pilot data consisted of 184 measures of hand skin temperature (Tsk) collected and analyzed from one volunteer. Skin thermistors (Steri-Probe type 499B, Cincinnatti Sub Zero, Cincinnatti OH) denuded of adhesive foam backing were attached with a minimal amount of adhesive to eight locations on the subject's right hand (each fingertip and spaced evenly over the palm). At various times of the day, after a 10-minute period of seated rest in a controlled temperature room (25 deg. C), data was collected simultaneously during 30-second intervals using a DITI system (MMS Med2000, Meditherm, QLD Australia) and a calibrated custom temperature system (Strawberry Tree, Cleveland OH) - both sensitive to temperature changes of 0.01 deg C. Sixteen of the 184 Tsk measures could not be analyzed for technical reasons; the remaining data were analyzed using linear regression and paired t-tests.

**Results:** Preliminary results indicate that Tsk obtained using DITI displays reliable and significant relationships with thermistor data at all locations investigated. At individual locations on the hand, correlation coefficients ranged between 0.93-0.99 (all  $p < 0.0001$ ). Analysis using all data yielded an overall correlation coefficient of 0.96 ( $p < 0.0001$ ). In comparison to contact thermometry however, DITI temperature data was consistently and significantly lower by an average of  $2.09 \pm 0.14$  (sem) deg. C across all measures ( $p < 0.0001$ ).

**Conclusions:** It appears that data from the Meditherm DITI system is precise and useful for assessing relative changes in hand skin temperature but did not accurately determine absolute temperatures. Nevertheless, the current data show that DITI has considerable promise as a tool for assessing skin surface temperatures in the sleep laboratory. It is anticipated that calibration of the DITI system to a black body radiator of known temperature would result in temperature measurements that are both accurate and precise.

Research supported by National Health and Medical Research Council (NH&MRC) and Australian Research Council (ARC).

### 554.R

#### SCREENING OF SLEEP DISORDERS USING A QUESTIONNAIRE IN THE ANNUAL HEALTH CHECK-UP PROGRAM

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**Introduction:** Annual health check-up program is widely operated in Japan mainly targeting young and middle-aged workers. More than a million people take this program every year. This program screens out various common medical conditions such as hypertension, diabetes mellitus and anemia, and malignancies. Sleep disorders are known to affect daily performance and sometimes cause accident while driving or at work, however, screening of sleep disorders has not been included in the health check-up program. The aim of this study was to introduce screening of sleep disorders using a questionnaire, firstly to evaluate its usefulness, and secondly, to reveal the prevalence of sleep problems among this population.

**Methods:** All the subjects who joined the annual health check-up program at Toyo-oka Hospital between September 1995 and April 1997 were included in this study. A questionnaire was designed to reveal sleep habit and any sleep problems. These were given to all the subjects and the responses were analysed statistically.

**Results:** Six hundred and fifty eight responses (474 males, 184 females) were used for analysis. Mean age of the subjects were 49.9 years (ranged 23 to 81 years). Mean sleep time was 426 minutes on weekdays. 31.4% of the subjects experienced sleep problems in the past, and 11.9% of them had sleep problems at the time of this survey. Inability of falling asleep, awakening during sleep, early morning awakenings were experienced in 5.4%, 9.6%, 6.9% respectively. Snoring is experienced in 54.0%, and frequent episodes of sleep apnea was witnessed in 2.0%. Among subjects having obesity, hypertension, or diabetes mellitus, sleep apnea was witnessed more frequently than in the normal subjects.

**Conclusions:** Sleep problems were complained in more than 10% of the subjects in our subjects, therefore, it would be valuable if we could introduce further sleep studies to those having sleep problems to detect their sleep disorders. As annual health check-up program is already widely used in Japan, adding sleep disorders questionnaire into this system could be a useful method in making initial screening of sleep disorders.

555.R

**AUTOMATIC SLEEP STAGING USING HEART PERIOD VARIABILITY IN NORMAL SLEEP**

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**Introduction:** The generation of sleep is closely tied to the output of the autonomic nervous system. Variations in systemic autonomic tone are observed between sleep stages: non-REM sleep has predominant parasympathetic tone and REM sleep has predominant sympathetic tone. Heart period variability (HPV) refers to the beat-to-beat variation in the timing between consecutive heartbeats. Analysis of this information provides information about the autonomic tone of the heart. The objective of this work is to determine whether the stage of sleep causes significant enough changes in HPV to allow identification of sleep stage based solely on this data.

**Methods:** HPV data from each sleep stage for 10 normal subjects were analyzed. Using approximately two-minute segments of R-R interval data (128 points), features based on time-domain and frequency-domain characteristics were extracted and covariance and mean statistics were computed for intrasubject and intersubject classification. Quadratic classifiers were constructed using these statistics. A two-stage classifier was used in the intersubject case to improve performance: the first stage determined the 2 most likely sleep stages and the second stage was tuned to differentiate those two sleep stages. Classification of sleep stage was performed for each 128-point window of data at 64-point increments.

**Results:** The correct sleep stage was selected in 96.7% of cases for the intrasubject classifier, in 53.6% of cases for the single-stage intersubject classifier, and 62.2% of cases for the two-stage intersubject classifier. The correct pairing for the first stage of the two-stage classifier was selected 85.9% of the time.

**Conclusions:** For a particular subject, there is sufficient information in the HPV data to allow identification of sleep stage. These changes do not appear to be the same between subjects given the relatively poor performance of the intersubject classifier. However, the intersubject classifier performed significantly better than chance. Based on this work, a computer-based classifier could be designed for a specific subject, which could then be used to grossly stage sleep in a sleep study.

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556.S

**CULPABILITY RATINGS OF SLEEPY AND INTOXICATED DRIVERS INVOLVED IN A FATAL MOTOR VEHICLE ACCIDENT**

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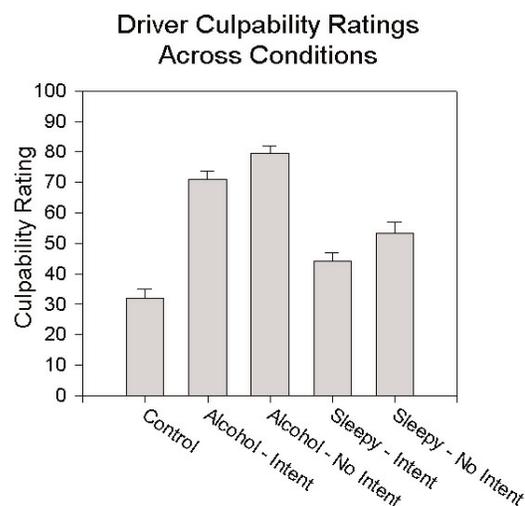
**Introduction:** Sleepiness is a major contributing factor to the occurrence of motor vehicle accidents<sup>1</sup> producing deficits comparable to those associated with legal intoxication.<sup>2</sup> The extent to which the public recognizes the dangers associated

with drowsy driving, however, remains unclear. The purpose of the present study was to assess public recognition indirectly by having participants judge the culpability of sleepy and intoxicated drivers involved in an accident.

**Methods:** Three hundred undergraduate students (mean age = 20.8 years), who gave their informed consent, were randomly assigned in equal numbers to read one of five vignettes describing a fatal motor vehicle accident. All vignettes described a person who, after attending a retirement luncheon for a colleague, strikes a child on the drive home. In two vignettes the driver consumes alcohol at lunch, in two the driver has been continuously awake since the previous night due to shift work. The driver's intention not to drive was indicated in one of each of the alcohol and sleepiness vignettes by the availability of a designated driver. Thus, the five experimental conditions included: control, sleepiness-no intent, sleepiness-intent, alcohol-no intent, and alcohol-intent. Subjects then rated the culpability of the driver on a 0-100 scale and listed the factors that they took into account when rating the driver's culpability.

**Results:** Analysis of variance yielded a significant difference between conditions ( $F(4, 295) = 45.4, p < .001$ ; See Figure). Post-hoc tests ( $p < .05$ ) revealed that: 1) the driver in the alcohol conditions was rated as more culpable than the driver in the sleepiness conditions, 2) alcohol and sleepiness conditions produced greater culpability ratings than the control condition, and 3) there was no significant effect of the intent to drive within the sleepiness and alcohol conditions. In the alcohol conditions 90% of participants listed alcohol as an influential factor in judging culpability whereas only 62.5% listed sleepiness/fatigue in the sleepiness conditions. However, those who clearly indicated that sleepiness was a factor in their judgment still rated the driver as less culpable than those who clearly took alcohol into consideration ( $t(181) = 7.34, p < .001$ ).

Figure 1



**Conclusions:** While participants attributed some degree of culpability to the sleepy driver the degree of responsibility was substantially less than that attributed to the intoxicated driver.

This discrepancy is inconsistent with recent performance-based findings<sup>2-3</sup> that have employed alcohol intoxication as a metric against which to compare the effects of sleepiness. The results of the present study are consistent with a lack of public awareness about the dangers of drowsy driving relative to drinking and driving and suggest that prevention strategies similar to those used to reduce alcohol-impaired driving should continue to be implemented in order to increase awareness of the dangers of drowsy driving.

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## 557.S

### RECOGNITION OF SLEEP DISORDERS IN A COMMUNITY-BASED SETTING FOLLOWING EDUCATIONAL INTERVENTION: PHASE II OF THE CHANDLER HEALTH CENTER PROJECT

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**Introduction:** We have previously reported very low rates of recognition of sleep disorders in minority and medically indigent populations in a community-based setting (recognition rate $\leq$ 0.1%)<sup>1</sup>. This omission is significant, since there is evidence that minority populations are at increased risk for sleep-disordered breathing and insomnia<sup>2,3</sup>. The present study was conducted to assess changes in recognition rates of sleep-related disorders following an educational intervention for medical and nursing staff.

**Methods:** In-service training on sleep and sleep disorders was conducted over a 4-year period and was targeted for all health professional staff at the health center. Educational intervention consisted of 1-2 hour in-service conferences for the attending physicians, residents, nurses, and allied health professionals. Patients screened at the health center with suspected sleep disorders were referred to a hospital-based sleep lab. Rates of recognition and referral for sleep-related disorders were compared over the 4-year period using the sleep lab database and patient chart review at the health center. Final diagnoses and treatment recommendations were tabulated for further analysis.

**Results:** The intervention program was highly rated and well attended by staff. A total of 11 patients were referred for polysomnographic (PSG) evaluation of sleep-related disorders during the 1-year period preceding the training. In the final year of the training program, 44 patients were referred for PSG

testing (see table below). Charts were available for review on 77/94 patients (82%). The reviewed sample consisted of 35M/42F, with a mean age of 29.3 $\pm$ 19.3 years. The majority of the sample was African-American or Latino (78%) and single (73%). The majority of patients (65%) received confirmed diagnoses of obstructive sleep apnea (OSA); 4% with primary snoring; 4% with periodic limb movement disorder (PLMD); 1% with insomnia; 1% with sleep enuresis.

Table 1

YEAR	# Referred Pts.	OSA	PLMD	Other Dx.	PSG Not Done or Lost to F/U
1996-97 (pre-training)	11	8	1	-	2
1997-98 (post-training)	16	10	-	-	6
1998-99 (post-training)	23	14	-	1	8
1999-2000 (post-training)	44	18	2	3	21

**Conclusions:** Rates of referral for sleep disorders were low prior to educational intervention in the health center, despite having a large population with co-morbid risk factors for OSA (e.g., HTN, obesity) and other primary sleep disorders. Over the 4-year period there has been a progressive increase in the reported rate of referrals for sleep disorders in this community-based setting. Despite broad coverage of sleep disorders during the training program, OSA was the primary diagnosis in the large majority of cases. Further examination of factors leading to the lack of recognition of other primary sleep disorders needs to be addressed in this patient group.

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## 558.U

### RESULTS FROM A COMMUNITY-BASED SLEEP PROGRAM FOR SENIORS IN CALGARY, ALBERTA

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**Introduction:** Non-drug treatments have demonstrated both short-term and sustained improvements in sleep using random clinical trials<sup>1</sup>. But seniors in Calgary cannot easily access

cognitive-behavioural treatment (CBT) for insomnia. The purpose of our sleep program was to adapt a CBT to a community setting making it more accessible. The goals of the project were as follows: to improve sleep quality and quantity for participants; to improve sleep knowledge and attitudes; to observe changes in sleep medication use.

**Methods:** Seniors (112) who were previously screened for chronic insomnia were invited to participate in a free community-based sleep program. A nurse with extensive sleep clinic experience did telephone assessments, screening for evidence of major sleep disorders, cognitive impairment and/or depression of 40 interested participants. Morin's cognitive-behavioural treatment (CBT) was adapted to the community setting. Three, six-week sessions with 15, 13 and 7 participants were offered at two seniors' facilities within Calgary. Participants were required to complete sleep diaries for one week prior to attending their first class (BSL) and for each week of attendance. A questionnaire assessing sleep knowledge and attitudes was completed at BSL and at the completion of the program (T=0). Three month (T=3) and six month (T=6) follow-ups were mailed, which included a sleep diary and questionnaire. Data collected included type of sleep complaint (SOL, WASO, EMA), duration of problem, frequency of problem, sleep efficiency (EFF), total sleep time (TST), attitude about sleep, and prescription sleeping pill use (duration and frequency).

**Table 1**

Participants' sleep parameter results recorded at baseline and upon program completion.

Sleep Parameter	BSL (n = 34)	T=0 (n = 30)
SOL (n)	20	11
WASO (n)	26	15
EMA (n)	5	13
SOL (min.)	54.1 ± 57.1	26.4 ± 21.2
WASO (min.)	63.7 ± 45.9	28.8 ± 20.5
Frequency (night/wk)	6.2 ± 1	4.0 ± 2.8
EFF Group 1 (%)	77.1 ± 11.0	82.3 ± 9.5
Group 2 (%)	62.2 ± 18.8	78.2 ± 9.1
Group 3 (%)	68.2 ± 17.5	85.7 ± 6.0
TST (hr.)	5.8 ± 1.7	6.0 ± 1.0

**Table 2**

Participants' attitudes and beliefs about sleep recorded at baseline and upon program completion.

Sleep Beliefs and Attitudes	Answer Yes (%)	
	BSL	T=0
Insomnia normal for seniors	20.6	7.1
Poor sleep = irritability/anxiety	60.6	42.3
Good habits = good sleep	20.6	40.7
Loss of control over sleep is worry	65.6	37.0
Able to control sleep quality	29.4	76.0
Past 3 mo. = sense of well-being	54.5	77.8
Social activities ruined by insomnia	64.7	32.1
Insomnia = daily tasks not done	42.9	36.6
Very/much concerned about insomnia	91.1	40.7

**Results:** Thirty-five seniors (27 women and 8 men) participated in three programs offered. Age of participants was 71.1 yr ± 6.9. Average duration of sleep problems was 14.7 yr ± 13.8. Completion of surveys and diaries at BSL, T=3 and T=6 was 97%, 86%, 31% and 26%, respectively. Only BSL and T=0 are reported here, however, improvements appear to be sustained at T=3 and T=6. Parameters showing improvement at T=0 included: complaint rate of SOL, WASO; minutes of SOL, WASO; insomnia frequency; and sleep efficiency. TST did not appear to change. See Table 1. Sleep attitudes and beliefs also showed improvement. See Table 2. Participants' sleep medication use decreased. The number reporting any use in previous 2- 4 weeks dropped from 22/30 at BSL to 11/30 at T=0. The frequency of use decreased from 5.0 ± 2.0 nights/week to 4.4 ± 3.0.

**Conclusions:** A portable community-based cognitive-behavioural sleep program has been developed that offers easy access to seniors with chronic insomnia. It appears to be effective in improving sleep efficiency and attitude toward sleep as well as decreasing continuous use of prescription sleep medications. A longer program of eight or ten weeks may be required to see an increase in total sleep time. The results warrant further investigation as to the benefits of a broadly based, non-drug treatment program for seniors.

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**559.U**

**THE EFFECTS OF CEDROL ON SLEEP OF YOUNG WOMEN**

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**Introduction:** The prevalence of insomnia during the preceding month in the general population of Japan is reported 21.4%, including difficulty initiating sleep (8.3%), difficulty maintaining sleep (15.0%), and early morning awakening (8.0%) 1). In addition, the article mentioned above reports that the psychological stress, and being unable to cope with stress were associated with an increased prevalence of insomnia in Japan. We have previously shown that cedrol, which is a sesquiterpene alcohol contained in cedarwood oil, significantly prolongs the R-R interval of the ECG, decreases diastolic and systolic blood pressures, prolongs the respiratory cycle, and deepens the respiration, which are physiological relaxation effect, making the parasympathetic nerve system dominant 2). Based on these effects on the parasympathetic nerve

system, cedrol is expected to affect the sleep.

**Methods:** To investigate the effects of cedrol on sleep, we designed two types of experiments, 1) eleven healthy young female volunteers were polysomnographically recorded for six consecutive nights, 2 adaptation, 2 placebo and 2 cedrol nights, in the sleep laboratory; 2) nineteen healthy young female volunteers wore actigraphs for two conditions of seven consecutive nights, placebo and cedrol nights, at their own home. Both experiments designed for single blind in a counterbalanced order in the follicular phase. The bedtime for each volunteer was decided with customary sleep-wake schedule during a week before the experiment. Sleep stages in PSG were judged by using Rechtschaffen and Kales criteria. Sleep-wake states in actigraphy were estimated by using Cole and Kripke criteria.

**Results:** 1) Total sleep time was significantly prolonged and sleep latency was shortened with cedrol than with placebo ( $p < 0.05$ ). Furthermore, sleep efficiency tended to increase ( $p < 0.10$ ). Wake-time after sleep onset (WASO) was no significant difference, but the appearance frequency tended to decrease with cedrol. 2) On the study of actigraphy at the subject's home, WASO significantly decreased and sleep efficiency tended to increase at nights with cedrol. The frequency of definite awakening, which continued for five minutes or longer during the first half period of the sleep, significantly decreased with cedrol ( $p < 0.05$ ).

**Conclusions:** The above findings showed that the sleep-initiating process became smooth and the sleep-maintaining function was improved by cedrol. Cedrol inhibited the excitement of the sympathetic nerve system and made the parasympathetic nerve system dominant, which may have made it easy to fall asleep. This study suggests that cedrol may play a useful role in providing a comfortable sleep environment.

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## 560.U

### EFFECTS OF IRREGULAR WORKING HOURS ON SLEEP AND ALERTNESS IN BRAZILIAN TRUCK DRIVERS.

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**Introduction:** Irregular working hours including night work cause changes in the sleep-wake time arrangements, which might affect the ability to drive safely. There is no a single strategy to avoid this problem. Many truck drivers working in irregular schedules drink more caffeine and others substances that may help to keep them awake during working time. This study aims to investigate the effects of irregular working hours on sleep and alertness in Brazilian truck drivers.

**Methods:** The investigation was carried-out with 35 truck drivers working on two transportation companies: 22 working on irregular schedules and 13 on fixed day shifts. The majority of the truck drivers (85%) from company A who work in an

irregular schedule uses stimulants regularly. Drivers working in company B reported no consumption of stimulants. All truck drivers filled out sleep logs and wore actigraphs (Ambulatory Monitoring TM) for 10 consecutive days to identify activity and rest episodes. Out of these records it was estimated the total minutes scored as sleep during 24-hour intervals. Sleepiness ratings were recorded every 3 hours using the KSS. Also the subjective quality of sleep was reported upon awakening. For statistical testing, 2-way analysis of variance (type of shift and transportation companies, as factors) were performed to test if the groups differ with respect to sleep duration and subjective sleep quality. Ratings of sleepiness during workdays were compared by means of ANOVA (time of day, transportation company and type of shift as factors).

**Results:** The irregular shift group showed a reduction of total sleep duration ( $F=4.26$ ;  $p=0.04$ ), but the groups did not differ with respect to the transportation companies. The analysis showed no significant differences between groups for subjective sleep quality. Results showed a significant effect for time of day and company ( $F= 2.36$ ,  $p=0.04$ ;  $F=5.62$ ,  $p=0.02$ , respectively). Effect of the type of shift was not found. The shorter sleep duration of the irregular working group did not reflect neither in their scores of subjective sleep quality nor in their ratings of sleepiness.

**Conclusions:** The reported consumption of stimulants by drivers working in an irregular schedule from company A can be a masking factor causing lower levels of sleepiness when compared with drivers from company B. The results suggest the need for extreme caution in assertions regarding the levels of subjective sleepiness in truck drivers, since the consumption of stimulants is a known practice among these workers. Moreover, an educational program as a countermeasure should be taken into account to reduce health-related problems in these drivers.

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## 561.U

### SLEEP TIME AND PATTERN AS REPORTED BY NORTH AMERICANS IN A 24-HOUR TIME-ACTIVITY DIARY

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**Introduction:** This is an analysis of the combined data from the National Human Activity Pattern Survey and the Canadian Human Activity Pattern Survey with respect to time spent in which the reply was sleeping or napping. It was an opportunity to examine modern sleep patterns from a large survey where sleep was not the primary question of interest but all subjects reported sleep on a full 24 hour period.

**Methods:** The National Human Activity Pattern Survey was a randomized sample of the continental USA and the Canadian Human Activity Pattern Survey used the same methodology to sample within four Canadian cities. Participants answered a 24 hour survey using Computer-Assisted technology investigating where they were and what they were doing during the pre-

vious day. The primary purpose of the surveys was to ascertain places and time spent in them to develop realistic exposure assessment models. However, for the purposes of this analysis, the activity of interest was sleeping and napping. Examining the amount of time spent sleeping and the hour of the day reported provides extensive normative data on sleep patterns from the modern era.<sup>9</sup>

**Results:** For adults only, there is a significant effect of age, occupational status and season but not of gender day of week or latitude:

**Table 1**

Age Group	n	Minutes Spent Sleeping/Napping				p-value
		Mean	STD	Lower 95% C.I.	Upper 95% C.I.	
18-35	3266	506	134	502	510	0.0001
36-65	4388	489	121	486	493	
66+	1477	516	96	510	522	
Employed	6051	489	121	486	492	0.0001
Unemployed	3258	521	123	516	525	

**Conclusions:** Modern data suggest an effect of age, season and employment status on reported total sleep in a 24 hour period in a population sample. Average sleep time between eight and eight and a half hours suggest sleep restriction is not usual even in young adults or the employed adults, contrary to popular beliefs.

**Research supported by Health Canada. Special thanks to the US EPA for allowing the use of their data**

### 562.U

#### AN ALGORITHMIC MODEL FOR REM SLEEP

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**Introduction:** The algorithmic theory of adaptation studies what must be the behavior of autonomous robots when they are confronted to changes of their environments making obsolete their previous knowledge. We proved [1,2] the double necessity of a continuous training and of a heuristic of forgetting. It is therefore mandatory to detect the least useful pieces of memory in order to eliminate them. Moreover, this process can be achieved more economically during phases of rest if they exist; so, we get an algorithmic model of REM sleep

**Methods:** This previously proposed model could be enhanced by more physiological data. Indeed, notions of short or long range memory could correspond to an ordering of pieces of information in three categories (very useful, useful or little useful) instead of two (useful, little useful). Recent experiences would be recorded individually in small neural networks highly flexible but exposed to accidental destruction. The nocturnal process would therefore not limit itself to the elimination of the least useful pieces of information. It would also include the displacement of the ones classified as the most useful toward a large network. Such neural network constitutes a model of long range memory which is less flexible but also less affected by an accidental destruction of a few of its individual neurons.

**Results:** The selection between the different categories of information needed a quiet period equivalent to sleep. To avoid new acquisition and no controlled movement during this period the robot had to be disconnected from its outputs (motor activity). Finally the selection of events during this period could be compared to a period of forgetting and memory consolidation.

**Conclusions:** Our work justifies, by merely algorithmic considerations, functions proposed by physiologists for the REM sleep

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### 563.U

#### SENSITIVITY OF THE WAKING EEG TO THE EFFECTS OF CAFFEINE IN THE EVENING

Drapeau C,<sup>1,2,3</sup> Kawinska A,<sup>1,2,3</sup> Frenette S,<sup>1</sup> Barbier S,<sup>1</sup> Filipini D,<sup>1</sup> Carrier J<sup>1</sup>

(1) Centre d'étude du sommeil, Qc, (2) Département de psychologie, Université de Montréal, Qc, (3) Groupe de Recherche en Neuropsychologie Expérimentale, Qc

**Introduction:** The electroencephalogram (EEG), recorded in the waking state, has been proposed as an objective measure of vigilance levels. Spectral power in the theta and alpha ranges of the waking EEG is particularly sensitive to the accumulation of wakefulness and increases with the number of hours of wakefulness (1,2,3). Furthermore, studies have shown strong associations between the waking EEG and other measures of vigilance such as subjective alertness and performance at a psychomotor vigilance task (PVT) (1,2,3). The aim of this study was to evaluate the sensitivity of the waking EEG to the effects on vigilance of an evening administration of 200 mg of caffeine.

**Methods:** Ten healthy subjects (5W, 5M, mean age:31.8 years), all moderate caffeine consumers (1-3 cups of coffee/day) were studied. Subjects were submitted to both a caffeine (200 mg) and a placebo (200 mg of lactose) condition in a double blind cross over design. One week separated both conditions. Subjects received one pill of caffeine (100 mg) or placebo (100 mg) three hours before their habitual bedtime and the remaining dose (100 mg), one hour before bedtime. Twenty minutes after the second capsule, subjective alertness (visual analog scale) and PVT performance were evaluated. Waking EEG with eyes open (C3-linked ears; sampling rate: 256 Hz) was recorded 5 to 10 minutes after the PVT. Artefact-free EEG signals were subjected to spectral analysis (FFTs) for consecutive 2-sec epochs and a 0.5 Hz resolution. Sleep latency at bedtime was defined as the time between lights off and the first 60 seconds of continuous sleep. Student T tests for dependent measures were used to compare the caffeine and the placebo conditions.

**Results:** Compared to placebo, subjects reported being more alert in the caffeine condition (p=0.03). The PVT also showed significant effects of caffeine. Optimum reaction time (ie, fastest 10% RTs per trial) and the fastest reaction time were

significantly reduced ( $p=0.05$  and  $p=0.01$  respectively) in the caffeine condition compared to the placebo (Figure 1). At bedtime, subject showed a longer sleep latency in the caffeine condition than in the placebo (20 Vs 9 min;  $p=0.04$ ). Spectral power in the theta and lower alpha frequencies of the waking EEG showed no significant difference between the two conditions (Figure 2).

Figure 1

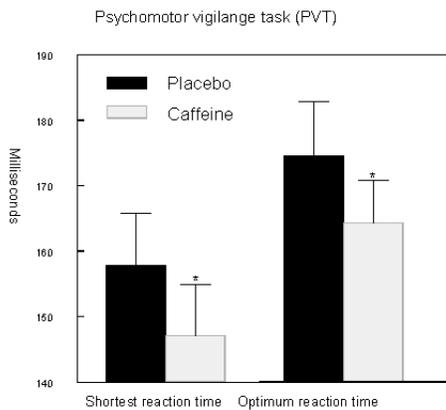
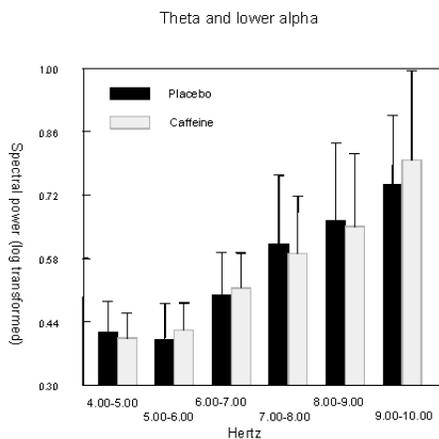


Figure 2



**Conclusions:** Compared to placebo, two doses of 100 mg of caffeine in the evening significantly increased subjective alertness, reaction time on the PVT and sleep latency at bedtime. However, in spite of the previously demonstrated association between the waking EEG and measures of subjective alertness and PVT performance, caffeine did not affect spectral bands of the waking EEG known to best represent modifications in alertness. Further studies should investigate the sensitivity of the waking EEG to detect slight changes in alertness.

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**564.U**

**ANCIENT GREEK PHILOSOPHICAL THEORIES OF SLEEP AND THEIR RELEVANCE TO MODERN SLEEP RESEARCH**

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**Introduction:** The philosophers of Ancient Greece were the first investigators to propose explanations of sleep in the Western tradition. We examined the physiological sleep theories of major philosophers and writers who lived from the 8th to the 4th century BCE with intent to determine the ancient origins of sleep medicine theory and its implications for modern sleep research.

**Methods:** Major works of Homer (*The Odyssey*, *The Iliad*), and Hesiod (*Theogony*, *Works and Days*) were examined in order to provide a background of sleep theory in prephilosophical mythological sources. All ancient literary fragments and testimonies regarding 15 major Presocratic philosophers were surveyed for evidence of sleep process speculation. The 6 philosophers who proposed such theories included Heraclitus (c. 540 BCE), Alcmaeon (c. 500), Anaxagoras (c. 500), Empedocles (c. 492), Diogenes (c. 480) and Democritus (c. 460). Following this the collected works of Plato (c. 427) were surveyed for theories of sleep processes. Relevant treatises of Aristotle (c. 384) were also reviewed (*Physics*, *On the Soul*, *History of Animals*, *On Sleep and Dreams*). All theories were compared, particularly with respect to the type of sleep explanation that was provided.

**Results:** The study of sleep in Ancient Greece reaches its apex in Aristotle, who proposes that any complete explanation of a physical process requires an account of four fundamental causes: the material cause (What physical components does it involve?), the formal cause (How do these components interact?), the efficient cause (What initiates the process?), and the final cause (What is the purpose of the process?). Earlier theories were analyzed within this paradigm. The prephilosophical sources (ie. Homer, Hesiod) focus on the efficient cause of sleep- they stress that sleep is initiated by the Olympian gods. In contrast to these sources, the early Presocratic philosophers focus on the material and formal causes of sleep. They are generally concerned with relating sleep to other biological

states (ie. Wake, Death), and do so by describing how these qualitative states are mediated by a single underlying biological process (eg. humidity of the body, according to Heraclitus). Plato's explanation of sleep is more extensive than those of the Presocratics in that he implicitly deals with all four modes of explanation, linking sleep to his physiological mechanism of perception, and describing it as necessary for health and recuperation. Aristotle, having created the four-pronged approach to physical explanation, works within his own model. His "material explanation" is roughly synonymous with "anatomical explanation" in modern biological terms. Similarly the "formal" and "efficient" explanatory modes can both be associated with modern "physiological" explanations. The "final" cause can be loosely associated with the modern "evolutionary" explanation of sleep.

**Conclusions:** Current multifaceted explanatory theories of sleep and the guiding rational principle for the scientific study of sleep have their explicit origins in Ancient Greece. Aristotle, who identified the material, formal, efficient, and final causes of the sleep process, is the pioneer of current concepts regarding the anatomical, physiological, and evolutionary theories of sleep.

### 565.U

#### ALERTNESS AND COGNITIVE PERFORMANCE BENEFITS ASSOCIATED WITH BRIEF DAYTIME NAPS

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**Introduction:** Recent research indicates that, following mild nocturnal sleep restriction, a 10-min nap may be at least as effective as a 30-min nap, in terms of improved alertness and cognitive performance within an hour of napping(1). This has important applied implications as well as challenging the homeostatic Process S model of sleep. The current investigation sought to extend these initial findings by comparing naps of varying duration for several hours post-nap.

**Methods:** Participants were 16 self-reported good sleepers (M=24.69 yrs, SD=6.67) who participated in a repeated-measures design comprising 5 conditions: no-nap, 5, 10, 20 and 30-min naps, with naps scheduled to terminate at approximately 15:00 hrs. Prior nocturnal sleep was restricted to between 02:00 and 07:00 hrs (M=4.78 hrs, SD=0.20). Objective alertness (sleep latency) was assessed pre-nap, 1, 2 and 3 hours post-nap. Symbol-Digit Substitution Task (SDST), Letter Cancellation Task (LCT) and serial reaction time (RT) performance were assessed prior to napping and at intervals beginning at 5, 35, 95 and 155 minutes post-nap, as were subjective measures of alertness, fatigue and vigour.

**Results:** With regard to objective alertness in the first 2 hrs of post-nap testing, the 10, 20 and 30-min naps produced significant and comparable improvements relative to the no-nap condition ( $p < .05$ ), while the 5-min nap did not differ significantly from no-nap. Three hours after napping there were no significant differences in objective alertness between the five nap conditions. In terms of cognitive performance, the 5-min nap did not differ significantly from the no-nap condition. The

10-min nap significantly improved LCT performance 5 and 35 minutes post-nap, and SDST performance 35 and 95 minutes post-nap, before returning to levels comparable to the no-nap condition. The 20-min nap showed a declining performance trend immediately after napping, followed by significantly improved LCT and SDST performance at 95 minutes post-nap, relative to no-nap. The 30-min nap showed a significant decline in SDST, LCT and RT performance immediately after napping (compared to the 10-min nap), followed by significantly improved LCT performance at 35 and 155 minutes post-nap (compared to no-nap). Subjective alertness, fatigue and vigour showed similar trends to the objective measures for all conditions.

Figure 1

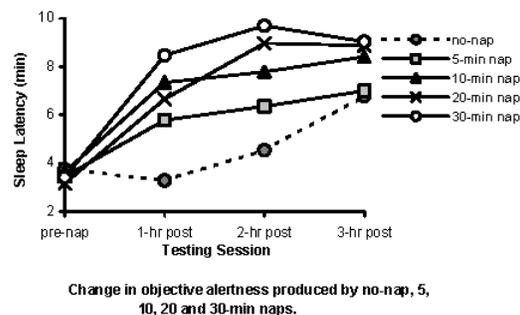
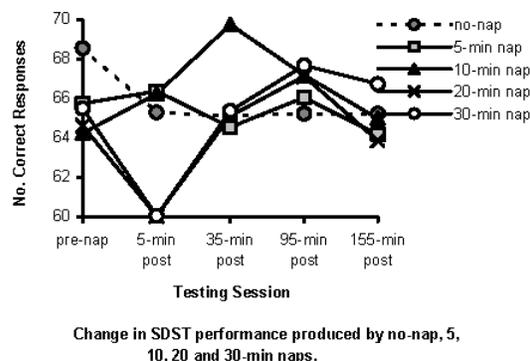


Figure 2



**Conclusions:** These findings suggest that following mildly restricted nocturnal sleep, 10, 20 and 30-min naps improved cognitive performance and objective alertness for at least 95 minutes, while the 5-min nap never varied significantly from no-nap. Immediately after napping, the 10-min nap produced performance benefits, while the 20 and 30-min naps appeared to produce a brief period of sleep inertia. Consistent with our earlier findings, at no time did alertness or performance benefits associated with the 20 or 30-min naps exceed the 10-min nap, suggesting that the benefits of brief naps may arise from processes other than the homeostatic Process S.

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566.U

SLEEP AND BURNOUT

Akerstedt TG,<sup>1</sup> Ekstedt M,<sup>1</sup> Söderström M,<sup>1</sup> Nilsson J,<sup>1</sup> Axelsson J,<sup>1</sup> d'Onofrio P,<sup>1</sup> Kecklund G<sup>1</sup>

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**Introduction:** Burnout has become almost epidemic in many industrialized nations accounts for close to a doubling of health care costs in Sweden during the last five years. The concept mainly involves excessive fatigue, but also a reduced cognitive ability and a reduced empathy with patients, clients, pupils, etc. Frequently, burnout patients also report disturbed sleep. The present study sought to investigate sleep in individuals with high burnout scores, but still at work and to compare them with non-burnout patients.

**Methods:** 20 individuals in an IT company were recruited based on high (2.75) and low scores (1.5) on the Melamed burnout inventory (10 per group) and equal amounts of men and women. The group was recorded for a week using actigraphy, sleep diaries, sleep polysomnography at home during a working day and a day off, ambulatory blood pressure measurements during the 24h after the polysomnography, saliva samples (for analysis of cortisol) during the day after polysomnography. In addition, one blood sample was obtained for analysis of immunological parameters. All subjects gave informed consent and the study was approved by the ethical committee of the Karolinska institute. The results were analyzed using a two-factor ANOVA with repeated measures for weekday/day off.

**Results:** The results showed that the high burnout group did not differ from the low burnout group for most standard sleep variables except for total number of arousals which were significantly higher in the high burnout group (see table). Further analyses showed that the difference was particularly pronounced during the first three hours of sleep. Heart rate was significantly higher in the burnout group (82±6 vs 66±3 beats per minute, F=4.5, p<.05). Blood pressure did not differ. No interactions were significant.

Table 1

	High Work	Low Work	High Off	Low Off	p for F-ratio
TST min	401 ±15	379 ±6	454 ±20	461 ±29	W<.001
Sleep eff %	.87 ±.02	.91 ±.01	.89 ±.01	.91 ±.01	
SWS %	7.05 ±1.37	8.34 ±2.82	6.80 ±1.73	5.53 ±1.37	
REM %	24.4 ±1.7	23.3 ±2.1	23.3 ±2.1	29.4 ±1.9	
Arousals #	12.1 ±1.3	8.0 ±1.4	13.0 ±1.2	8.5 ±1.4	B<.05
Sleep lat min	19.3 ±6.8	14.7 ±1.7	12.1 ±3.3	14.2 ±3.4	

W=difference between working days and days off.

B=Difference burnout - nonburnout.

"Work"=work days, "Off"=days off.

**Conclusions:** The results indicate that sleep in high burnout subjects still at work is not substantially impaired except for a high frequency of arousals.

567.U

EPWORTH SLEEPINESS SCALE OUTCOME IN 2000 ADULT BRAZILIANS

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**Introduction:** The Epworth sleepiness scale (ESS) measures the subjective daytime sleepiness degree. This investigation determines the profile of ESS-measured subjective sleepiness across a population sample of healthy adults by means of: 1. ESS means and the average reported sleep time (RST)2. Prevalence rate of subjects with ESS scores > than 10 points.

**Methods:** ESS was applied to 2000 individuals. Three groups were created: Group A (18-39 years); group B (40 to 59, and C (60 and up). The t test (p=90%) detected statistically significant differences for ESS mean values in females between Groups A versus B and A versus C. No ESS mean score statistical difference was determined among males from Groups A, B and C. There was a mean ESS score statistical difference for females Groups A versus B and A versus C and between males versus females in Group B. The values are portrayed as: mean value (x) ± std. deviation(s).

**Results:**

Table 1

	GROUP A (18-39)		GROUP B (40-59)		GROUP C (60-87)	
N	829 (41.45%)		809 (40.45%)		362 (18.10%)	
ESS > 10	36.8%		29.2%		28.5%	
<b>AVERAGES</b>						
AGE	29.61 ± 5.88		48.82 ± 5.52		67.97 ± 5.92	
ESS	6.11 ± 3.81		7.37 ± 4.40		7.12 ± 5.02	
RST	7.01 ± 1.15 (N=682)		6.82 ± 1.40 (N=675)		7.07 ± 1.45 (N=350)	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
N	416 (50.2%)	413 (49.8%)	417 (51.4%)	392 (48.2%)	164 (45.3%)	198 (54.7%)
ESS > 10	35.1%	38.5%	34.3%	23.7%	29.9%	27.3%
<b>AVERAGES</b>						
AGE	30.34 ± 5.70	28.90 ± 5.94	47.65 ± 5.34	48.41 ± 5.69	68.10 ± 6.19	67.87 ± 5.70
ESS	8.17 ± 4.15	8.41 ± 3.92	7.88 ± 4.38 <b>D</b>	6.83 ± 4.37 <b>D</b>	7.58 ± 4.43	6.73 ± 5.45
RST	6.85 ± 1.05 <b>D</b> (N=281)	7.12 ± 1.20 <b>D</b> (N=401)	6.57 ± 1.38 <b>D</b> (N=236)	7.01 ± 1.39 <b>D</b> (N=339)	7.13 ± 1.43 (N=152)	7.02 ± 1.47 (N=197)

N: Number of subjects; ESS: Epworth Sleepiness Scale; RST: Reported Sleep Time; **D**: Statistical Difference (p=90%)

**Conclusions:** Group A females presents a higher ESS and ESS>=10 prevalence rate when compared with females from groups B and C. This confirms increased ESS-measured degree of sleepiness in younger females from Group A. This is in keeping with a longer sleep need in young pre-menopausal females. Group B males display an elevated ESS>=10 prevalence rate as compared with females. Additionally, a statistically significant difference for mean ESS between genders in group B and the presence of group A versus B=C and the mean ESS difference in females (group B females showed lower mean ESS) were recorded. Higher prevalence of sleep-related breathing disorders in middle-aged males, hormonal changes brought about by menopause and insomnia in middle-aged females may account for these findings. ESS-measured subjective sleepiness shows a trend for decreased sleepiness index in middle-aged females.

**References:**

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**568.U**

**SLEEP IN SOUTH AFRICAN UNIVERSITY STUDENTS: INFLUENCE OF STUDY AND LIFESTYLE**

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**Introduction:** University (college) students are exposed to academic and social demands that impact on their sleep; students as a group worldwide are sleep deprived<sup>1</sup>. It still is not clear, however, to what extent lifestyle and university work pressures may influence sleep in male and female students of different ethnic groups, particularly in South Africa. We therefore conducted an exploratory study to investigate the influence on sleep of factors such as university work, caffeine consumption, and exposure to traumatic events in South African students.

**Methods:** We collected questionnaires about sleep, work and daytime habits over the previous month, from 986 students (21±3 y; 53% female), of different ethnicities (39% Caucasian; 40% Black; 15% Indian; 2% Coloured), in their second year of study at a South African university.

**Results:** The students reported an average (SD) time in bed of only 7h22min (1h12min). 54% of the students thought that this amount was insufficient, the majority of whom (42%) reported that studying for university courses was the main cause. Male and female students reported spending similar amounts of time studying for their university courses, which also did not differ according to ethnic group. Students who spent more than 20 hours per week on extra work for university were more likely to go to bed later ( $\chi^2(6)=35.5$ ,  $P<0.001$ ) and spend less time in bed (ANOVA  $F_{s2,775S}=38.8$ ,  $P<0.001$ ) compared to students who worked less than 10 hours per week. Finally, 34% of students, and more females than males ( $\chi^2(3)=12.6$ ,  $P=0.006$ ), reported that worrying about university work often impacted negatively on their sleep. Interestingly, most students (69%) thought that better sleep would improve everyday functioning and 77% of students wanted more information about sleep. Not only did academic work influence sleep, so did daytime behaviors. Male and female students who drank at least five cups of caffeinated beverages per day were more likely to have a poorer sleep quality ( $\chi^2(2)=10.7$ ,  $P=0.005$ ) and spend less time in bed (ANOVA  $F_{s2,803S}=5.4$ ,  $P=0.005$ ) compared to students who had little or no caffeine. Most students (76%) napped, with 17% of students reporting that they napped often. Male and female students were equally likely to nap, but Black students were more likely to nap than were Caucasian students ( $\chi^2(3)=18.3$ ,  $P<0.001$ ). Napping, however, was not significantly associated with time in bed. Finally, an alarming proportion of students (18%) had experienced a traumatic event, which affected their sleep; these students were more likely to have a sleep onset latency greater than 45 minutes ( $\chi^2(3)=8.9$ ,  $P=0.03$ ) and a poorer sleep quality

( $\chi^2(1)=7.9$ ,  $P=0.005$ ) than were other students.

**Conclusions:** The high workload at university negatively impacts on sleep duration, regardless of gender or ethnicity. South African students need to be educated about better sleep habits that will help them to maximize their already-reduced sleep time. Also, young South Africans are exposed to a high incidence of traumatic events, which negatively influences their sleep, and which supports the recommendation of others<sup>2</sup> for trauma intervention in these students.

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(2) Peltzer K. Traumatic experiencing and post traumatic psychological symptoms in South African University students. *Cent Afr J Med*, 1998, 44:280-283.

Wednesday, June 12

## 569.A

## DIFFERENT PATTERNS OF ELECTRICAL STIMULATION OF THE PONTINE RETICULAR FORMATION RESULT IN LONG-LASTING, DIFFERENTIAL EFFECTS ON REM SLEEP AND WAKEFULNESS

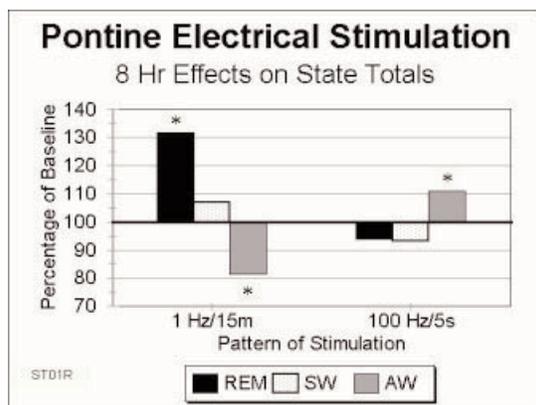
Marks GA,<sup>1</sup> Birabil CG<sup>1</sup>

(1) University of Texas Southwestern Medical Center

**Introduction:** Pharmacological inhibition of cAMP production in the caudal, oral pontine reticular formation (PnOc) of the rat results in a long-lasting increase in the expression of REM sleep (1). We hypothesize that a transient inhibition of cAMP produces long term intracellular changes responsible for the long-lasting modulation of REM sleep and that this mechanism also underlies similar REM sleep-induction by adenosine A1 and muscarinic m2 or m4 agonists injected into the PnOc. Long term neuromodulation in the forms of depression (LTD) and potentiation (LTP) can be produced in various brain regions chemically and by electrical stimulation. Production of LTD is associated with the inhibition of cAMP and can be induced by low frequency electrical stimulation. If a form of LTD underlies the REM sleep modulation by cAMP inhibition, then low frequency electrical stimulation of the PnOc may result in long-lasting REM sleep augmentation. High-rate, tetanic stimulation can induce LTP associated with increases in cAMP. This pattern of electrical stimulation should not be effective in increasing REM sleep.

**Methods:** Under anesthesia, Long-Evans Hooded rats were surgically prepared for chronic sleep recording and additionally implanted, bilaterally, with bipolar stimulating electrodes aimed at the PnOc. The stimulation procedure was conducted within one hour after lights-on (12/12) with one week between experimental conditions. Animals were removed from their cage and placed in a lighted box for 15 min while receiving single pulses unilaterally either at a rate of 1 Hz for 15 min or 100 Hz for 5 sec. Four trials of sham stimulation served as baseline control. Following stimulation, animals were placed back in their home cage and recorded for eight hours.

Table 1



**Results:** When electrodes were located in the PnOc, the 1 Hz stimulation resulted in significant increases in REM sleep during the post, eight hour recording period compared to control. The increase was similar to that observed with cAMP inhibition in that it was predominantly due to increased REM period frequency, accompanied by decreases in wakefulness and no reduction in REM latency. The 100 Hz stimulation resulted in significant increases in wakefulness with smaller reductions in both REM and slow wave sleep.

**Conclusions:** These data indicate the presence of activity-dependent mechanisms in the pontine reticular formation subserving the long term modulation of both REM sleep and wakefulness. These mechanisms may be dependent on alterations of cAMP in the induction of LTD and LTP.

**References:**

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Research supported by NIH grant RO1 MH57434

## 570.A

## HYPOCRETINERGIC IMMUNOREACTIVITY AND IN VITRO EFFECTS OF HYPOCRETIN IN THE NUCLEUS PONTIS ORALIS OF THE GUINEA PIG

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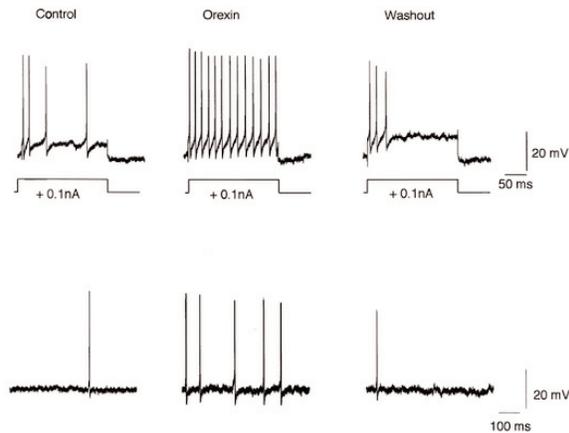
**Introduction:** In the present study we examined the innervation of neurons of the nucleus pontis oralis (NPO) in the guinea pig by hypocretinergic fibers and terminals and the effects of this peptide on neurons within this structure, which is critical for the control of wakefulness and active sleep.

**Methods:** Four adult guinea pigs were employed for immunohistochemical studies. The animals were perfused transcardially with a fixative containing 4% paraformaldehyde, 15% saturated picric acid and 0.25% glutaraldehyde in 0.1 M phosphate buffer. Frozen sections of the brain stem were obtained with a cryostat and processed for the immunohistochemical detection of hypocretin peptides, as previously described (Pose et al., 2000). For electrophysiological studies, brain stem slices were obtained from adult guinea pigs (see Pedroarena et al., 1999). Intracellular recordings with sharp microelectrodes were obtained from neurons in the NPO at a level approximately 0.5 mm rostral to the trigeminal motor nucleus. The excitability and basic electrophysiological properties of NPO neurons in this region were examined prior to, during and after bath and/or micropressure application of hypocretin.

**Results:** The cell bodies of NPO neurons are of different size. They range from small (10-15  $\mu$ ) to medium-large (20-30 $\mu$ ) sized. Most NPO neurons are innervated by hypocretinergic fibers (see Zhang et al., APSS Abstracts, 2002). Hypocretinergic fibers in this nucleus were thin (0.2 to 0.5 $\mu$ ) and typically

displayed varicosities along their trajectory. In many instances, varicose hypocretinergic fibers ended in bouton-like structures in close apposition to the soma and/or proximal dendrites of NPO neurons. Most fibers ended in small neurons in this nucleus. Hypocretin had strong excitatory effects on NPO neurons; it consistently produced a decrease in rheobase accompanied by an increase in input resistance. In those neurons which exhibited spontaneous discharge, hypocretin increase the frequency of discharge. The typical effects of hypocretin on a NPO neuron are shown in Figure 1.

Figure 1



**Conclusions:** The present data reveal that hypocretinergic fibers and terminals are located in close apposition to morphologically differentiated neurons in the NPO. This, in turn, indicates that there is hypocretinergic innervation of different types of phenotypically differentiated neurons in this nucleus. In ongoing experiments we have collected preliminary evidence indicating that hypocretin fibers innervate GABAergic and glutamatergic NPO neurons which are two of the most abundant types of neurons in this nucleus. In the present study we have begun examining the types of responses hypocretin elicits from NPO neurons, which were consistently excitatory. The fact that hypocretin elicits an increase in input resistance suggests that this peptide suppresses a potassium conductance in these cells. The present data, which reveal hypocretinergic excitatory innervation of both inhibitory and excitatory cells in this nucleus, also indicates that hypocretin plays a role in the control of behavioral states that are regulated by the nucleus pontis oralis.

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## 571.A

### POWER SPECTRAL ANALYSIS OF CORTICAL EEG IN MICE DEVOID OF PRP

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**Introduction:** Transmissible spongiform encephalopathy (TSE) is a neurodegenerative disorder characterized by abnormal accumulation of abnormal prion protein (PrP) or scrapie (PrPSc). Fatal familial insomnia (FFI) is one of the genetic PrP diseases in humans. Like TSE, in FFI there is a significant reduction of sleep, loss of neurons and astrogliosis. It is still unclear whether these changes are a consequence of loss of normal PrP protein function or the accumulation of abnormal prion protein. Because of the potential involvement of prion in sleep processes (1, 2), we investigated the effects of removing PrP on power spectra and event related evoked potentials (ERP).

**Methods:** We characterized sleep patterns in mice whose PrP gene was knocked out (KO), and C57BL/10 mice (wild type) as a control group. Animals were implanted with a set of electrodes for sleep recording. One week after surgery they were habituated to the recording conditions for 72h. The electroencephalogram (EEG) was scored for 24 h. Fast Fourier analysis was performed in 6 sec epochs during wakefulness (W), slow-wave sleep (SWS) and rapid eye movement (REM). To characterize the sensory profile of these mice, we studied brainstem (BAEPs), cortical visual (VEPs), as well as midlatency auditory (MLAEPs) evoked potentials. The evoked potentials were recorded and averaged peak latencies were calculated between animals and as group means using an ANOVA.

**Results:** PrPKO and wild type mice showed no significant differences in the frequency and total amount of W, SWS, or REM sleep. However PrPKO mice showed a different REM sleep distribution and a significantly greater percentage of REM sleep during the second half of the dark period. A decrease in the percentage of relative power was found in REM sleep in the 3.0-8.0 Hz bandwidth range ( $p < 0.05$ ). A significant increase in the percentage of relative power was found also in REM sleep in the 8.0-12.0 Hz bandwidth range ( $p < 0.05$ ). Also, a significant increase in relative power was found in SWS sleep in the 12.0-30.0 Hz bandwidth range ( $p < 0.05$ ). Compared to control mice, the latencies of the wave N2 of VEPs is significantly shortened in PrPKO mice ( $p < 0.01$ ). Likewise, PrPKO mice showed a significant reduction in the latency of waves P2 and P6 of BAEPs ( $p < 0.01$ ).

**Conclusions:** These data suggest that absence of PrP produces different effects in the power spectral profile of the EEG during SWS and REM sleep. These effects may underlie the changes found in the sleep patterns of the KO mice compared to controls. Also, sensory projections may be altered in PrPKO mice.

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## 572.A

### SELECTION OF SHORT-"SLEEPING" FLIES

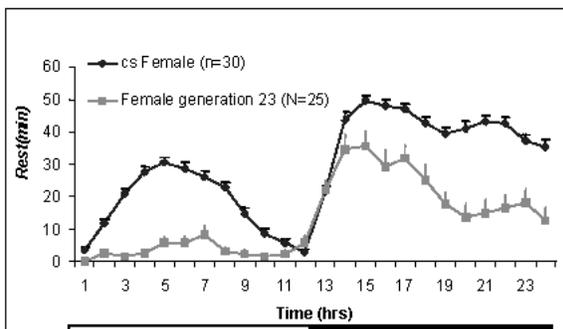
Israel SL,<sup>1</sup> Shaw PJ<sup>1</sup>

(1) The Neurosciences Institute

**Introduction:** Although little is known about the molecular basis of sleep, studies in mammals indicate that mechanisms involved in sleep regulation are under the control of genetic factors and are heritable<sup>1</sup>. Nonetheless, the ability to link complex phenotypes to single genes has been somewhat limited. Indeed, several studies indicate that small gene effects can give rise to large behavioral differences<sup>2</sup>. Laboratory selection provides an excellent paradigm for modeling natural selection, generating multiple small gene interactions which are now amenable to fine scale molecular analysis. With that in mind, we initiated a selection study to identify phenotypic extremes characterized by reduced amounts of daily rest.

**Methods:** Daily rest was evaluated in 3 day old female Canton (Cs) flies maintained at 25 °C, under a 12hr:12hr light:dark cycle using the *Drosophila* Activity Monitoring System (Trikinetics) as previously described<sup>3</sup>. Flies were monitored for 72 hours and females resting less than 400 min/day were selected and bred with male flies resting less than 500 min/day. In subsequent generations, the criteria were tightened such that only female flies resting fewer than 150 min/day were selected while total amounts of rest could not exceed 250 min/day in male flies. Cs flies that did not undergo the selection process served as a comparison group.

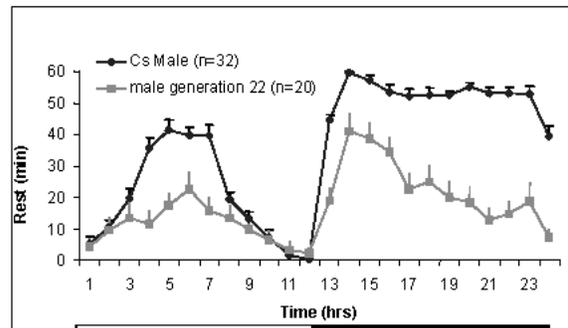
Figure 1



**Results:** The mean amount of daily rest in selected female flies gradually declined from 700 min/day to 312 ± 34 min/day ( $p < .01$ ; Figure 1). Mean daily rest also declined from 859 ± 45 min/day to 402 ± 58 min/day in male flies ( $p < .01$ ; Figure 2). Figures 1 and 2 show the number of minutes of rest per hour

for each hour of the 24 hour day for selected flies and their controls.

Figure 2



**Conclusions:** Laboratory selection was effective in dramatically reducing the requirement for daily rest in *Drosophila melanogaster* and likely reflects the natural interactions of genes involved in the regulation of rest. Future studies will explore the interactions of these genes using QTL analysis and cDNA microarrays.

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## 573.A

### IN VITRO EFFECTS OF CHOLINERGIC, NITRIC OXIDE, ADRENERGIC AND GABAERGIC NEUROTRANSMITTERS AND MODULATORS ON NEURONS OF THE NUCLEUS PONTIS ORALIS IN GUINEA PIGS

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**Introduction:** The present study is part of a long term project to examine the circuitry and neurotransmitters as well as the biochemical and electrophysiological phenotype of neurons of the nucleus pontis oralis (NPO) vis a vis the generation and/or control of wakefulness and active sleep (AS). The NPO is a brain region critical for the occurrence of AS; there is also emerging evidence that suggests an important role of this nucleus in waking mechanisms (Xi et al., 1999). The present study focuses on a restricted region of the NPO in guinea pigs that we have previously determined to be the most efficacious for the induction of AS by cholinergic stimulation and for the induction of wakefulness by the activation of GABAergic mechanisms. In addition to being innervated by cholinergic

processes, NPO cells are innervated by nitrergic, adrenergic and GABAergic fibers (Morales et al., APSS Abstracts, 2002). Accordingly, we examined the effects of these different neurotransmitters/modulators and/or of their agonists on neurons in the NPO.

**Methods:** Brain stem slices, obtained from adult guinea pigs, were used for the present study. The methodological procedures have been previously described (Pedroarena et al., 1999). Intracellular recordings with sharp microelectrodes were obtained from neurons located in the NPO at a level just rostral to the trigeminal motor nucleus. The excitability and basic electrophysiological properties of NPO neurons were examined prior to, during and after the bath application of the following substances: carbachol, DETA-NO (as a NO donor), adrenergic agonists and muscimol.

**Results:** The response of NPO cells to carbachol was excitatory or inhibitory depending on the cell recorded. Excitatory effects consisted either of an increase in the frequency of discharge and/or a decrease in rheobase, whereas the inhibitory effects ranged from a decrease in the frequency of discharge to the complete elimination of spike generation; rheobase was also increased in these neurons. NO-donors induced an excitatory response consisting of depolarization and an increase in neuronal discharge. Noradrenergic agonists increased the excitability of these cells via alpha receptors. In all cases, muscimol had a strong inhibitory effect; following its application, neurons ceased discharging throughout the remainder of the recording period (in some cases up to 30 minutes after washout). Interestingly, after the application of muscimol, the excitatory effects of carbachol, DETA-NO and/or adrenergic agonists were no longer present.

**Conclusions:** The present data are interpreted based upon the known or presumed behavior, during AS, of cholinergic-nitrergic neurons in the LDT-PPT, noradrenergic neurons in the locus coeruleus and GABAergic neurons within the NPO. A portion of the cholinergic-nitrergic neurons discharge during AS. Our data suggest that this may result in the synergistic activation of these cells by acetylcholine muscarinic receptors and an increase in cGMP mediated by NO activation of a soluble guanylyl cyclase. This activation, we postulate, compensates for the withdrawal of noradrenergic effects on NPO neurons due the cessation of their discharge during AS. In addition, we found that a subpopulation of NPO neurons are inhibited by carbachol. It is possible that they are wake-executive neurons that are expected to be inhibited during AS. Strong GABAergic inhibitory effects provide a cellular basis for our findings that GABA, microinjected in the NPO, results in wakefulness, which occurs as a result of the inhibition of AS on executive neurons in this nucleus. Our data indicate that different systems of neuromodulators, acting on different intracellular signaling mechanisms, can modify the pattern of discharge and the excitability of nucleus pontis oralis neurons in the guinea pig.

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### 574.A

#### INNERVATION OF NEURONS IN THE NUCLEUS RETICULARIS PONTIS ORALIS OF THE GUINEA PIG

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**Introduction:** In the present study we examined the morphological characteristics and the neurotransmitter phenotype of neurons within the nucleus pontis oralis (NPO) of the guinea pig. As in other mammals in this species the NPO is a critical region for the generation of active sleep (AS) as evidence by microinjection of cholinergic agonists and for the induction of wakefulness (W) by the activation of GABAergic mechanisms (Tortero et al., APSS abstracts, 2002). In addition, we examined the innervation of neurons within this nucleus regarding the different neurotransmitters and/or neuromodulators contained in afferent terminal fibers.

**Methods:** Ten adult guinea pigs were employed for immunohistochemical studies. The animals were perfused transcardially with a fixative containing 4% paraformaldehyde, 15% saturated picric acid and 0.25% glutaraldehyde in 0.1 M phosphate buffer. Frozen section of the brain stem were obtained with a cryostat and processed for the immunohistochemical detection of hypocretin peptides, as previously described (Pose et al., 2000).

**Results:** The great majority of small cells were GABAergic. These neurons were intersped among all other neurons in the NPO. Most medium-large neurons displayed glutamate-like immunoreactivity. In a number of large neurons we were unable to identify their neurotransmitter phenotype. Glutamatergic cells tend to be concentrated in the ventral portions of the NPO. Interestingly, glycinergic and a small number of serotonergic neurons, whose function is unknown were also observed in the NPO. NPO neurons were innervated by fibers containing cholinergic, nitrergic, hypocretinergic, serotonergic, noradrenergic, GABAergic, and glycinergic-like immunoreactivity. These fibers displayed varicosities along their trajectories and appeared to end in bouton-like structures in close apposition to the somas and/or proximal dendrites of NPO neurons. Interestingly, it appeared that most hypocretinergic fibers projected to small GABAergic neurons. With respect to the other phenotypically identified fibers we did not detect any preferential distribution for any group of neurons.

**Conclusions:** The present data are the structural foundation for our electrophysiological studies on the action of neurotransmitters in both the in vivo and/or in vitro preparations in the guinea pig (See for example, Xi et al., Morales et al., Pose et al., and Chase et al., APSS abstracts, 2002) vis a vis behavioral studies. The complement of different neurotransmitter

systems impinging upon NPO neurons indicate a complex control of these cells during different behavioral states.

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**575.A**

**THE GUINEA PIG AS A MODEL SPECIES FOR MODERN NEUROSCIENCE RESEARCH**

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**Introduction:** My real name is *cavia porcellus*, but almost everyone calls me “guinea pig”. I am writing this abstract because I believe that I may be an ideal species for neuroscience and especially sleep research. I am a precocial animal, so my sleep mechanisms are well-developed at birth. My lifespan is short enough so that it is possible to examine age-documented changes, which is not feasible in long-lived species. The duration and frequency of my episodes of active sleep during head restraint are comparable to that which occurs when I am unrestrained (Escudero et al., 1996). I can be used with the Rechtschaffen disc-above-water apparatus for sleep deprivation; on the other hand, give me a running wheel and I can get aerobic exercise while investigators monitor my motor behavior. I also look elegant wearing an actigraph for activity measures. Neither the cat, rat, mouse or dog are able to be employed in conjunction with all of the preceding techniques and procedures. My skull, which is stronger than that of the rat or mouse, can be used to secure recording electrodes, dialysis probes, and other devices. My tentorium cerebelli is not calcified as it is in the cat, which permits a vertical descent for electrodes into critical sleep-related brainstem nuclei. But how is my sleep (especially active REM) regulated? Can active sleep be induced by injecting cholinergic agonists into the nucleus pontis oralis, which is difficult to accomplish in the rat, but is well established in the cat?

**Results:** Eight of my species were anesthetized with urthane; subsequently, carbachol (0.05 to 0.1µl in 4 µg/µl of saline) was microinjected into the nucleus pontis oralis. Compared with control injections of saline, an active sleep-like state consisting of EEG desynchronization, atonia, and hippocampal theta activity occurred with a latency of 1 to 3 minutes and lasted for approximately 20 minutes. Utilizing this technique, others have begun a study of GABAergic interactions in this nucleus vis-à-vis the control of sleep and wakefulness (Torterolo, et al., APSS Abstracts, 2002) which are coordinated with data from the slice preparation (see Pose, et al., APSS Abstracts, 2002); in addition, an analysis of the hypocretinergic system reveals that it is comparable to that of the cat and rat (Zhang, et al., APSS Abstracts, 2002).

**Conclusions:** I can modestly state that there are no other

species that can be used in as many cross-disciplinary procedures as myself. In vitro slice studies, in vitro acute and in vivo chronic experiments (including intracellular recording) can be undertaken, thus avoiding the almost insurmountable problems involved in relating data obtained with different techniques in different species. The discovery of similarities in sleep mechanisms will reinforce the importance of the preservation of the process in question, and the discovery of differences will provide new perspectives on how the nervous system can perform its functions. I therefore believe that my species may be ideal for studies of sleep and wakefulness.

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**576.A**

**EFFECTS OF NMDA ON THE ADENOSINE ACTIVITY IN THE LDT CHOLINERGIC NEURONS**

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**Introduction:** Adenosine has been proposed as a “sleep factor” that regulates the transition from waking to sleep. Adenosine promotes sleep and increases EEG slow wave activity in a manner similar to that observed at the onset of sleep (1), whereas adenosine antagonists, such as caffeine and theophylline, suppress sleep. Cholinergic neurons of the laterodorsal tegmentum (LDT) are known to be involved in EEG arousal and thalamocortical activation during REM sleep. It was previously shown that the glutamate receptor agonist N-methyl-D-aspartate (NMDA) caused an A1 adenosine receptor mediated presynaptic depression of excitatory synaptic transmission in CA1 region of guinea pig hippocampal slices by increasing extracellular adenosine concentration (2). Arrigoni et al. (3) showed that adenosine reduced spontaneous glutamatergic miniature excitatory postsynaptic currents (mEPSCs) frequency in the LDT neurons, without affecting the amplitude, a pre-synaptic inhibition. We investigated an NMDA-evoked increase in adenosine-mediated pre-synaptic inhibition in the LDT slice preparation.

**Methods:** In vitro electrophysiological recordings using the blind whole-cell patch-clamp technique were performed to assess the responses of LDT/PPT cholinergic neurons to NMDA and adenosine A1 receptor antagonist 8-cyclopentyltheophylline (CPT) on spontaneous glutamatergic mEPSCs. Coronal slices containing the LDT/PPT were obtained from male Long Evans rats (21-30 d old). mEPSCs were recorded in the presence of TTX (1 µM).

**Results:** NMDA (10 µM) reduced mean mEPSC frequency (5.94±0.83 Hz in control; 4.50±0.61 Hz in NMDA; paired t

test,  $p < 0.001$ ) with no significant effect on the mean of mEPSC amplitude ( $8.11 \pm 0.62$  pA in control;  $7.89 \pm 0.60$  pA with NMDA; paired t test;  $p = 0.062$ ). CPT ( $1 \mu\text{M}$ ) blocked the NMDA induced reduction with no effect on either frequency or amplitude ( $5.20 \pm 1.08$  Hz in CPT;  $4.50 \pm 0.61$  Hz in CPT+NMDA; paired t test,  $p = 0.285$ ;  $6.96 \pm 0.63$  pA in CPT;  $7.17 \pm 0.60$  pA with CPT+NMDA; paired t test;  $p = 0.502$ ).

**Conclusions:** NMDA was able to reduce mEPSC frequency with no effect on the amplitude in LDT cholinergic neurons, indicating a presynaptic site of action on glutamatergic afferents. CPT was able to block the NMDA inhibition without significant effect on mEPSC frequency. These findings suggest that NMDA activation might inhibit LDT neurons and facilitate the transition to NREM sleep by increasing adenosine concentration.

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**577.A**

**EFFECTS OF ANANDAMIDE AND OLEAMIDE ON THE SLEEP-WAKING CYCLE DEPEND ON DIURNAL VARIATIONS**

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**Introduction:** Anandamide and oleamide are lipids that bind to the cannabinoid receptor 1 (CB1R). Anandamide and the CB1R are located in the hippocampus, brainstem and hypothalamus<sup>2</sup>. In addition, anandamide induces NREM and REM sleep in rats<sup>3, 4</sup>. In turn oleamide increases NREM and decreases REM sleep<sup>5</sup>. Both anandamide and the CB1R exhibit diurnal variations, with a maximum expression of anandamide and the lowest expression of the CB1R at 01:00am; and the opposite expression at 01:00pm<sup>6</sup>. This evidence suggests that, the effects of anandamide and oleamide on the sleep-waking cycle depend on diurnal variations.

**Methods:** Eleven male rats (250-300) were maintained under a controlled light-dark cycle (lights on: 08:00am), and food and water ad libitum. The subjects were implanted for standard sleep recordings. One week after surgery, rats were divided into three groups and were ip injected with either: vehicle ( $n=4$ , a 5% solution of ETOH in saline), anandamide ( $n=4$ , 4mg/kg), or oleamide ( $n=3$ , 4mg/kg). The polysomnographic recordings started immediately after injection, and lasted for

four hours. The same procedure was followed during the light and the dark phase of the cycle.

**Results:** Anandamide induced a significant reduction of both waking and REM sleep while increasing NREM sleep during the light phase. Anandamide increased NREM and REM sleep during the dark phase of the cycle. Regarding oleamide, it induced a significant decrease of waking and an increase of NREM sleep during the dark phase. No changes were observed during the light phase of the cycle.

**Conclusions:** Our data indicates that endocannabinoids play a role in the regulation of vigilance. In particular by regulating the generation of NREM and REM sleep. These effects seem to depend on diurnal variations.

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**578.A**

**THE ROLE OF ADENOSINE A1 RECEPTORS IN SLEEP AND BEHAVIORAL AROUSAL; FOCAL GENE DELETION USING THE CRE-LOXP SYSTEM.**

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**Introduction:** A1 receptors play an important role in promoting sleep, but it is unknown which regions mediate this response. We have developed a technique to knock out A1 receptors in specific brain regions employing the Cre-loxP system. Previously, we investigated the role of A1R in sleep using a constitutive A1R knockout mouse (A1R\_KO). During the 24 hrs (baseline), the A1R\_KO mice slept 11% less than their wild type sibs. The KO's also showed greater amounts of sleep after sleep deprivation as compared to WT sibs due to slower rate of recovery to baseline sleep levels. In the A1R\_KO mice, power spectral analyses showed that the ability to increase delta power from waking to sleep is diminished. Furthermore, the percent increase in delta power following sleep deprivation compared to baseline was significantly reduced in KO mice (60% in WT and 8% in KOs). Now we have created a transgenic mouse line that we can use to study the role of A1R more precisely. In the cre-loxP system, the bacteriophage enzyme Cre recombinase recognizes loxP

sequences and causes a recombination, removing the DNA between loxP sequences. We are using stereotaxic injections of adeno-associated (AAV) viral vectors to directly introduce Cre recombinase into specific regions of the mouse brain.

**Methods:** The Cre-loxP system employing AAV-cre was validated using lacZ reporter mice. These mice contain a transgene coding for B-galactosidase (B-gal) with a stop sequence flanked by loxP sequences (floxed). Upon exposure to Cre the stop sequence is deleted and B-gal is produced. Mice were allowed to recover for 2 weeks after stereotaxic microinjection of AAV-cre. Transgenic mice were then created in which the coding exon 5 of the A1 receptor is floxed by loxP sites. Two different experimental approaches will be used. First, with bilateral AAV-cre microinjections, we will compare floxed A1R mice to their wild type (WT) siblings on general behavioral measures such as total time sleeping and sleep rebound after mild sleep deprivation. Second, unilateral injections will allow us to use the mouse as its own control for EEG recordings during baseline and after sleep deprivation.

**Results:** Stereotaxic injection of AAV-cre into localized regions of lacZ reporter mice induces long-lasting, robust expression of cre in neurons localized near injection sites. These neurons express B-gal indicating transfection and recombination by AAV-cre. Stereotaxic injection of AAV-cre in A1 floxed mice induces long-lasting robust decreases in A1 expression as measured by in situ hybridization and autoradiography. Preliminary behavioral data with these mice will be presented.

**Conclusions:** From the data obtained using A1\_KO mice, we conclude that A1R is important to facilitate both the transition from waking to sleep and the generation of delta power. We expect that local deletion of A1R in basal forebrain cholinergic arousal centers will result in, among other measures, increased time awake. The development of this transgenic mouse model allowing local deletion of the A1 receptor will allow us to further decipher its role in sleep and behavioral arousal. This technique for focal gene deletion should also be extremely useful in a variety of other studies.

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### 579.A

#### THE EFFECT OF ANANDAMIDE AND OLEAMIDE ON THE P300 POTENTIAL IN THE RAT DEPENDS ON THE LIGHT-DARK CYCLE

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**Introduction:** P300 is an electrophysiological response of the brain associated with the detection of novelty, surprise or salient environmental stimuli. P300 potential alteration is correlated with an attentional deficit. On other hand, Anandamide and Oleamide have been described as endogenous molecules that bind to the CB1 receptor whereby causing effects on locomotion, memory and sleep similar to those induced by D9 THC. Recently, data obtained by our group has described diurnal variations of CB1R expression (maximum at 13:00 PM

and minimum at 1:00 AM). The expression has a correlation with the minimum and maximum (respectively) behavioral activity in the rat. The effect of Anandamide and Oleamide on the CNS can be variable, depending on the time-point of the day.

**Methods:** We use 15 Wistar rats implanted for electrophysiological recordings and were evaluated in a passive auditory detection task. Both P300 and a Brainstem auditory evoked potential (BAEP) were recorded 15 minutes after Anandamide (4mg/kg), Oleamide (4mg/kg) or the vehicle (Saline 95% + Etoh 5%) ip. injection at 1:00 AM or at 13:00 PM.

**Results:** Our results show that Oleamide produces a significant decrease on the amplitude of P300 potential at the 13:00 PM and 1:00 AM, while Anandamide only produces a significant decrement at the 13:00 PM and has no effect at 01:00 AM. On the other hand, the BAEPs exhibited only a significant amplitude reduction on V component. These results suggest the importance of the endocannabinoids on the regulation of mechanisms of arousal therefore on the capacity to attend environmental stimuli.

**Conclusions:** Oleamide seems to induce an effect that does not depend on diurnal variations; while Anandamide effects seem to depend on such variations. Anandamide's effect also correlates with the maximum expression of the receptor.

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### 580.A

#### SEVERELY DISORDERED SLEEP/WAKE CYCLE IN KV3.1/KV3.3-DEFICIENT MICE

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**Introduction:** The Kv3 family of voltage-gated K<sup>+</sup>-channels influence the rapid repolarization of neurons following initiation of the action potential and are implicated in controlling high-rate firing and neurotransmitter release. Two members of this family, Kv3.1 and Kv3.3, are often coexpressed in neurons and, within their distribution in brain, these neurons reside in structures implicated in the mechanisms of sleep and waking. Thus, alteration in the function of these Kv3 channels have the potential to impact the expression of sleep/wake behavior. Mice with gene-targeted null mutations for subunits of Kv3.1 and Kv3.3 channels, individually, express relatively subtle phenotypic differences compared to wild-type controls. In combination, however, the double-knockout (DKO) displays severe myoclonus and tremor as well as a significant

increase in constitutive motor activity. Inasmuch as DKO mice spend a higher proportion of time active, it suggests that sleep/wake behavior also is altered in these mice. We now show in electrographically monitored animals that Kv3.1/Kv3.3 DKO mice have profound alterations of their sleep/wake cycle.

**Methods:** Male, DKO mice (n=9) were compared to their double heterozygous mutant (DHET) (n=14) and wild-type (WT) (n=12) siblings. All animals were instrumented for chronic sleep recording including the cortical and hippocampal EEG, and nuchal EMG. Following recovery from surgery and adaptation to the recording environment, mice were recorded for 24 hours on a 12/12 light/dark cycle. The records were visually scored in 15-sec epochs into wake, SW sleep and REM sleep. Hourly amounts of each stage were determined as well as period frequencies and durations. Spectral analysis was performed on cortical EEG samples obtained from the second hour after lights-on.

**Results:** The sleep/wake behavior of DKO mice was significantly different from DHET and WT on a variety of parameters. Consistent with activity measures, DKO mice slept 40% and 22% less in the light and dark, respectively. Both SW and REM sleep were reduced. SW sleep was reduced due to a large shift to short duration periods, in spite of a tendency to increase period frequency. The reduction in REM sleep was restricted solely to the light and was due to a large reduction in period frequency. The frequency distribution of REM period durations in DKO mice was bimodal indicating a distinct and differential suppression of short- compared to long-duration REM periods. The power spectra of the cortical EEG of DKO mice showed a large increase in the gamma band compared to DHET and WT mice. This increase appeared in all states and was most pronounced in SW sleep.

Table 1

	WT (12)		DHET (14)		DKO (9)	
	Light	Dark	Light	Dark	Light	Dark
<b>Total Sleep (%)</b>						
wake	37.3 ± 4.9	57.9 ± 6.1	39.5 ± 1.5	56.6 ± 5.7	62.3 ± 8.3	65.7 ± 9.7
SW	52.8 ± 4.2	37.1 ± 5.3	49.2 ± 1.1	37.6 ± 4.7	31.4 ± 4.4	29.5 ± 5.4
REM	9.7 ± 1.4	5.0 ± 1.3	11.3 ± 0.8	5.7 ± 1.3	6.2 ± 1.0	4.8 ± 0.8
<b>Period Duration (min)</b>						
wake	1.91 ± 0.21	4.12 ± 0.70	1.80 ± 0.12	3.11 ± 0.30	2.33 ± 0.22	3.14 ± 0.50
SW	2.11 ± 0.20	2.14 ± 0.23	1.97 ± 0.10	1.84 ± 0.12	1.19 ± 0.12	1.21 ± 0.22
REM	1.00 ± 0.08	1.24 ± 0.09	0.98 ± 0.05	1.04 ± 0.07	1.86 ± 0.19	1.81 ± 0.28
<b>Period Frequencies</b>						
wake	165.0 ± 20.1	127.6 ± 14.8	163.0 ± 8.2	147.5 ± 15.1	203.7 ± 19.2	178.6 ± 25.3
SW	192.1 ± 12.9	139.0 ± 15.2	187.8 ± 11.4	158.8 ± 15.1	200.1 ± 14.2	188.8 ± 26.2
REM	78.0 ± 10.5	30.7 ± 3.3	87.6 ± 8.9	41.2 ± 3.9	26.2 ± 2.6	21.0 ± 2.7

**Conclusions:** The combined disruption of function of Kv3.1 and Kv3.3 channels results in a severe alteration of sleep/wake behavior. DKO mice express a poor ability to maintain SW sleep. This may be related to a chronically increased CNS activation reflected in the increased high-frequency activity of the EEG and motor hyperactivity. This same activation may favor the maintenance of REM sleep, but compromises its initiation.

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## 581.B

### SENSITIVITY OF SLEEP STAGES TO PAINFUL THERMAL STIMULI

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**Introduction:** In a recent study, Lavigne et al applied fixed thermal stimuli (cool, warm and hot) to subjects during sleep (1). They found that a greater percentage of arousals occurred during stage 2 sleep than during slow wave and REM sleep when they applied a “moderately” hot painful stimulus. We aimed to measure arousal temperature thresholds during different sleep stages when a thermal stimulus of increasing intensity was applied.

**Methods:** A Thermal Pain Perception Scale (TPPS) was designed during a pilot study performed on 10 healthy, pain-free subjects. The scale consists of five heat pain specific adjectives (in order of increasing intensity) namely: hot; pricking; hurting; burning; pain tolerance. Thermal stimuli were applied using a Peltier thermode. The TPPS was used in the definitive study after validation. Nine healthy subjects with a mean age of 22.0 years (SD 2.9) and free of pain complaints and sleep problems participated in the definitive study and spent three non-consecutive nights in the sleep laboratory. The first night was an adaptation night. The last two nights were randomised. On one night, thermal stimuli were presented to awake subjects every two hours from 19h00 to 07h00. Subjects were asked to report at what temperatures they felt the sensations from the TPPS. McGill Pain Questionnaires and visual analogue scale ratings were completed after every such stimulus. On the other night thermal stimuli were applied to the forearm several times during each stage of sleep. The temperature was increased, from a starting temperature of 37 °C, at a rate of 0.1 °C/s until an arousal was noted. Marks were made on the sleep recording when the temperature of the thermode reached the TPPS temperatures from the ‘awake’ night. Parametric and non-parametric repeated measures ANOVA statistical tests were used for all comparisons.

**Results:** Subjects were aroused at significantly lower median temperatures during stage 2 sleep (46.5 °C) than slow wave sleep (47.6 °C; P<0.01) or REM sleep (47.2 °C; P<0.05). These temperatures corresponded to temperatures between “hurting” and “burning” sensations on the TPPS for stage 2 sleep, and between “burning” and pain tolerance for slow wave and REM sleep stages. No significant differences were observed for arousal temperatures between slow wave and REM sleep. There were no significant differences in either the subjective or objective (TPPS) assessments of pain perception from 19h00 to 07h00 during the awake night.

**Conclusions:** Our study indicates that there is an increased arousal threshold to thermal noxious stimuli during slow wave and REM sleep stages when compared to stage 2 sleep. The differences are not due to a circadian variation in pain sensation, but rather to innate characteristics of the sleep stages themselves.

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**582.B****EVIDENCE FOR FRACTAL CORRELATION PROPERTIES IN THE VARIATIONS OF PERIPHERAL ARTERIAL TONE DURING REM SLEEP**

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**Introduction:** Previous studies utilizing detrended fluctuation analysis (DFA) technique to analyze heart rate variability during sleep revealed higher fractal exponent during rapid eye movement (REM) sleep than non-rapid eye movement (NON-REM) sleep. The aims of this study were to: 1) determine if the same REM-related long-term correlations also exist in the variations of peripheral arterial tone; and 2) to compare the fractal-like behavior in peripheral arterial tone between patients with congestive heart failure (CHF), mild breathing disorders in sleep and normal controls.

**Methods:** Peripheral arterial tone was recorded during sleep simultaneously with conventional channels to monitor sleep stages from 12 CHF patients (age range: 80-41 yrs) 8 patients with mild breathing disorder in sleep (age range: 31-66 yrs.) and 12 healthy controls (age range: 16-45 yrs). For each subject, at least two 15-minute time series were constructed from the inter-pulse intervals and from the pulse wave amplitudes during REM and sleep stage 3-4 (NONREM) sleep.

**Results:** Fractal scaling exponents obtained by DFA of the pulse wave interval and pulse wave amplitude time series, were significantly higher for REM than sleep stage 3-4, for all three groups. In each of the groups and in both sleep stages the fractal scaling exponents based on pulse wave amplitude was significantly higher than that based on pulse rate variability. Across groups age was significantly correlated with the fractal exponent based on the pulse wave amplitude during both REM and sleep stage 3-4.

**Conclusions:** Variations in peripheral arterial tone during REM sleep show fractal correlation properties which are similar to those shown in heart rate variability. Since peripheral arterial tone is a surrogate of sympathetic activation, it indicates that variations in the sympathetic activation during REM sleep have a fractal-like behavior.

**Research supported by Supported by Itamar-Medical Ltd.**

**583.B****EXCESSIVE OCULOMOTOR ACTIVITY DURING NON-RAPID EYE MOVEMENT SLEEP IN PATIENTS TAKING SELECTIVE SERATONIN REUPTAKE INHIBITORS (SSRIS)**

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(1) Cleveland Clinic Foundation

**Introduction:** Excessive eye movements (EMs) during non-rapid eye movement sleep (NREM) have been previously described in patients taking fluoxetine. One prior study found that 48.8% of 41 patients had prominent EMs in NREM sleep (Schenck). The purpose of this study was to characterize EMs during NREM sleep in patients taking fluoxetine and compare these findings to another group of subjects taking sertraline.

**Methods:** Twenty-eight subjects treated with fluoxetine (N=19) and sertraline (N=9) were included. Patients were identified through the Sleep Disorders Center database searching by current medication usage. All subjects underwent overnight polysomnograms (PSG) from January through March 2001 at the Cleveland Clinic Foundation Sleep Disorders Center. Polysomnographic data were restored and retrospectively reviewed. Twenty minutes of consolidated sleep was reviewed in each of the following stages: stage 1, 2 and slow wave sleep (SWS, 3/4). Due to the first night effect, SWS was considered not evaluable in subjects with less than 10% TST spent in that stage. EMs were differentiated from typical slow roving EMs of stage 1 sleep by their high amplitude, greater abundance, and tendency to cluster toward the transition to stage 2 sleep instead of at the transition of wake to drowsiness. For each subject, the presence of excessive EMs during each stage of NREM sleep were noted.

**Results:** 28 subjects were identified. The mean age was 46.3 yr. (15-78 yr.) overall; 46.4 yr. (15-69 yr.) for the fluoxetine group and 47.3 yr. (36-78 yr.) for the sertraline group. Overall, 57% of subjects were men (58%: fluoxetine; 55%: sertraline). Excessive EMs were observed during NREM sleep in 24 (86%) of 28 subjects (94%: fluoxetine; 67%: sertraline). Further analysis revealed that excessive EMs were present in stage 1 sleep in 83% of patients overall (83%: fluoxetine; 83%: sertraline); in stage 2 in 96% overall (95%: fluoxetine; 100%: sertraline); and in SWS in 13% overall (17%: fluoxetine; 0%: sertraline). Time spent in SWS was insufficient to assess EMs in 50% of subjects overall (42%: fluoxetine; 33%: sertraline). Excessive EMs were noted in one stage only (always in stage 2) in 17%; stage 1 and 2 in 71%; and stages 1, 2 and SWS in 12% of subjects. EMs were extremely prominent during NREM sleep in two subjects with sleep apnea during CPAP titration PSGs.

**Conclusions:** When carefully analyzed, excessive EMs were present during NREM sleep in virtually all subjects studied taking fluoxetine and approximately 2/3rds of those taking sertraline. The most common expression of excessive EMs was during both stages 1 and 2 sleep. The percentage of subjects in whom SWS was considered insufficient may have resulted in an underestimation of excessive oculomotor activity during that stage. Further studies are required to determine whether this polysomnographic feature is unique to the SSRIs.

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**584.B**

**ADENOSINERGIC MODULATION OF BASAL FOREBRAIN NEURONS DURING SLEEP AND WAKING IN UNRESTRAINED RATS**

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**Introduction:** The cholinergic basal forebrain (BF) plays an important role in behavioral and electrocortical arousal(1). Adenosine is a sleep-promoting substance that has been proposed to induce sleep by inhibiting neurons in the BF and brain stem. Both A1 and A2 adenosinergic receptors have been implicated in mediating sleep-promoting effects of adenosine(2). We found previously that adenosine exerts tonic inhibitory influences on BF neurons during waking and non rapid-eye movement (nonREM) sleep(3). Here, we have examined A1 and A2 receptor-mediated influences of adenosine on sleep and wake-related discharge of BF neurons. We used the method of extracellular unit recording with microdialytic delivery of adenosine A1 and A2 agonists adjacent to the recorded neurons to compare their effects on BF neurons during sleep and waking.

**Methods:** Five Sprague-Dawley rats were surgically implanted with EEG and EMG electrodes for chronic recording of sleep-wake states, five pairs of microwires into BF for recording extracellular neuronal activity, and a guide cannula at ~0.5 mm lateral to the microwires for delivering adenosine A1 or A2 receptor agonists adjacent to the recorded neurons with a microdialysis probe (membrane length, 1 mm). The activity of BF neurons was continuously recorded during (a) 3-5 sleep-waking episodes during artificial cerebrospinal fluid perfusion (baseline), (b) during perfusion of an A1 receptor agonist, N6-cyclopentyladenosine (5-10  $\mu$ M), or an A2 receptor agonist, CGS21680 (1-5  $\mu$ M) for 10-15 min, and (c) during wash out

**Results:** CPA significantly decreased the discharge (mean  $\pm$  SEM) of BF neurons ( $n=33$ ; 5 $\mu$ M, 9 neurons; 10  $\mu$ M, 24 neurons) during both waking ( $5.09 \pm 0.54$  vs.  $2.73 \pm 0.33$ ,  $P < 0.0001$ , student paired t-test) and nonREM sleep ( $4.26 \pm 0.52$  vs  $2.56 \pm 0.39$ ,  $P = < 0.0001$ ) without any significant difference in percent suppression between the two states ( $-48 \pm 4\%$  vs.  $-41 \pm 6\%$ ,  $P = 0.978$ ). When grouped according to their discharge patterns, of 33 neurons, 15 were WRNs, 4 were SRNs, and 14 were SInS. In presence of CGS21680 ( $n=9$ ), BF neurons did not exhibit any significant change in their activity during either waking ( $3.85 \pm 1.06$  vs.  $3.94 \pm 0.73$ ,  $P = 0.935$ ) or nonREM sleep ( $3.09 \pm 1.01$  vs.  $4.61 \pm 1.03$ ;  $P = 0.215$ ). Of 9 neurons, 5 were WRNs.

**Conclusions:** These preliminary results suggest that in naturally awake and sleeping animals, adenosine exerts tonic

inhibitory influences on BF neurons primarily through A1 receptor.

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**585.B**

**ARE K COMPLEXES AND DELTA WAVES DIFFERENT? A MATHEMATICAL MODEL AND ITS APPLICATION**

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**Introduction:** It is not clear the functional role or the distinction between delta waves and K complexes in the current literature. This study raises again the hypothesis that delta waves and K complexes are morphologically and functionally different. The rationale is supported by the creation of an extended tonic and phasic EEG generation model with physiological background. This model is able to generate a whole night sleep EEG with preservation of the macrostructure and phasic events.

**Methods:** According to this model, delta burst and isolated delta waves are the tonic or permanent response of the model under control of the sleep ultradian NREM-REM sleep regulator by setting the trend and changes of the delta generators synchrony. On the other hand, an external stimuli elicits a phasic or, as in linear systems analysis terminology, a transient response. The final response to the external stimuli or event-related response is composed by the sum of the two tonic and phasic components simultaneously. This wide range of morphologic differences are controlled by the current tonic states or sleep stage and the significance or intensity of the stimulus. The model provides then a mean to detect these EEG components through a model based estimation and detection approach. Scorers were instructed to classify isolated delta band (0.1 to 4Hz) activity into isolated delta burst or K complexes according to the "non-estacionarity", i.e., sudden change and morphological resemblance to the simulated results. The same data was analyzed by the model based automatic detector. This detector marked with some degree of probability the K complexes. The selectivity and specificity of the automatic detector in relation to the visual analysis was performed.

**Results:** This model can explain the whole range of variation in the tonic delta waves but also the scope of variations of the K complexes. It also provides illustration containing simulation of these two different EEG components and a mean to detect them, through a model based estimation and detection approach. Figures with examples of the model based results and the scored delta and Ks will be presented.

**Conclusions:**

### 586.C

#### NBI-34060 (A NON-BENZODIAZEPINE SEDATIVE-HYPNOTIC): LACK OF A PHARMACOKINETIC GENDER EFFECT

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**Introduction:** Gender differences in pharmacokinetics (PK) have been reported for a number of benzodiazepines, and for the non-benzodiazepine sedative-hypnotics, zaleplon (1) and zolpidem (2), peak plasma (C<sub>max</sub>), total exposure (AUC), and half-lives (T<sub>1/2</sub>) are up to 50% greater in women compared to men. These differences may explain the increased rates of adverse events found among females in zolpidem clinical trials (3). This study explores the potential for gender related PK changes with NBI-34060, a new non-benzodiazepine sedative hypnotic.

**Methods:** Twenty-four young healthy subjects (12 male and 12 females; 18-40 yrs.) took part in this nighttime PK study. Subjects were administered NBI-34060 15 mg and blood samples collected up to 12 hours for the analysis of plasma concentrations using HPLC-MS-MS. The PK were computed using WinNonLin and ANOVA used to detect statistical differences.

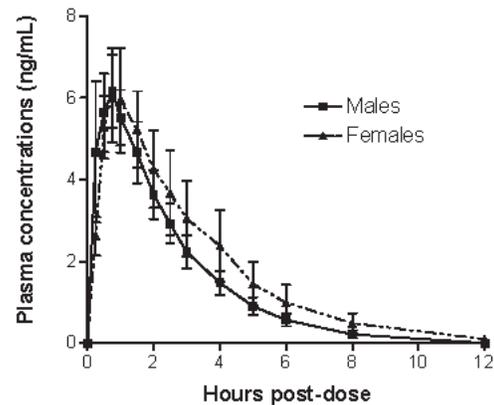
**Results:** NBI-34060 was rapidly absorbed within an hour and rapidly eliminated in all subjects, and by eight hours after drug administration, plasma levels had dropped to less than 10% of the peak. There were no statistically significant differences between the genders for any PK parameter. There was also no relationship between body weight and any PK parameter.

Table 1

Pharmacokinetics of NBI-34060 in Male and Female Subjects Following Administration of NBI-34060 15mg, Mean (SEM)

Gender	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/ml)	AUC (ng <sup>2</sup> hr/ml)	T <sub>1/2</sub> (hr)
Males	0.73 (0.13)	7.3 (1.5)	17.4 (2.5)	1.97 (0.31)
Females	0.82 (0.12)	7.4 (1.2)	22.8 (6.0)	1.71 (0.25)
p-value	0.64	0.89	0.84	0.51

Figure 1



**Conclusions:** Although marked gender differences in the metabolism of drugs in humans are uncommon, they are mostly associated with drugs metabolized by the hepatic isoform CYP 3A4 (2). For some benzodiazepines (midazolam, alprazolam, triazolam), these differences result in higher plasma levels in males. Therefore, it is not clear why zaleplon and zolpidem should exhibit slower clearance in females. Alternative metabolic pathways have been observed for both compounds and these may contribute to the gender differences. There is also a possibility that the GI tract CYP 3A4 may be involved. For NBI-34060, metabolism occurs equally through CYP 3A4 and a non-microsomal, esterase pathway which is not known to be gender dependent. Perhaps it is this alternative pathway, together with the finding that GI tract CYP 3A4 metabolism does not appear to occur, which provides a rationale for the lack of gender differences in the PK of NBI-34060.

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- (3) FDA Supervisory overview (NDA19-908) Zolpidem (1991) pp 42 DHHS.

### 587.C

#### THE PHARMACOKINETICS OF THE NON-BENZODIAZEPINE SEDATIVE-HYPNOTIC, NBI-34060 IN ELDERLY SUBJECTS

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**Introduction:** Elderly patients with primary insomnia who take sedative-hypnotics, may experience side effects due to concurrent diseases, polypharmacy, increased sensitivity, or altered pharmacokinetics (PK). Physiological changes, including impaired renal and hepatic function, result in reduced drug clearance. This occurs for certain benzodiazepines but also for the non-benzodiazepine, zolpidem, producing plasma levels

up to 3 times higher in elderly compared to the young with a doubling of the half-lives, and an age related increase in frequency of adverse events (1). This study examines the potential for age-related PK changes with NBI 34060.

**Methods:** Twelve young adult (6 male, 6 female; 18-45 yrs.) and 13 elderly subjects (7 male, 6 female; 65-79 yrs.) were randomized into a double-blind, placebo-controlled, four night, repeat dose study. Nine subjects from each group received NBI-34060 15 mg, and 3 young adult and 4 elderly subjects received placebo. Blood samples for PK analysis were collected up to 12 hours on Nights 1 and 4, and analyzed by HPLC-MS-MS. Next day impairment was assessed by DSST, SCT, and VAS.

**Table 1**

**Pharmacokinetics of NBI-34060 in Young and Elderly Subjects Following Administration of 15mg NBI-34060 on Nights 1 and 4**

Group	T <sub>max</sub> (hr)	C <sub>max</sub> (ng/ml)	AUC (ng•hr/ml)	T <sub>1/2</sub> (hr)
Young (Night 1)				
Mean (SEM)	2.3 (0.5)	14.3 (2.9)	46.0 (8.2)	1.5 (0.1)
Median	2.0	12.3	39.9	1.6
Young (Night 4)				
Mean (SEM)	1.8 (0.5)	16.1 (3.2)	44.3 (7.2)	1.6 (0.1)
Median	1.3	16.5	50.1	1.6
Elderly (Night 1)				
Mean (SEM)	2.7 (0.6)	15.1 (3.2)	61.2 (14.4)	1.8 (0.1)
Median	3.0	11.5	50.0	1.7
Elderly (Night 4)				
Mean (SEM)	2.6 (0.8)	16.7 (3.8)	69.5 (17.1)	2.2 (0.1)
Median	2.3	11.9	51.1	2.3

**Results:** NBI-34060 was rapidly absorbed and eliminated in both young and elderly subjects. There were modest increases in T<sub>max</sub>, AUC, and t<sub>1/2</sub> in the elderly but there were no significant differences between young and elderly subjects for any PK parameter on either sampling night (ANOVA, p>0.25), nor were there apparent gender differences. NBI-34060 was equally well tolerated with a comparable frequency of AEs in young and elderly subjects. As expected a greater frequency of sedative effects was reported for NBI-34060 relative to placebo. However, there was no next day impairment, as measured by DSST, SCT, or VAS relative to placebo upon awakening for either group.

**Conclusions:** Reduced drug clearance in elderly subjects is thought to largely contribute to their increased sensitivity to certain sedative-hypnotics. For those benzodiazepine (diazepam, alprazolam, bromazepam, triazolam) (2) and non-benzodiazepine sedative-hypnotics (zolpidem (1) and zopiclone (3)) that are metabolized mainly by the cytochrome P450 pathway, higher plasma levels are associated with increasing age (2). Compounds metabolized via non-microsomal pathways tend to exhibit fewer age effects. This may explain why NBI-34060, metabolized equally by CYP 3A4 and the non-microsomal esterases, and not excreted in the kidney, shows minimal young/elderly kinetic differences. These preliminary data also indicate that NBI-34060 is well tolerated with no next day impairment in elderly subjects.

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## 588.C

### THE EFFECT OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS ON SLEEP EFFICIENCY IN PATIENTS WITH EXCESSIVE DAYTIME SOMNOLENCE

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**Introduction:** Many factors can affect sleep efficiency. Selective serotonin reuptake inhibitors (SSRI) are known to disrupt sleep but data on their effect on sleep efficiency is limited. SSRI seem to decrease sleep efficiency in healthy volunteers<sup>1</sup> and depression<sup>2</sup>, though this seems to be reversible upon discontinuation of the medication. Whether this effect occurs in patients with excessive daytime somnolence (EDS), whose sleep efficiency may be affected by their underlying sleep disorder, has not been studied. We examined the effect of SSRI on sleep efficiency in patients referred for EDS.

**Methods:** The records of 206 patients who underwent polysomnography for EDS in our accredited Center for Sleep Disorders were reviewed. The sleep efficiency, apnea-hypopnea index (AHI), and the use of SSRI were recorded. Data analysis was performed using SAS statistical software in which mean values were compared using the two sample T-test methodology. Statistical significance was calculated at &#61537;=0.05.

**Results:** 206 patients were studied (153 males and 53 females). Of these, 11 women (20.8%) and 11 men (7.2%) were on SSRI (p=0.0060). There was no statistically significant difference in the AHI between males and females (42.0 vs 38.5, respectively) nor was there any significant difference in AHI between patients on SSRI when compared to those not on SSRI (36.9 vs 41.6, respectively). There was no significant difference in the sleep efficiency between males and females (68.5 vs 65.7, respectively) nor was there any significant difference in sleep efficiency between patients on or off SSRI (64.3 vs 68.2, respectively). Analysis of female subsets, however, revealed that women on SSRI medication had a lower sleep efficiency when compared to women not on SSRI (68.5 vs 54.9, respectively, p=0.0285). Further, women on SSRI had a lower sleep efficiency when compared to men on SSRI (54.9 vs 73.7, p=0.0364). We have previously reported that the subjective depressive ideation based on a self-administered questionnaire was not significantly different between males and

females in this group<sup>3</sup>.

**Conclusions:** There was a decrease in the sleep efficiency in females on SSRI versus those not on SSRI. In addition, females on SSRI had a lower sleep efficiency when compared to men on SSRI. It appears that the use of SSRI in females with EDS has a negative impact on sleep efficiency. A similar affect was not observed in the male subgroup. The mechanism of this remains unknown. Prospective studies are recommended to conclusively evaluate the effect of SSRI on sleep efficiency.

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## 589.D

### EXPERIMENTAL MANIPULATION OF SLEEP ONSET DREAM CONTENT

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**Introduction:** The study of mentation reports from the sleep onset period allows both reliable experimental manipulation of dream content and objective measurement of dream incorporation. Such studies can provide new information about the process of dream construction.

**Methods:** Subjects played the arcade game *Alpine Racer II* for three 45-minute sessions on day 1 and two 45-minute sessions on each subsequent day. Sleep onset dream reports were collected as previously described (Stickgold et al., 2000).

**Results:** Fourteen of 16 subjects (88%) playing the arcade game *Alpine Racer II*® and 3 of 3 controls who only watched others play, reported intrusive visual images of the game over 3 nights of hypnagogic mentation collection. In addition, 11 players (69%) and 1 of 3 controls reported kinesthetic or vestibular imagery. On night one, 46% of reports (26 of 57) included visual game images and 23% included kinesthetic imagery. Frequencies dropped (ANOVA,  $p < 0.001$ ) to approximately one-third these rates by Night 3 (16% visual, 7% kinesthetic) despite continued game play. Reports normally included explicit reference to the game, although 4 of 8 subjects with downhill skiing experience reported imagery from actual prior ski trips. Subjects' subjective reports of level of involvement averaged 0.51 (visual analog scale, range: 0 - 1) on day 1 for subjects who reported imagery, but only 0.23 for those who did not (t-test,  $p < 0.001$ ). In contrast, improvement in performance did not correlate with frequency of imagery (Pearson correlation,  $p > 0.2$ ). Sleep onset reports were collected from an additional 6 subjects in a delayed onset proto-

col. In this case, subjects went to sleep normally, were allowed to sleep for two hours, and were then awakened and kept awake for 10 minutes. They were then allowed to return to sleep, and the standard sleep onset report collection protocol run. Of these subjects, only one (17%) had imagery of skiing, while five (83%) had related imagery (e.g., "falling down a hill") that did not explicitly involve skiing.

**Conclusions:** Together with earlier studies, these results suggest that incorporation of waking events into hypnagogic images can (1) be highly stereotypical, (2) include older, semantically related images, (3) incorporate multiple sensory modalities, (4) decay quickly across days ( $\tau = 0.54/\text{day}$ ), (4) be driven more by emotional involvement than learning, and (4) occur similarly in amnesics with bilateral hippocampal damage. In addition, the stereotypic nature of the reports appears to evolve to more abstractly associated images with time across the night, even when still collected from the sleep onset period.

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## 590.D

### TWO FORMS OF SLEEP PARALYSIS DREAM IN THE STUDENT POPULATION?

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**Introduction:** Little is known about the precise content of dreams that accompany Sleep Paralysis (SP) experiences. The Typical Dreams Questionnaire (TDQ) assesses the lifetime prevalence of 55 of the most typical dream themes (1), many of which characterize SP reports, and was thus used to examine the nature and prevalence of SP.

**Methods:** Subjects were students enrolled in Introductory Psychology courses at 3 major Canadian Universities. Of 1348 subjects participating, 341 were from McGill U, 388 from Trent U, and 619 from U Alberta. In the Alberta sample, 167 students (12.4%) did not specify their gender and were dropped from the sample. Of the 1181 remaining subjects, 28.9% were men ( $20.1 \pm 3.6$ ) and 71.1% were women ( $19.7 \pm 4.0$ ). TDQs were administered during regular course hours. An SP scale was calculated as the sum of 5 TDQ items that we felt characterize the fear, inhibition and sense of presence attributes central to the phenomenology of SP experiences (2,3), i.e., Item 4-being frozen with fright; Item 15-being tied, unable to move; Item 29- vividly sensing, but not necessarily seeing or hearing, a presence in the room; Item 39-being smothered, unable to breathe; and Item 44-being half awake and paralyzed in bed. A 2 X 3 ANOVA with Gender (Men,

Women) and Region (McGill, Trent, Alberta) as independent variables was conducted for the SP scale. Responses to all 55 TDQ Items were subjected to Principal Components Factor Analysis with Varimax rotation and Kaiser normalization.

**Table 1**

Two principle component SP factors (N=1181)					
TDQ Item	Prev*	Name	fac6	fac13	
44. paralyzed	27.2	Paral-Pres+	<b>0.624</b>	0.203	
29. sensing a presence	48.3	Paral-Pres	<b>0.592</b>	-0.016	
45. seeing a face.	23.5	Paral-Pres	<b>0.454</b>	0.028	
3. trying again & again	53.5	Paral-Pres	<b>0.329</b>	0.179	
15. tied, unable to move	21.4	Inhibition	0.156	<b>0.626</b>	
39. smothered	24.2	Inhibition	0.193	<b>0.512</b>	
8. locked up	24.0	Inhibition	0.026	<b>0.413</b>	
31. school	67.1	Inhibition	0.140	<b>-0.405</b>	
*Prevalence; +Paralysis-presence			% Var	<b>3.387</b>	<b>2.743</b>

**Results:** There was a main effect on the SP scale for Gender only ( $F_{1,1175}=10.14, p=.001$ ); women scored higher ( $1.70\pm 1.36$ ) than did men ( $1.42\pm 1.36$ ). From the Factor Analysis, a 16-factor solution emerged which included all 55 Items and accounted for 51% of the variance. Two Factors appeared to characterize SP as indicated by significant correlations with the SP scale: Factor 6 (Paralysis-presence;  $r=.616, p<.001$ ), and Factor 13 (Inhibition;  $r=.500, p<.001$ ) (see Table). Women loaded higher (.035) than did men (-.085) on Factor 6 ( $p<.05$ ), but there was no gender difference for Factor 13.

**Conclusions:** There may exist two typical forms of SP dream, one involving felt paralysis and a sense of presence, the other involving generalized inhibition—including difficulty breathing. The well-known SP gender difference (2) obtains only for the first form.

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**591.D**

**ADULT AND CHILDHOOD RECURRENT DREAMS: A CONTENT ANALYSIS.**

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**Introduction:** Between 60 to 75% of college students and older adults report having had one or more recurrent dreams

(RD) at some point in their lives (1). RD tend to occur in times of stress and are associated with a relative deficit in self-reported levels of well-being (2). The goal of the present study was to investigate the actual content of adult and childhood RD.

**Methods:** RD were reported in a sleep and dream questionnaire included in our usual battery of questionnaires administered to our subjects. Retrospective accounts of RD were classified as being from adulthood if they first occurred after the age of 18, and from childhood if they ceased to recur before the age of 12. Eighty RD from adulthood and 29 from childhood met the following inclusion criteria: occurred over a period of at least 6 months and the content was rated by the subject as being always or almost always identical. Dream reports were scored using the standard H/V (3) scales of Emotion, Good fortune, Misfortune, Success, and Failure and were also categorized according to their thematic content.

**Results:** Table 1 presents the percentage of RD from adulthood and childhood which contained specific dream content categories. Over 70% of all RD were described as being unpleasant and fear or apprehension was the most frequently reported emotion. Dream content was described as being pleasant in approximately 9% of the RD with happiness and surprise being the most frequently cited emotions. Adult RD were more likely than childhood RD to contain failures while success was equally rare in both groups. About 60% of the RD contained misfortunes and the dreamer was the recipient of the misfortune in 70% of all cases. The most frequently reported theme was one in which the dreamer is being chased. The dreamer in childhood RD was usually pursued by monsters, wild animals, or witches whereas adult RD contained predominantly human characters such as burglars and strangers. Pleasant recurrent dreams included discovering new rooms in a house, flying, excelling at a particular task, and finding oneself in a bountiful environment.

**Table 1**

Content Category	% RD Adulthood	%RD Childhood
Negative Emotion	71	80
Positive Emotion	9	7
Both pos & negative	12	7
Neutral affect	11	7
Failure	15	3
Success	5	7
Misfortune	59	62
Good Fortune	4	3
Being chased	14	28
Being attacked	10	10
Discovering new room	8	3
Being trapped	6	7
Facing natural forces	6	3
Dreamer injured or ill	6	3
Falling	6	7

**Conclusions:** The results show that the content of most RD is negative in nature and highlight key differences between adult and childhood RD. Since failures in dreams result from a character's personal limitations and inadequacies, the data suggest

that RD from adulthood are more likely to reflect issues of personal competence than issues beyond the subject's control. Finally, it should be noted that the thematic content of almost 20% of all RD is idiosyncratic and that positive recurrent dreams may be more prevalent than previously thought.

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## 592.D

### LIFETIME PREVALENCE OF SLEEP PARALYSIS DREAMS AMONG SLEEP-DISORDERED PATIENTS

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**Introduction:** Sleep Paralysis (SP) is a component of the narcolepsy tetrad of symptoms, although its specificity has not been thoroughly investigated. The Typical Dreams Questionnaire (TDQ) assesses the lifetime prevalence of SP and other typical dream themes (1). We investigated the specificity of SP to narcolepsy by assessing the prevalence of the components of SP experiences among sleep-disordered patients.

**Methods:** From January 1997 to January 2001, 788 patients were both recorded with polysomnography in the Sleep Disorders Clinic and completed the TDQ. Each patient received a single ASDA diagnosis and answered positively to at least one item of the TDQ. Of the 788 patients, 280 were excluded because of multiple diagnoses or sample sizes of less than 10. Of the 508 included patients, 46.9% were men (48.1±14.3 yrs) and 53.1% women (43.3±15.1 yrs). Control subjects (n=72) were either diagnosed as normal or had participated as control subjects in various experiments; these were recorded during the same time period in the same laboratory. Of the 72 controls, 36.1% were men (36.5±12.0 yrs) and 63.9% were women (38.7±13.1 yrs). Five TDQ items were selected which reflected the fear, inhibition and sense of presence attributes of SP experiences, i.e., Item 4-being frozen with fright; Item 29-vividly sensing, but not necessarily seeing or hearing, a presence in the room; Item 39-being smothered, unable to breathe; and Item 44-being half awake and paralyzed in bed; Item 45-seeing a face very close. 2X2 chi-square tests were conducted for the presence/absence of each item among seven types of sleep disorders.

**Table 1**

	%subjects who dreamed at least once of each item				
	4	29	39	44	45
Controls (n=72)	48.6	45.8	22.2	29.2	19.4
<b>Patients</b>					
SAS (n=54)	31.5	27.8*	38.9*	24.1	14.8
Narc (n=41)	39.0	51.2	31.7	63.4***	31.7
Somn (n=33)	36.4	33.3	39.4	36.4	9.1
Insom (n=65)	40.0	35.4	20.0	24.6	10.8
IH (n=90)	48.9	37.8	26.7	42.2	17.8
RBD (n=27)	22.2*	55.6	18.5	29.6	7.4
RLS (n=198)	35.4*	33.3	24.2	25.3	7.6**

\*p<.05; \*\*p<.01; \*\*\*p<.001

**Results:** Patients with Narcolepsy (Narc) were more likely (63.4%) than controls (29.2%) to have dreamed of item 44 (half awake and paralyzed...p<.001), but the two groups did not differ on the other items. Patients with Sleep Apnea Syndrome (SAS) had a higher lifetime prevalence on item 39 (being smothered...38.9%) than did controls (22.2%; p<.05), but a lower prevalence of item 29 (sensing...a presence...27.8% vs. 45.8%; p<.05). Patients with REM Behaviour Disorder (RBD) and Restless Legs Syndrome (RLS) had lower prevalences on item 4 (frozen with fright). Patients with Somnambulism (Somn), Psychophysiological Insomnia (Insom), and Idiopathic Hypersomnia (IH) did not differ from controls on any item.

**Conclusions:** The sense of presence, inhibition and fear aspects of SP dreams seem dissociable; only the motor inhibition aspect is characteristic of the dreams of patients with Narcolepsy. Nonetheless, SAS patients experience inhibition in the form of dreamed smothering. Lower prevalences of SP components appear to characterize other disorders in which motor activity is affected (RBD, RLS).

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## 593.E

### THE EFFECTS OF FACTORS SECRETED FROM THE SCN ON SLEEP-WAKE BEHAVIOR

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**Introduction:** Suprachiasmatic nucleus (SCN) transplants can restore circadian rhythms of wheel-running behavior in SCN-lesioned animals. This restoration does not require neuronal connections, suggesting that secreted factors can control circadian outputs. In a screen of SCN-secreted factors affecting locomotor activity, we found that TGF $\alpha$  was rhythmically

expressed in the SCN. The receptor for TGF $\alpha$  is abundant in the subparaventricular zone (SPZ), a major target of SCN afferents and a region shown to be necessary for the expression of some circadian rhythms. When chronically infused into the third ventricle, TGF $\alpha$  potently inhibits wheel-running activity. To determine whether TGF $\alpha$  or other factors secreted from the SCN affect sleep-wake behavior, we recorded the EEG/EMG of hamsters during chronic infusions of these factors.

**Methods:** Adult hamsters were instrumented with EEG/EMG electrodes, and a cannula connected to an osmotic minipump was implanted into the third ventricle. The minipump was filled with either artificial CSF or 3-5  $\mu$ M concentrations of the peptide/protein of interest. In addition, a telemetric device was inserted into the peritoneal cavity to measure core temperature and bodily movement. Sleep-wake behavior was scored as NREM, REM, or wake on 48-hour recordings one week into the infusion.

**Results:** In hamsters infused with TGF $\alpha$ , the daily amounts of NREM, REM, and wake were comparable to those of control animals. However, the circadian regulation of sleep-wake behavior was markedly disrupted. TGF $\alpha$ -infused animals exhibited a regular and reproducible ultradian rhythm of 5-6 cycles per day. This was paralleled by a similar ultradian rhythm of body temperature. Bodily movements exhibited no circadian rhythmicity.

**Conclusions:** The ultradian rhythms of sleep-wake behavior and body temperature produced by TGF $\alpha$  infusions closely resemble the patterns seen in animals with focal excitotoxic lesions of the SPZ. These results suggest that TGF $\alpha$  plays a critical role in the circadian regulation of sleep-wake behavior, possibly by acting as an inhibitory signaling molecule between the SCN and the SPZ. In addition, SPZ cells bearing the receptor for TGF $\alpha$  likely play an essential role in this pathway.

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### 594.E

#### FLIGHT DECK LIGHT EXPOSURE OF PILOTS DURING LONG-HAUL TRIPS BETWEEN THE UNITED STATES AND JAPAN

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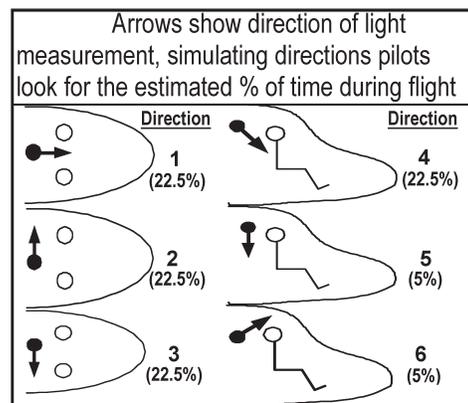
(1) Biomathematical Modeling Unit, Brigham and Women's Hospital/Havard Medical School, (2) NASA Ames Research Center, Fatigue Countermeasures Program/San Jose State University, (3) NASA Ames Research Center, Fatigue Countermeasures Program,

**Introduction:** Performance and alertness of pilots are a concern to everyone on an aircraft. Long-haul commercial pilots are particularly susceptible to performance and alertness degradations due to the long hours of wakefulness required for transcontinental flights and the crossing of multiple time zones that can result in circadian misalignment. Using a mathematical model (1) that is based on circadian phase and sleep/wake times, we can predict a pilot's performance when concentra-

tion is most imperative (e.g., at take-off or landing). The circadian portion of the model requires, as an input, the intensity of light exposure an individual receives. Currently, there is little data available concerning light levels to which pilots are exposed on flight decks during long-haul flights. Therefore, we recorded flight deck light intensities during two regularly scheduled revenue long-haul flights.

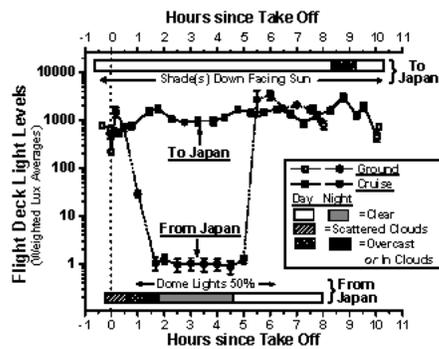
**Methods:** Light readings were collected on a commercial airline Boeing 747-400 aircraft flight deck with permission from the Federal Aviation Administration and the flight crew during two trip segments; from San Francisco, California to Narita, Japan, and again on the return trip. A NASA researcher measured light intensity using an IL-1400 Light Meter (International Light, Newburyport, MA) with the sensor placed between the two pilots at eye level and pointed in six different directions (Figure 1). Measurements were taken during: taxi (at departure and arrival locations); on the runway prior to take-off; on climb out and descent through 18,000 feet; at the level-off altitude (top of climb); every 30 minutes en route; and at block-in when the flight terminated at the arrival gate. The crew was instructed to maintain the flight deck lighting environment consistent with their normal operating procedures throughout the flights. Additional data collected included: universal coordinated time; latitude and longitude coordinates; aircraft heading; altitude; weather conditions; and cockpit lighting conditions. From observations and discussions with pilots, we estimated that pilots spend an average of ~22.5% of their flight time looking in each of the first four directions and ~5% in directions five and six (Figure 1). We used these estimates to calculate a weighted average ( $\pm$  SEM) of the six light measurements recorded at each time point during the trips (Figure 2).

Figure 1



**Results:** We found no effect of weather or aircraft heading on light level on the flight deck during the daytime or the nighttime. The average  $\pm$  SEM light level during cruise was 1,513  $\pm$  129 lux during the daytime, and 1.05  $\pm$  0.04 lux during the night. The daytime light levels while on the ground were slightly lower than during flight (642  $\pm$  80 lux).

Figure 2



**Conclusions:** These results give us an indication of the approximate amount of light received by pilots in the cockpit during long-haul flights. However, light measurements from multiple long-haul flights are needed in order to better understand how factors such as season, weather, time of day, altitude, and location affect cockpit light levels.

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**595.E**

**SELF-REPORT NAPPING IN IRREGULAR WORK SCHEDULES**

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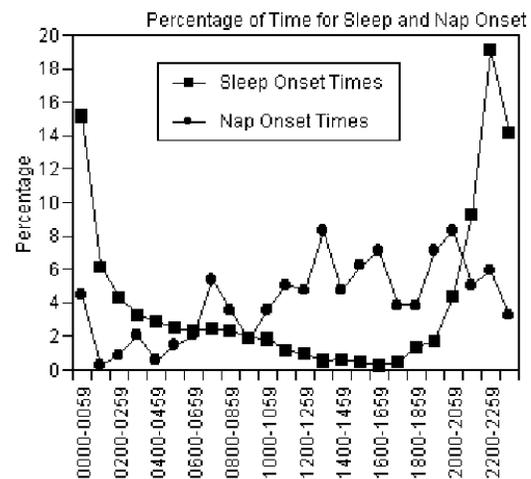
**Introduction:** Many shift work schedules in industrialized societies result in very irregular work times. One example of this is in locomotive engineers. Because most locomotive engineers work under on-call schedules, their rest periods are often disrupted by their work requirements. As such, locomotive engineers would be expected to take advantage of napping opportunities. The purpose of the current study was to examine the frequency of self-report napping in locomotive engineers and to examine the relationships between napping and other sleep indices as well as work-related variables.

**Methods:** The data were initially collected and reported through the Volpe National Transportation Systems Center (1). The current study used self-report data on 14 days of work/rest activity from 124 locomotive engineers (mean age: 44.2±6.3). Each day in the data set was defined from wake-up time to wake-up time following major sleep episodes. Major sleep episodes were typically classified as isolated sleep periods of at least 4 hours in length, resulting in 1455 major sleep periods. All other sleep episodes were classified as naps, resulting in 336 naps. As a first step in the analysis, the frequency at which sleep onset occurred for major sleep episodes and naps

was calculated for each hour of the day. Pearson correlations between nap duration and sleep duration before the nap, sleep duration after the nap, sleep onset time, and time reporting to work and getting off of work were also calculated.

**Results:** The engineers reported an average main sleep episode length of 7.6±2.03 hours and an average nap length of 2.99±1.63 hours. In spite of their irregular work schedules, the engineers reported going to sleep for their main sleep episode between 10 PM and 1 AM almost 50% of the time (Figure 1). In contrast, nap onset times remained relatively high throughout the day and only decreased at night. Furthermore, the results indicated that the correlations between nap length and the sleep and work variables were small (Pearson r range from -.10 to -.19).

Figure 1



**Conclusions:** The current results indicate that the main sleep episodes reported by the engineers were strongly influenced by the human endogenous rhythm to be awake during the day and asleep at night. Furthermore, the length of the naps did not affect the major sleep episodes. The nap lengths reported by the engineers differed from those in middle-aged day-workers, who reported an average nap length of 15.55±21.74 minutes (2). Thus, the current data suggest that the napping behavior of the engineers was affected by their irregular work schedules but was not strongly related to the duration of their main sleep episodes. These results have implications regarding the strategic use of naps as a fatigue countermeasure in shift work schedules.

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tion or the Department of Transportation.

### 596.E

#### EXERCISE FACILITATES RESETTING OF THE CIRCADIAN PACEMAKER IN DIM LIGHT

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**Introduction:** Shift workers and individuals who travel across many time zones, such as international airline pilots, are exposed to markedly abnormal rest-duty cycles, leading to a loss of an appropriate phase relation between the 24-hr sleep/wake cycle and the endogenous circadian timing system. Misalignment of circadian phase is associated with sleep disruption and deterioration of alertness and cognitive performance, and can result in lapses of attention during the extended duty hours. To prevent such misalignment, non-pharmacological countermeasures, such as exercise, to facilitate adaptation of the human circadian pacemaker to the imposed duty-rest schedule have been investigated (1).

**Methods:** We conducted a study investigating the effects of exercise on physiologic adaptation to shift work and/or transmeridian travel under strictly controlled dim light (< 2 lux). Eighteen young, fit male subjects completed a 15-day randomized clinical trial in which circadian phase was measured in a constant routine before and after exposure to a week of nightly bouts of exercise or a control condition. Plasma samples collected every 30-minutes were analyzed for melatonin to determine circadian phase. The time at which the rising portion of the plasma melatonin curve crossed a level that was 25% of the peak value of the curve (2) was defined as the melatonin onset (DLMO<sub>25%</sub>). Core body temperature was continuously monitored by means of a rectal temperature sensor (Yellow Springs Instrument Company, Yellow Springs, OH).

**Results:** Subjects who completed three 45-minute bouts of cycle ergometry (~ 70% of maximum heart rate) each night showed a significantly greater shift in DLMO<sub>25%</sub> as compared to non-exercising controls (p=0.039). Body temperature data were unusable in two subjects in the exercise group and more variable in the remainder; no statistically reliable difference in the circadian phase of body temperature between the two groups could be detected.

**Conclusions:** The potential efficacy of exercise as a circadian countermeasure could have important implications for the treatment of circadian rhythm disorders, such as jet-lag and shift-work dysomnia. Further investigation of the optimal timing of exercise is required to maximize the effectiveness of multiple nightly-bouts of exercise as a means of rapidly facilitating entrainment of the endogenous circadian pacemaker to abnormal sleep/wake cycles.

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### 597.E

#### TITLE: WITH LIMITED INPUT DATA, KRONAUER'S LIGHT MODEL MAKES ACCURATE CIRCADIAN PHASE PREDICTIONS ON AVERAGE, BUT MAKES LARGE ERRORS IN SOME INDIVIDUAL PREDICTIONS

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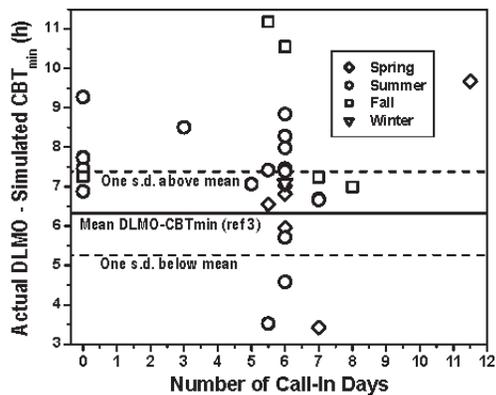
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**Introduction:** A mathematical model of the effects of light on the human circadian system was developed that accurately estimates core body temperature minimum (CBT<sub>min</sub>) given prior light exposure levels (1). The purpose of this project is to evaluate the accuracy of this model using only a subject's study dates and habitual sleep/wake times as input.

**Methods:** Thirty-one healthy young subjects (20-39 yrs; 16 male, 15 female) participated in a 10-day shift work protocol. Presented here are data from the beginning of the study: four day-shifts followed by a 6-h Constant Posture (CP) conducted in <8 lux to assess subjects' dim light salivary melatonin onset (DLMO) (SaliSaver, ALPCO). Subjects slept ad lib, but were instructed to call in at each wake and bed time. Model simulations of each subject's protocol were completed using light exposure estimates from a study in Montreal(2): 0 lux during sleep; 40 lux during wake before sunrise and after sunset; and either 600 lux (June-August), 350 lux (March-May; September-November), or 100 lux (December-February) during wake in daylight hours. Call-in times were used to estimate actual sleep times. When a subject missed >4 calls, the subject's habitual sleep/wake times reported prior to the study were substituted for the missing values. Otherwise, any missing call-in time(s) were defined to be the average of the bed or wake times before and after the missing value(s). For each subject, we subtracted from the DLMO during their CP, the light model's predicted CBT<sub>min</sub> from that circadian cycle. We compared this with the typical difference between those markers (average ± s.d. = 6.32 ± 1.06 hrs, see figure) calculated from initial Constant Routines in 23 young healthy subjects in another similar study(3). A 2-way ANOVA was run to determine whether the factors 'season' and/or 'number of call-in days' contributed to prediction accuracy.

**Results:** Neither factor significantly affected the accuracy of the model predictions. Therefore, we re-ran the simulations using habitual sleep/wake times to estimate all of the subjects' sleep times. These simulations predicted the CBT<sub>min</sub> to fall within the typical time range on average and for 12 of the individuals. However, they were 1.07 to 4.86 hours off for the remaining 19 subjects.

Figure 1



**Conclusions:** On average, Kronauer's light model accurately estimates circadian phase using inputs derived only from a subject's habitual sleep/wake times and study dates. However, in >50% of the subjects, the model misestimates circadian phase in an unpredictable manner. This indicates that although limited input data can produce correct circadian predictions on average, more exact light data are necessary to improve accuracy for individual subjects.

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## 598.E

### EFFECTIVENESS OF MELATONIN IN THE TREATMENT OF DELAYED SLEEP PHASE SYNDROME

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**Introduction:** Delayed Phase Syndrome (DSPS) is the most common circadian sleep disorder. Treatment options include chronotherapy and bright light treatment. The use of melatonin has also been described in the past, but reports of its effects on sleep time parameters have been limited. Previous work in our laboratory (1) demonstrated that melatonin treatment in subjects with DSPS results in significant advances in the circadian rhythms of core body temperature and melatonin. The pres-

ent study examined whether the advancement in circadian rhythms following melatonin treatment is associated with normalization of sleep times and/or alteration in "morningness / eveningness".

**Methods:** Subjects with DSPS were assigned in a double blind fashion to either placebo (n=3) or melatonin (n=6). Sleep diaries were recorded, and activity monitors (Actiwatch) were worn by all subjects throughout the study. Following a baseline period of 7 days, oral melatonin (0.3 to 3.0 mg) or placebo was administered at 3 to 5 hours before the Dim Light Melatonin Onset (DLMO) for 4 weeks. Actiwatch data from five weekdays during the baseline period were compared to values obtained during five weekdays of the last (4th) week. In addition, we analyzed Horne-Ostberg (H-O) scores. Subjects filled out H-O questionnaires at baseline, at 2 weeks and finally at 4 weeks of treatment. Standard scoring of the questionnaire places individuals into five categories: Definitely Evening Type (16-30); Moderately Evening Type (31-41); Neither Type (42-58); Moderately Morning type (59-69), and Definitely Morning Type (70-86).

**Results:** In the melatonin-treated group, wake times advanced ( $-1.0 \pm 0.4$  hr; t test;  $p < 0.05$ ). In subjects receiving placebo, wake times did not change significantly ( $-0.4 \pm 0.6$  hr). By the 4th week of drug administration, 4 out of 5 subjects receiving melatonin who were initially categorized as "Definitely Evening Type", changed to "Moderately Evening Type" (n=2/5) or to "Neither Type" (n=2/5). One subject in the melatonin-treated group remained unchanged. In contrast, all individuals receiving placebo for 4 weeks remained unchanged in their "morningness / eveningness" scale measured by the H-O score. These results were evaluated by linear regression analysis, using normalized H-O scores at 0, 2 and 4 weeks of the study. During this period of time, the H-O score remained unchanged in the placebo group (slope  $3.3 \pm 3.5$  percent/week). However, melatonin-treatment resulted in a significant time-dependent increase in H-O scores (slope  $14.4 \pm 0.3$  percent/week;  $p < 0.05$ ).

**Conclusions:** These results demonstrate that melatonin not only advances the phase of circadian rhythms, but also advances the wake time. In addition, melatonin treatment improves subjective measures of performance in the morning as indicated by the decreased level of "eveningness" on the H-O score. These findings indicate that melatonin (0.3 to 3.0 mg) taken at the appropriate time is an effective treatment for the symptoms and signs of DSPS in a clinic based setting.

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599.E

**THE CIRCADIAN RHYTHM OF RESPIRATION ASSESSED USING A FORCED DESYNCHRONY PROTOCOL IN HUMANS**

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**Introduction:** In humans there is a daily rhythm in breathing, metabolism and respiratory control sensitivity, with each variable decreasing during nocturnal sleep. There is also an increase in the set-point arterial PCO<sub>2</sub> during sleep. These daily changes could be caused by the behavioral rhythm of sleep and wakefulness and/or by an underlying circadian rhythm. We and others have recently demonstrated a significant circadian rhythm in metabolism, respiration and respiratory control measures in humans during constant routine protocols involving sleep deprivation<sup>1,2,3</sup>. In the current study, we determined whether or not these circadian rhythms in respiration and metabolism persisted during a forced desynchrony protocol (FD) (i.e., without sleep deprivation). We also determined whether or not such rhythms could underlie the sleep-induced changes in respiration and metabolism observed in humans.

**Methods:** 8 subjects (aged 20-33 years; 6 male) were studied throughout 10 days in a FD protocol. Following 2 acclimation days, subjects underwent 7 repetitions of a 28 h FD cycle (18.67 hour wake + 9.33 hour sleep opportunity). This caused subjects to shift their sleep-wake cycles relative to their circadian rhythms. Subjects stayed in dim light (<8 lux) to ensure circadian rhythms would 'free-run'. Respiratory variables were measured in the semi-recumbent posture at 4-hour intervals in each wake period. Thus, measurements were taken during all phases of the endogenous circadian cycle. PETCO<sub>2</sub> (an estimate of arterial CO<sub>2</sub>), ventilation, O<sub>2</sub> consumption and CO<sub>2</sub> production were measured using a turbine flow meter and flow-weighted samples of expired air (Turbofit, Vacumetrics, CA). To account for differences among subjects, data were expressed as percentage deviation from the mean. Phase of the endogenous circadian pacemaker was estimated from core body temperature (CBT). Measurements were assigned a circadian phase (0° = CBT min), grouped into bins of 60° duration (~4 h), and subjected to repeated measures ANOVA. Phases of group mean data were calculated using a cosinor analysis with a fundamental (360 degrees) and one harmonic.

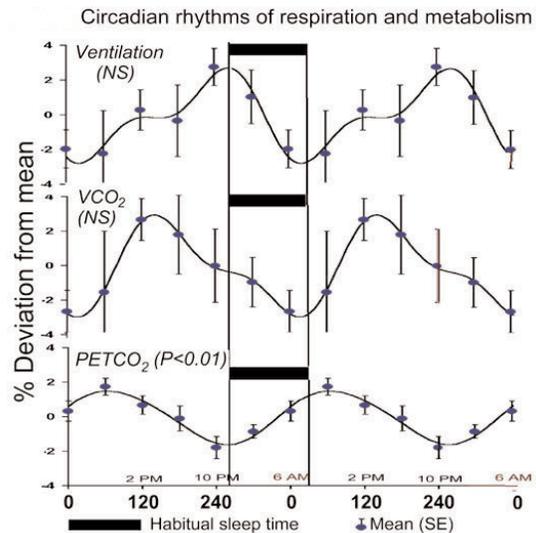
**Table 1**

	Amplitude (+/-)	Peak Phase	P <
P <sub>ET</sub> CO <sub>2</sub>	1.5	70	0.01
CO <sub>2</sub> Production	2.4	140	NS
O <sub>2</sub> Consumption	1.5	125	NS
Ventilation	2.1	265	NS

**Results:** There was a highly significant circadian rhythm in PETCO<sub>2</sub>, but changes in CO<sub>2</sub> production, O<sub>2</sub> consumption, and ventilation failed to reach significance (Table 1). The figure (double plotted) shows that PETCO<sub>2</sub> increased due to cir-

cadian influences between 240 and 60 circadian degrees (i.e., across the usual sleep period), while ventilation and CO<sub>2</sub> production decreased across the usual sleep period. There were equally large fluctuations in these variables across the circadian day.

**Figure 1**



**Conclusions:** These data demonstrate a small but highly significant circadian rhythm in estimated arterial PCO<sub>2</sub>, likely reflecting a changing chemosensory set point. The changes in PETCO<sub>2</sub>, ventilation and metabolism across the usual sleep period are in the same direction as occur during sleep. The current data using a forced desynchrony protocol failed to observe the significant circadian variations in ventilation and metabolism that other studies have observed in humans during constant routine protocols involving sleep deprivation<sup>1,2,3</sup>. It remains to be determined whether the circadian changes in CO<sub>2</sub> set-point result in less stable regulation of arterial PCO<sub>2</sub> in patients with respiratory or metabolic disorders or under conditions of altered metabolism (e.g. exercise).

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## 600.E

## PHENOTYPIC CHARACTERIZATION AND GENETIC SCREENING OF CIRCADIAN PHASE DISORDERS

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**Introduction:** Advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS) are human circadian phase disorders characterized by relatively early/late phases of the sleep period. Familial cases of ASPS coupled with the identification of a mutation in the human Per2 gene causing this phenotype in one such family reveal a genetic basis for this disorder (1). Other familial cases of ASPS that do not have the mutation in hPer2 implicate different genes. Similarly, the reported correlation between DSPS subjects with polymorphisms in the human Per3 gene also suggests a genetic component to the circadian timing of the sleep/wake rhythm. Mutations in a number of the genes comprising the circadian clock exhibit phenotypes of altered circadian timing. Human homologs of these clock genes provide a wealth of candidate genes for studies of ASPS and DSPS. Current clinical diagnostic criteria are limited to self-reports of bedtimes and exclusions of possible confounding conditions. Research criteria based in part on physiologic measures, e.g. the timing of the circadian rhythm of melatonin, are being driven by the need for more accurate phenotypic quantification required for the genetic characterization of these phase disorders.

**Methods:** Diagnoses of ASPS and DSPS were determined using the International Classification of Sleep Disorders (ICSD) criteria. Diagnoses also required a morning/evening type score on the Horne Ostberg questionnaire and/or an advance/delay of at least 2 hours of their dim light melatonin onset (DLMO) relative to values reported for "normal" subjects (2). Characterization of the phenotype also included wrist actigraphy, maintenance of a sleep diary, and core body temperature. Genetic screening of the hPer2 and hPer3 genes is currently underway. If no polymorphisms are found in these genes, samples will be screened for other known circadian genes.

**Results:** To date we have diagnosed 2 subjects with ASPS and 22 with DSPS. Preliminary results from the DSPS subjects evaluated so far showed a delay of several phase measures. The mean±SD time of the core body temperature nadir was 05:54±01:23 (N=7), and the mean time of the DLMO was 23:42±02:11 (N=11). All the Horne Ostberg scores were in the evening (16-30) and moderate evening (31-41) type ranges with the mean score of 29.9±4.5. 5 diagnosed subjects (2 ASPS and 3 DSPS) are potentially familial cases.

**Conclusions:** Careful phenotypic characterization ASPS and DSPS cases, followed by genetic screening for known polymorphisms may identify cases that are not caused by known mutations. Further screening of these cases for other circadian genes may lead to the identification of a new gene(s) responsible for these phenotypes. The expanded phenotypic and genetic characterization of these sleep disorders has implica-

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## 601.E

## NEGATIVE EFFECTS OF WAKE DURATION, CIRCADIAN PHASE, AND CAFFEINE ADMINISTRATION ON SELF-ASSESSMENT

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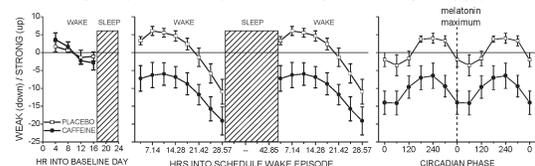
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**Introduction:** Previous research has documented sleep/wake homeostatic and circadian modulation of self-report of mood state (1). We have recently reported in a forced desynchrony protocol that repeated administration of a low-dose of caffeine is associated with positive, neutral, and negative effects on a variety of neurobehavioral measures (2). The present data analysis explores the modulation of self assessment by duration of prior wake, circadian phase, and caffeine.

**Methods:** In an environment free of obvious time cue, following 3 baseline days (16hr wake/8hr sleep), subjects entered a forced desynchrony protocol, with 14 repetitions of a 42.85hr light/dark cycle (28.57hr wake/14.28hr sleep), with hourly ingestion of caffeine (n=8; 0.3mg/kg/hr) or identical appearing placebo (n=8) during scheduled wake episodes. Every 30 minutes during scheduled wake episodes, computerized self assessments were collected, with 16 visual analog scales.

Figure 1

VAS scale of "Strong-Weak", modulation by duration of prior scheduled wake, circadian phase, and caffeine or placebo. Values are shown for baseline days (left), folded at the forced period (42.85 hr, middle), and at each subjects' circadian period (right).



**Results:** Separate repeated-measures, mixed model ANOVAs were conducted for each self assessment variable, for the

effects of the duration of prior scheduled wake (wake), circadian phase assessed by plasma melatonin (phase), and drug condition (drug), with Huynh-Feldt correction. Data were first averaged within subject, in 8, 3.57hr bins for wake and 6 bins for circadian phase, and expressed as deviation from each subjects' mean value from the baseline (16hr) wake episodes. Nearly all variables showed significant modulation from duration of prior scheduled wakefulness and circadian phase, and many showed modulation from drug condition. For all significant effects of drug condition (see Figure for an example), caffeine had a negative effect on the self assessment variable.

Table 1

Self Assessment VAS Scale	drug	wake	drug x wake	phase	drug x phase	wake x phase	3 way inter.
SLEEPY-alert	6.24 *	41.18 ****	n.s.	2361 ****	n.s.	3.68 ****	n.s.
calm-EXCITED	3.81 †	n.s.	2.07 (0.14)	3.80 *	n.s.	n.s.	n.s.
strong-WEAK	9.2 **	35.40 ****	n.s.	1919 ****	n.s.	2.93 ***	n.s.
GROGGY-clear headed	4.47 †	33.09 ****	n.s.	1955 ****	n.s.	3.00 ***	n.s.
well coordinated-CLUMSY	5.82 *	33.09 ****	n.s.	1862 ****	n.s.	3.28 ***	n.s.
Energetic-SLUGGISH	6.38 **	39.16 ****	n.s.	2059 ****	n.s.	2.77 ***	n.s.
contented-DISCONTENTED	n.s.	14.25 ****	n.s.	1293 ****	n.s.	1.95 *	n.s.
TROUBLED-tranquil	n.s.	8.02 **	n.s.	8.13 **	n.s.	1.61 *	n.s.
MENTALLY SLOW-quick witted	5.49 *	34.88 ****	n.s.	1779 ****	n.s.	2.71 **	n.s.
TENSE-relaxed	n.s.	3.61 *	n.s.	n.s.	n.s.	1.42 (0.13)	n.s.
Attentive-DREAMY	4.12 †	41.28 ****	n.s.	1826 ****	n.s.	2.85 ****	n.s.
INCOMPETENT-competent	2.27 (0.15)	26.68 ****	n.s.	1920 ****	n.s.	3.01 **	n.s.
Happy-SAD	n.s.	10.88 ***	n.s.	1543 ****	n.s.	1.70 *	n.s.
HOSTILE-friendly	n.s.	7.28 **	n.s.	9.20 ****	n.s.	1.43 (0.15)	n.s.
Interested-BORED	n.s.	10.62 ***	n.s.	2798 ****	n.s.	1.61 *	n.s.
WITHDRAWN-socialable	n.s.	11.70 ***	n.s.	1303 ****	n.s.	1.42 (0.17)	n.s.

\*\*\*\*p<0.0001; \*\*\* p<0.001; \*\* p<0.01; \* p<0.05; †p<0.10; n.s. p>0.20; CAPS = direction of drug effect

**Conclusions:** These results confirm previous findings of the robust homeostatic and circadian modulation of various self-report mood parameters (1). The data extend to include the modulation from low-dose, sustained administration of caffeine over many days, finding both no effect and negative effects on mood state, including subjects receiving caffeine feeling less alert, energetic, and coordinated. Taken with our previous analyses (2), non-acute caffeine administration appears to possess both beneficial and detrimental effects on a wide array of neurobehavioral functions. Most effects on self assessments were negative, which is surprising in view of caffeine's widespread use as a stimulant.

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**602.E**

**AN ENDOGENOUS CIRCADIAN RHYTHM IN SENSATIONS OF RESPIRATORY DISCOMFORT: RELATIONSHIP TO NOCTURNAL ASTHMA**

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**Introduction:** In many patients with asthma, their pulmonary function worsens and their asthma symptoms increase at night, producing the condition known as nocturnal asthma<sup>1,2,3</sup>. The relative influence of sleep per se and of circadian rhythms (independent of sleep) on the expression of nocturnal asthma has not been addressed using validated circadian techniques. We tested whether or not there exists an endogenous circadian rhythm (unrelated to sleep) in sensations of respiratory discomfort in asthma by using a forced desynchrony protocol.

**Methods:** We studied 8 adult subjects (4 asthma, 4 controls) during wakefulness throughout all phases of the circadian cycle, achieved by scheduling a recurring artificial day length of 28 hours while subjects lived in a 'time isolation' laboratory for 10 days. Subjects reported levels of 4 respiratory symptoms (respiratory discomfort, chest tightness, breathing effort, shortness of breath) using a Borg scale (range 0-10). Assessments were made every 4 hours both at baseline and while breathing through an external resistive load (20 cmH2O/l/sec). The resistance was added in order to accentuate respiratory discomfort. Phase of the endogenous circadian pacemaker was estimated from core body temperature (CBT). Measurements were assigned a circadian phase (0 degrees = CBT minimum), grouped into bins of 60 circadian degrees (approx. 4 hours) and subjected to repeated measures ANOVA to assess circadian rhythmicity.

**Results:** Patients with asthma had significant circadian rhythms in all 4 qualities of sensation for both baseline and resistance breathing, with minimal sensations at a circadian phase that translates to ~10 PM and with peaks in sensations ~6 AM (corresponding to time of lowest pulmonary function). Group mean Borg ratings for all qualities of sensations were <2 at baseline and increased during resistance breathing (to <4). The change in Borg scale ratings from peak to trough across the circadian cycle was 0.5 to 0.7 for all qualities of sensation during both baseline and resistance breathing. Control subjects had little reported sensations at baseline, but had significant increases during resistance breathing to group mean Borg ratings of 7, 2, 7 and 5 for discomfort, tightness, effort and shortness of breath, respectively. Thus, the controls had a greater sensation response to applied external resistance than occurred in the patients with asthma. The controls had a small significant circadian variations in sensations during resistance breathing (and a low amplitude circadian rhythm in pulmonary function, with minimum at ~6 AM). The minimal sensations in the controls occurred at ~10 AM (compared to ~10 PM in the asthma patients).

**Conclusions:** Endogenous circadian rhythms in respiratory sensations exist. The minima of these circadian rhythms occurred at different circadian phases in patients with asthma and control subjects. In asthma, heightened sensation occurred in the early morning. This endogenous circadian rhythm may

contribute to the increased frequency of asthmatic related complaints throughout the night and early morning. Since pulmonary function was also lowest at this time in the asthma subjects, the heightened sensation in the morning may be a reflection of an underlying circadian change in pulmonary function in asthma.

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### 603.E

#### DAILY CAFFEINE CONSUMPTION, DAYTIME SLEEPINESS, AND CHRONOTYOLOGY

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**Introduction:** Previous research has demonstrated a relationship between chronotype and caffeine consumption. Specifically evening types (E-types) were found to consume larger amounts of caffeine than morning types (M-types). 1 It has been suggested that E-types engage in less adaptive sleep hygiene without corresponding elevations in daytime sleepiness. 2 Caffeine consumption in higher doses (over 500 mg per day) may be a possible means by which E types decrease their daytime sleepiness. 2,3 The purpose of this study was to examine daily caffeine use and its effects on daytime sleepiness in M-types and E-types. It was postulated that E-types would consume greater amounts of caffeine compared to M-types and that a negative correlation would be found for caffeine dose and daytime sleepiness in E-types.

**Methods:** Two hundred randomly selected college students participated in the study. The sample consisted of 58 males (29%) and 143 females (71%), age range 18-58 (M=23.5). Subjects completed a packet containing a demographics questionnaire, self-report survey of caffeine use, Epworth Sleepiness Scale (ESS) and Horne-Ostberg Morningness/Eveningness Questionnaire (HOMEQ). Subjects were grouped into E-type or M-type groups based on their HOMEQ score.

**Results:** Average daily caffeine doses between E-types and M-types were compared with a Mann-Whitney U test. E-types indicated a higher daily consumption of caffeine compared to M-types ( $U = 430$ ,  $p < 0.001$ ). The relationship between caffeine dose and daytime sleepiness was determined by a Spearman rho rank order correlation. There was no significant correlation observed between daytime sleepiness and caffeine dose when both groups were combined ( $\rho = 0.030$ , ns). E-types and M-types were both divided into two subgroups based on average daily caffeine doses with subjects indicating greater than or equal to 500 mg being assigned to the high dose

groups. No significant relationships were found for the M-type low dose group ( $\rho = -0.154$ , ns) and E-type low dose group ( $\rho = 0.050$ , ns). A significant negative relationship was observed for the E-type high dose group ( $\rho = -0.552$ ,  $p < 0.05$ ). Only three of the 39 M-types in this study indicated average caffeine doses of greater than 500 mg.

**Conclusions:** As expected, and in support of previous research, E-types indicated a higher average daily consumption of caffeine compared to M-types. The results of this study suggest that one possible mechanism utilized by E-types for decreasing daytime sleepiness is caffeine consumption of greater than or equal to 500 mg/day. Future research on the use of caffeine and other stimulants in E-types and M-types is warranted at this time.

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### 604.E

#### EFFECTS OF LIGHT PULSE DURATION AND INTENSITY IN MODEL SIMULATIONS OF HUMAN PHASE RESPONSE CURVES

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**Introduction:** A mathematical model of the effects of light on the human circadian pacemaker has been developed that accurately predicts the results of several phase response curve (PRC) studies in humans (1). It is quite costly and time-consuming to conduct these types of intensive studies, which limits the range of stimuli that can be fully characterized using experimental means. Kronauer's light model enables us to easily generate PRCs to a wide variety of light stimuli in order to fill in the gaps of current experimental knowledge and to provide testable hypotheses for future studies.

**Methods:** In this simulation study, we used Matlab (Math Works, Natick, MA) scripts to generate model predictions for PRCs to: 1) a single 5h light stimulus of varying intensity (0 - 100,000 lux); and 2) a single 10,000 lux stimulus of varying duration (0 - 16 hrs). Circadian period was assumed to be 24.2 h. The simulation protocol consisted of: 3 baseline days (8 hr sleep in 0 lux, 16 hr wake in 150 lux); a pre-stimulus constant routine (CR, 28 to 52 hours long; 10 lux); recovery sleep (8 hr in 0 lux); a 16 h stimulus day with the stimulus centered in the middle of the wake period in a background of 0 lux; 8 hr sleep in 0 lux; a post-stimulus CR (28 to 52 hours), and 8 hr of recovery sleep (0 lux). Initial phase was defined to be the predicted time of the core body temperature minimum (CBTmin) closest to the end of the pre-stimulus CR. Final phase was defined to be the CBTmin in the post-stimulus CR that was

three circadian cycles (~72 h) away from the initial phase. Phase shift was defined to be final phase minus initial phase.

**Results:** In both sets of simulations, the PRCs have larger delay than advance regions, reflecting the ~72h of the >24h period between the two CRs. In Figure 1, as intensity of the 5h-stimulus increases, the model predicts larger amplitude type 1 PRCs with steeper slopes in the critical region (near CBTmin). In Figure 2, as the duration of the 10,000 lux stimulus increases, the critical region of the type 1 PRCs moves later, the amplitude increases greatly from 0h to 4h, and then more gradually up to the 12h stimulus. The 16h stimulus covers both the advance and delay portions of the PRC, reducing its effectiveness and PRC amplitude.

Figure 1

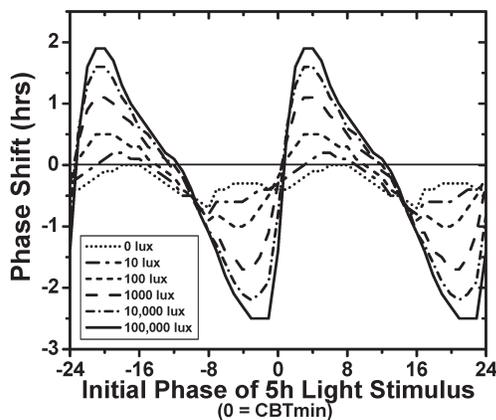
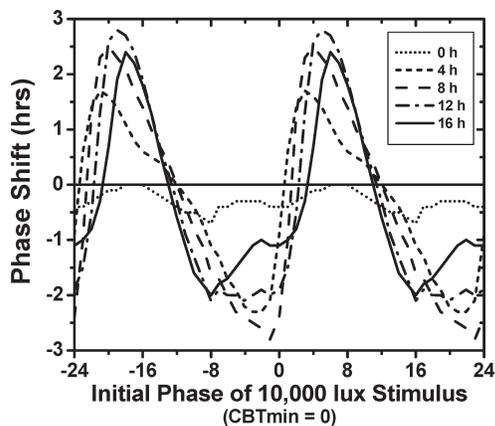


Figure 2



**Conclusions:** Kronauer's light model predicts type 1 PRCs for all the stimuli tested. We must investigate the effects of even longer 100,000 lux stimuli to see if the predicted PRCs remain type 1. The critical region remains centered over the CBTmin when the stimulus is 5h, but as the duration increases, the critical region moves later. These hypotheses must be tested by

experimental means to determine their accuracy.

**References:**

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**Research supported by NIMH grant RO1-MH45130; NIA grants RO1-AG06072, PO1-AG09975 and KO1-AG00661; NHLBI grant 5T32-HL07901; AFOSR grant F49620-95-1-0388; ARO grant DAAD19-99-1-0241; NASA-NSBRI cooperative agreement NCC9-58; NASA grants NAG9-524 and NAGW-4033; NASA cooperative agreement NCC2-1167**

**605.G**

**SCHOOL AND WEEKEND NIGHT SLEEP PATTERNS IN MIDDLE SCHOOL STUDENTS: A PILOT STUDY**

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**Introduction:** Adolescent sleep habits have commanded attention because the combination of having a biologically based phase shift in sleep with early school start times is producing sleep deprivation and impairing adolescents' daytime functioning. Adolescents receive less than their ideal amount of sleep during the week and try, unsuccessfully, to make up for this sleep debt on weekends (1). Although young adolescents face early school start times and require long sleep hours, little is known about their sleep patterns and behaviors. This pilot study examined sleep patterns and degree of sleep loss in a sample of 7th grade middle school students.

**Methods:** 26 7th grade boys and girls recruited from a Maryland middle school health class maintained daily sleep diaries for 8 days. Students recorded bedtimes, wake times, and other sleep/wake habits. From the diaries, mean bedtime (BT), wake time (WT), and total sleep time (TST) were computed for school and weekend nights. Students also completed the Sleep Habits Questionnaire (1) from which "...how much sleep [do] you think you would need each night to feel your best every day," identified students' perceived ideal total sleep per night. Students' degree of sleep deprivation was determined by comparing diary reported total sleep with questionnaire reported ideal sleep. Paired samples t-tests compared school versus weekend-night sleep differences and differences between students' actual versus ideal total sleep.

**Results:** On school nights, mean BT was 22:06 (SD=:48), WT was 6:24 (SD=:30), and TST was 493 min (SD=42 min). On weekends, mean BT was 23:00 (SD=:54), WT was 8:00 (SD=1:24 min), and TST was 546 min (SD=78). In comparison to school nights, students went to bed 55 min later on weekends (p < .001), awakened 96 min later (p < .001), and slept 43 min longer on weekends (p < .02). Furthermore, diary reported total sleep was significantly less than students' perceived ideal total sleep. Students reported needing 8 - 11 hours sleep per night to feel their best each day (M=9 hrs 12 min;

SD=60). On average, 7th graders reported that they obtained 57 min less sleep per night on school nights ( $p < .001$ ) and 6 min less per night on weekends (ns) in comparison to their perceived ideal total sleep times. These discrepancies were used to project the cumulative amount of sleep loss over the entire week. Overall, students obtained 5 hours 6 min less sleep per week than their reported ideal ( $p < .001$ ).

**Conclusions:** Overall, middle school students' sleep patterns were similar to those of older adolescents. The 7th graders went to bed late on both school and weekend nights. They awakened early on school days and "slept in" on the weekend. They obtained less than their ideal amount of sleep on school nights, culminating in an average of 5 hours of sleep deprivation over the entire week. Results suggest that 7th graders have already begun to develop poor sleep habits that are likely to persist into adolescence and adulthood.

**References:**

(1) Wolfson AR, Carskadon MA: Sleep schedules and daytime functioning in adolescents. *Child Development*, 69, 1998, 875-887.

## 606.G

### RESTLESS LEGS AND PERIODIC LIMB MOVEMENT DISORDER SYMPTOMS IN YOUNG CHILDREN: RESULTS OF A SURVEY

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(1) Brown Medical School

**Introduction:** Several recent studies have found an association between frequent periodic limb movements in children and behavioral problems, including ADHD (1). Furthermore, an association between RLS/PLMD and iron deficiency anemia has been described in adults and, more recently, in children. The prevalence of RLS and PLMD in either the general pediatric population or in potentially high-risk populations, however, is unknown. The purpose of this study was to investigate the relationship among RLS/PLMD symptoms, sleep disturbance, behavioral problems, and iron deficiency anemia/lead intoxication in a sample of inner city early school-aged children.

**Methods:** A convenience sample of 162 healthy patients between the ages of 3 and 7 years inclusive (mean age 65.7 months, SD 16.5) presenting for well child or acute care at a pediatric primary care clinic located in a pediatric teaching hospital participated in the study. Parents completed the following measures: 1) the RLS/PLMD Pediatric Screening Questionnaire (RPSQ), a 12 item survey developed for this study, 2) the Children's Sleep Habits Questionnaire (CSHQ), and 3) the Child Behavior Checklist (CBCL). Data on Hgb/Hct and lead levels for each subject were obtained from the medical record. Subjects meeting symptomatic criteria for RLS/PLMD, defined as scoring above predetermined threshold score using selected items from the RPSQ, were then compared on the independent variables to children who did not meet the criteria.

**Results:** A total of 26 subjects (16.0 %, mean age 67.5 SD 15.5 months) met the criteria on the RPSQ for RLS/PLMD; there were no significant age, gender, or ethnicity differences between groups. The mean total RPSQ scores for the 2 groups

were significantly different ( $p < .001$ ). The RLS/PLMD group was significantly more likely to have a family member diagnosed with RLS/PLMD ( $p = .004$ ); The RLS/PLMD group had a significantly higher score on the Sleep Onset Delay subscale ( $p = .04$ ) of the CSHQ as well as on a single CSHQ item relating to restless sleep ( $p = .005$ ). Total ( $p = .002$ ), Internalizing ( $p = .005$ ), and Externalizing CBCL t-scores ( $p = .01$ ) were all significantly higher in the RLS/PLMD group. However, the RLS/PLMD group was not significantly more likely to have a reported history of anemia, and the mean Hgb within 12 months of the index visit for the two groups was not significantly different. There were also no significant differences in maximum lifetime lead levels between the RLS/PLMD and control groups.

**Conclusions:** Young children with symptoms suggestive of RLS/PLMD were more likely to have a positive family history of RLS/PLMD, to have significantly more disturbed sleep and to have significantly more behavioral problems than asymptomatic control children. This relationship did not appear to be associated with iron deficiency anemia or elevated lead levels.

**References:**

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**Research supported by a grant from the Restless Legs Syndrome Foundation.**

## 607.G

### SLEEP STUDY IN INFANTS WITH CONGENITAL CARDIAC DISEASE: PRELIMINARY RESULTS

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(1) Instituto do Coração - HCFMUSP

**Introduction:** Adults with congestive heart failure present a high prevalence of sleep disordered breathing. In contrast, there are very few studies on infants with congenital cardiac disease. Congenital cardiac disease can be divided in cyanotic and acyanotic, depending on the levels of O<sub>2</sub> Saturation at rest.

**Methods:** We performed hospital-based sleep studies in eleven consecutive children with severe congenital cardiac disease, mean age:  $8 \pm 2.9$  months (range 6 to 12 months). The patients were divided in 6 cyanotic cardiac disease (CCD) and 5 with acyanotic cardiac disease (ACD). Patients with previous cardiac surgery, neurological or infectious diseases were excluded; infants taking sedative medication were also excluded. The sleep studies were performed with an EMBLA digital system (16 channels, Flaga hf. Medical Devices). The studies were performed and scored based on the guidelines for cardiopulmonary sleep studies in children (ATS 1996).

**Results:** The sleep studies showed the following features: mean sleep efficiency index: of 70.8% ( $\pm 27.8$ ) for the CCD group and 82.5% ( $\pm 10$ ) for the ACD group,  $p = 0.09$ . The apnea hypopnea index (AHI) was 16.2 ( $\pm 15.9$ ) for CCD and 7.3 ( $\pm 5$ ) for the ACD group,  $p = 0.49$ ; mean duration of apneas: 12.5 sec ( $\pm 8.9$ ) for CCD and 8.2 sec ( $\pm 2.3$ ) for ACD,

$p = 0.20$ ; mean O<sub>2</sub> Saturation:  $92.3 (\pm 73.5)$  for CCD and  $96.2 (\pm 1.6)$  for ACD,  $p = 0.002$ ; mean arousal's index:  $3.8 (\pm 6.6)$  for CCD and  $7.4 (\pm 3.7)$  for ACD,  $p = 0.80$ . Considering the AHI > 1 as abnormal, 91% of the infants presented sleep disturbance.

**Conclusions:** Our preliminary study suggests that children with congenital cardiac disease present a high prevalence of respiratory sleep disturbances and decrease of sleep efficiency. We found no significant differences in the sleep of infants with ACD versus CCD, but this can be related to the small number of patients studied. Sleep disorders in patients with congenital cardiac disease is largely ignored.

**References:**

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**608.G**

**INCREASED INTRACRANIAL PRESSURE IN ASSOCIATION WITH REM-RELATED RESPIRATORY DISTURBANCES IN A 3-YEAR-OLD CHILD**

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(1) University of Michigan Health System

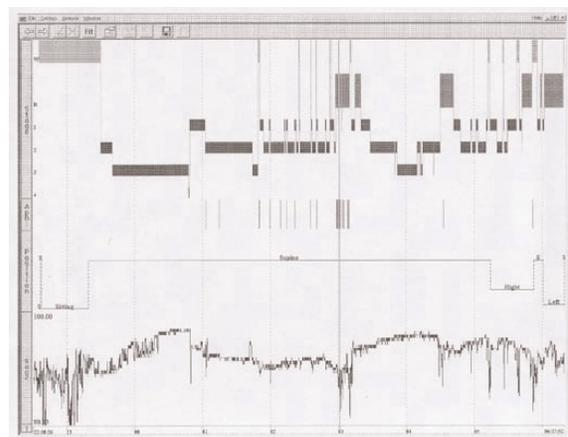
**Introduction:** Increased intracranial pressure (ICP) represents a rarely reported complication of obstructive sleep apnea hypoventilation syndrome. We review the unusual case of a young boy in whom episodic nocturnal elevation of ICP was the presenting manifestation of his REM-related respiratory disturbances. The 3-year-old patient has a history of seizures and shunted hydrocephalus with at least 65 previous shunt revisions performed at an outside institution. He presented acutely with two days of unsteady gait and occasional vomiting and with a seizure on the day of admission. CT of the head revealed a slight increase in the size of the fourth ventricle and the patient's ventriculo-peritoneal shunt was subsequently revised. Postoperatively, the patient continued to have nocturnal elevations of ICP sometimes exceeding 50 mm Hg despite a functional shunt. A polysomnogram was ordered when it was discovered that the patient had multiple risk factors for sleep-disordered breathing, including prominent snoring and labored respiration during sleep.

**Methods:** A portable polysomnogram was performed in the pediatric ICU with concurrent monitoring of intracranial pressure via a left frontal ICP monitor. The study recorded central and occipital EEG, EOG, submental EMG, airflow, EKG, thoracoabdominal motion, anterior tibialis EMG, pulse oximetry, and end-tidal CO<sub>2</sub>. The tracing was scored manually in 30-second epochs.

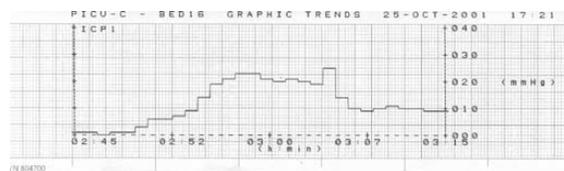
**Results:** The polysomnogram recorded 391 minutes of sleep during the 467 minute study, yielding a reduced sleep efficiency of 83.6%. Apneic episodes (apneas or hypopneas of at least 10 seconds duration) occurred on average 3.7 times per hour for the study as a whole, but 14.9 times per hour during the 56.5 minutes of REM sleep recorded. Nine obstructive apneas exceeding 10 seconds were recorded, all during REM

sleep. Increased intracranial pressure as high as 26 mm Hg was recorded during several REM periods [figures 1 and 2], correlating closely with periods of frequent apnea and/or elevation of end-tidal CO<sub>2</sub> above 50 mm Hg. Hypoxemia with these events was mild, and SaO<sub>2</sub> remained above 89%. Continuous video EEG recording was performed the night following the polysomnogram. The patient continued to exhibit periods of increased ICP during sleep, but EEG revealed no subclinical seizure activity in conjunction with these events.

**Figure 1**



**Figure 2**



**Conclusions:** This case illustrates the potential for REM-related respiratory disturbances (apnea and hypercapnea) to cause episodic increases of ICP in a child despite the presence of a functional shunt. Potential mechanisms of action include alteration of cerebral blood flow due to hypercapnea or other gas exchange abnormalities.

**References:**

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**Research supported by N/A**

609.G

**POLYSOMNOGRAPHIC FINDINGS AND BEHAVIOR IN CHILDREN SCHEDULED FOR ADENOTONSILLECTOMY OR HERNIA REPAIR**

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**Introduction:** Behavioral morbidity associated with sleep-disordered breathing (SDB) can include inattention, hyperactivity, and excessive daytime sleepiness, but few reports have paired validated measures of these problems with polysomnographic data. Such analyses could help determine whether SDB is a direct cause of these behavioral outcomes, and help define what polysomnographic findings are most predictive of important outcomes.

**Methods:** We recruited 46 children (23 girls) aged 5 to 12 years and scheduled for adenotonsillectomy or hernia repair (n = 7) to participate in an ongoing research protocol. Pre-operative outcome variables included mean sleep latency (MSL) in a Multiple Sleep Latency Test; the Hyperactivity Index T-score (HIT) of the Connors' Parent Rating Scale, Revised (long version); and a DSM-IV-based ADHD symptom scale (IHS, inattention/hyperactivity scale)[1]. Polysomnography usually included esophageal pressure (Pes) monitoring (n = 33) and end-tidal CO2 monitoring (n = 43). Two-breath or longer hypopneas were scored when a decrement in airflow (thermocouples) or excursion of the chest or abdomen was followed by arousal or oxygen desaturation > 3%. Respiratory event-related arousals (RERAs) were scored as crescendo increases in negative Pes of 5 or more cm of water during 5 or more breaths prior to an arousal. Periodic leg movements during sleep were scored by published criteria [2].

**Table 1**

Mean values for key variables

	Mean (s.d.)
Mean Sleep Latency (MSL, min)	16 (4)
Inattention / Hyperact. Scale (IHS)	0.79 (0.59)
Hyperactivity Index T Score (HIT)	53 (12)
Age (years)	7.8 (1.8)
Obstructive apnea index	2.9 (7.6)
Apnea hypopnea index	8.2 (12.6)
Respiratory disturbance index	8.5 (12.8)
Min oxygen sat (%)	91 (6)
Max end-tidal CO2 (mm Hg)	55 (5)
% epochs with end-tidal CO2 > 50	22 (30)
Most negative Pes (cm water)	38 (25)
% epochs with Pes < -10 cm water	59 (61)
Arousal index	13 (10)
Periodic leg movement index	2.8 (5.7)

**Results:** The subjects showed a wide range of sleepiness, hyperactivity, and SDB (Table 1) but values did not differ between children scheduled for adenotonsillectomy and those scheduled for hernia repair. The obstructive apnea index (num-

ber per hour of sleep) was ≥ 1 in 19 children, the apnea hypopnea index was ≥ 5 in 18 children, and the periodic leg movement index was ≥ 5 in 8 children. Regression of MSL, IHS, and HIT on explanatory variables produced R-squared values shown in Table 2. A multiple regression of IHS on the respiratory disturbance index, minimum oxygen saturation, and periodic leg movement index explained 20% of the variance in IHS (p = 0.02) but the only independently predictive explanatory variable was the periodic leg movement index (p = 0.02). Scored RERAs showed no outcome-based utility, but the most negative Pes was the only variable that showed a trend toward an association with MSL.

**Table 2**

Regression results (R-squared)

	MSL	IHS	HIT
Obstructive apnea index			
Apnea hypopnea index		0.08*	
Resp disturbance index		0.08*	
Min oxygen sat		0.09†	
Max end-tidal CO2			
% epochs ETCO2 > 50			
Most negative Pes	0.11*		
% epochs Pes < -10			
Arousal index		0.10†	
Periodic leg mvmt index		0.09†	0.11†
Tonsillectomy vs. hernia			

\* p < 0.10; † p < 0.05; all other cells N.S.

**Conclusions:** Polysomnographic measures of SDB severity show only limited association with selected behavioral outcomes suspected to be among the most important consequences of SDB. Scoring of hypopneas, perhaps more than RERAs, may improve outcome-based assessment for SDB. In this sample composed mainly of children with enlarged tonsils, periodic leg movements during sleep again emerged as the most consistent polysomnographic correlate of inattentive and hyperactive behavior [2].

**References:**

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610.G

REPORTS OF ADHD INATTENTIVE AND HYPERACTIVE/IMPULSIVE SYMPTOMS AMONG HEALTHY CHILDREN UNDER RESTRICTED OR OPTIMIZED SLEEP CONDITIONS

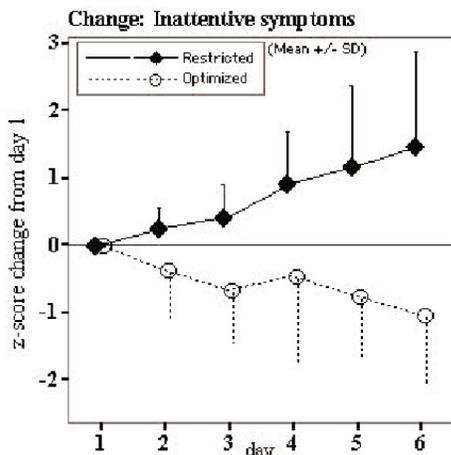
Fallone GP,<sup>1</sup> Carskadon MA<sup>1</sup>

(1) E.P. Bradley Hospital Sleep and Chronobiology Research Laboratory, Brown Medical School, Providence, RI,

**Introduction:** Our previous study of healthy children revealed an increase in parent ratings of child behavior problems following a week of restricted sleep (1) but we have not examined how sleep changes might affect ratings of specific symptoms associated with behaviorally-based disorders, such as Attention-Deficit/Hyperactivity Disorder (ADHD). We report here preliminary data from a pilot study of daily parent ratings of ADHD symptoms for healthy children during Optimized or Restricted sleep conditions.

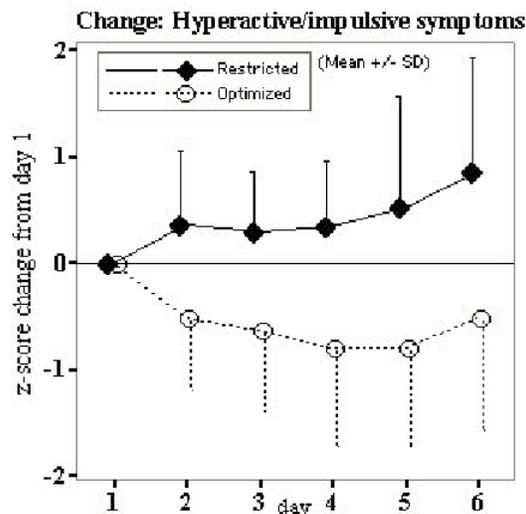
**Methods:** We studied 12 girls and 6 boys (ages 6.7 to 13.3) screened for medical and psychological health and participating in ongoing laboratory protocols. Our selection process was one of convenience; while sex ratios for each group were the same (6 girls, 3 boys), children in the Optimized group were significantly older (mean = 10.9 yrs vs. 8.4 yrs). A parent completed a symptom checklist for six nights while his or her child followed an Optimized (10 hours per night) or Restricted sleep schedule at home. Restricted schedules limited sleep to 8 hours for children younger than 8 years of age (n = 4, 2 girls) and 6.5 hours for older children (n = 5, 4 girls), primarily by delaying bedtime. The symptom checklist included the 9 inattentive and 9 hyperactive/impulsive symptoms from current diagnostic criteria (2). Parents rated items on a scale from 0 "Not true at all" to 3 "Very much true", completing the scale after scheduled bedtimes. Scores within each symptom category were summed to arrive at daily Inattentive and Hyperactive/impulsive subtotals. Because of the age difference between Optimized and Restricted groups, we transformed symptom subtotals to z-scores within groups and then used the standard scores to calculate daily changes relative to baseline (day 1) scores for each child.

Figure 1



**Results:** We examined change scores for Inattentive and Hyperactive/impulsive subtotals between groups (Optimized vs. Restricted) across days with repeated-measures analysis of variance. Group-by-day interactions were significant for Inattentive ( $F(5,80) = 9.9, p < .001$ ) (Figure 1) and Hyperactive/impulsive change scores ( $F(5,80) = 3.1, p < .05$ ) (Figure 2). Post-hoc comparisons showed significant differences between groups by the third night of the schedule for Inattentive change scores ( $t(1,16) = 3.4, p < .01$ ) and by the fourth night of the schedule for Hyperactive/impulsive change scores ( $t(1,16) = 3.1, p < .01$ ).

Figure 2



**Conclusions:** These data support our previous findings and suggest that parents' perceptions of ADHD symptoms in otherwise normal children will show cumulative effects of inadequate sleep across several nights. We are intrigued not only by the cumulative increase in symptom ratings noted among the Restricted group but also by the relative decline in symptom ratings observed among the Optimized sleep group. Inferences about these relations are seriously limited by the sampling method and age differences, but these results merit further inquiry.

**References:**

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Research supported by NR04279; MH52415; MH01358

611.G

PVT PERFORMANCE AMONG CHILDREN IN COMPARISON TO ADULTS

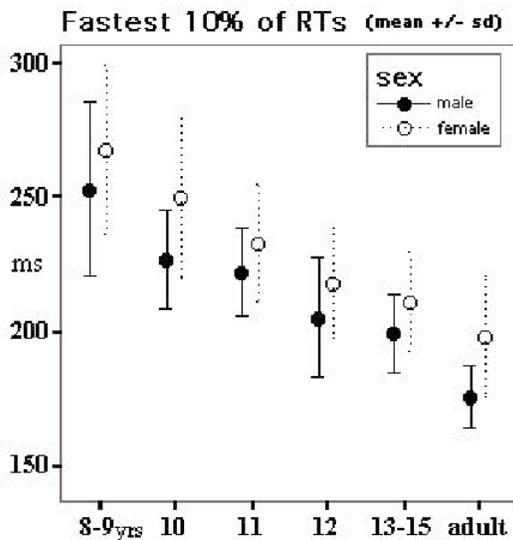
Fallone GP,<sup>1</sup> Carskadon MA<sup>1</sup>

(1) E.P. Bradley Hospital Sleep and Chronobiology Research Laboratory, Brown Medical School, Providence, RI

**Introduction:** The 10-minute psychomotor vigilance task (PVT), a simple visual reaction time test, shows robust and consistent changes in adult humans as a function of homeostatic drive for sleep and circadian rhythmicity (1). Little is known about performance of children and adolescents on this measure. To examine the potential usefulness of the PVT in youngsters, we compare first-trial PVT performance of children to that of young adults

**Methods:** Child participants included 77 boys (mean age=11.7 y; sd=1.6) and 72 girls (mean age=11.3; sd=1.5). Adult participants included 10 men (mean age=24.5 y; sd=4.3) and 10 women (mean age=21.9; sd=4.3). Children and adults participated in separate protocols. During the week before data collection, children followed either a self-selected school-night sleep schedule or an optimized sleep schedule of at least 10 hours. Adults followed a fixed 8- or 10- hour sleep schedule. Participants arrived at the sleep laboratory in the early evening and received an introduction to the handheld PVT-192 (AMI; Ardsley, NY ) before their first trial, which occurred between 6 and 8 PM. We used ANOVA to examine median reaction time (RT) for correct responses, mean fastest 10% of RTs, mean slowest 10% reciprocal RTs (1/RT), and total lapses (RTs greater than 500 milliseconds), with age group and sex entered as factors. Age groups were: 8-9 yrs (n = 23; 10 f), 10 yrs (n = 26; 17 f), 11 yrs (n = 53; 25 f), 12 yrs (n = 27; 12 f), 13-15 yrs (n =20; 8 f), and adult.

Figure 1



**Results:** Main effects of age group were observed for median RT (F=30.4), fastest RT (F=29.4), slowest 1/RT (F=20.3), and lapses (F=20.3) [all df (5,157); p <.001]. Main effects of sex

were observed for median RT (F=12.7) and fastest RT (F=18.4) [df (1,157); p <.001]. The Figure displays fastest RT. No interactions were observed. Post-hoc comparisons revealed that performance of 8-9 year olds was distinct from all other age groups for median RT, slowest 1/RT, and lapses; only the 13-15 group showed no differences from the adult group (Table).

Table 1

Mean (SD) PVT Performance				
Age (yrs)	Median RT	Fast RT	Slow RRT	Lapse
8-9 <sup>a</sup>	356 (53) b,f	259 (32) c,f	1.60 (.36) b,f	12 (8) b,f
10 <sup>b</sup>	312 (41) a,d,f	242 (28) d,f	2.03 (.36) a,e,f	5 (4) a
11 <sup>c</sup>	301 (34) a,e,f	227 (20) a,e,f	2.02 (.29) a,e,f	5 (3) a
12 <sup>d</sup>	273 (36) a,b,f	211 (22) a,b,f	2.25 (.60) a,f	3 (5) a
13-15 <sup>e</sup>	263 (25) a,c	204 (17) a,c	2.45 (.43) a,c	2 (2) a
Adult <sup>f</sup>	236 (26) a,d	187 (21) a,d	2.73 (.41) a,d	1 (1) a

Subscripts denote post-hoc differences (p <.05).

**Conclusions:** These cross-sectional data demonstrate age-related improvements in PVT performance into adolescence and persistent sex differences on certain measures. Both findings are consistent with developmental data on visual RT (2). While predictable, large developmental differences in baseline performance are likely to complicate interpretation of PVT decrements among children under conditions of inadequate sleep. The particularly poor performance of our youngest participants indicates that they may simply be too young for the PVT and/or that parameters need adjustment. For example, the RT data suggests an age-adjusted lapse criterion of 890 ms for 8-9 year-olds. In conclusion, use of the PVT is questionable for young children and viable in adolescents.

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612.G

SLEEP HABITS OF JUVENILE DETAINEES IN THE CHICAGO AREA

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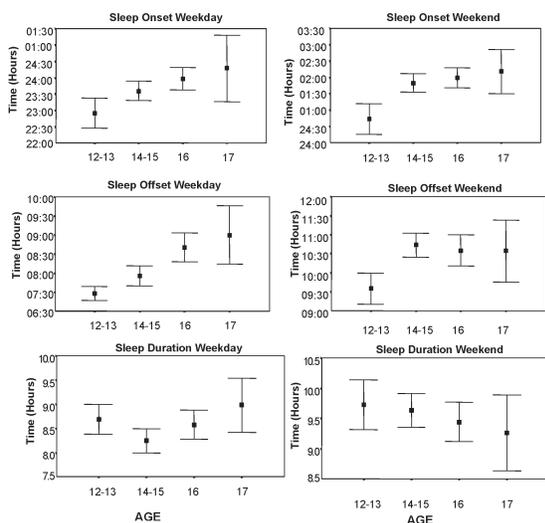
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**Introduction:** Previous research has indicated that sleep-wake habits of teenagers vary from those of adults and younger chil-

dren and that many adolescents experience chronic partial sleep deprivation. It has been consistently reported that sleep duration among adolescents increases significantly on weekends compared to weekdays, which has been interpreted to indicate that adolescents do not get enough sleep on weekdays and need to make it up on the weekends. The suggestion has also been made that in this group sleep deprivation may play a role in lower grades (1) and with behavioural problems (2). A unique opportunity presented itself to collaborate on a project investigating the mental and physical health and well being of individuals at entrance to the Cook County Juvenile Temporary Detention Center.

**Methods:** 729 young people between 12-17 years of age were interviewed. Subjects were interviewed by trained examiners on a series of surveys including: alcohol, drug and mental disorders, functional impairment, educational deficits, criminal history, medical history and socio-demographic risk factors. In the medical section there were 16 sleep related questions, including what time do you usually go to bed and wake up and how long does it take you to fall asleep on weekday and weekends. For the purposes of this analysis the following variables were investigated: sleep onset weekday and weekend, sleep offset weekday and weekend, sleep duration weekday and weekend by age using ANOVA. In addition, we report the percentage of detainees feeling refreshed upon waking, feeling sleepy a lot during the day and drug use to help get to sleep.

Figure 1



Graphic representation of sleep onset, offset and durations on weekdays and weekends of juvenile detainees aged between 12-17 years.

**Results:** Preliminary analyses show that overall there is a mean ( $\pm$ stdev) weekday sleep duration of  $8.5 \pm 2.1$  hrs, weekend sleep duration of  $9.58 \pm 2.4$  hrs, weekday sleep onset of  $23:30 \pm 2.36$ , weekend sleep onset of  $01:40 \pm 2.24$ , weekday sleep offset of  $7:55 \pm 2.24$ , weekend sleep offset of  $11:04 \pm 2.36$  (military time in hours and minutes). Sleep duration on weekdays is significantly shorter than on weekends ( $p > 0.0001$ ). 71% of the subjects reported feeling refreshed upon waking, but 45 % report feeling sleepy a lot during the day and 15% regularly use drugs to help them sleep. Analysis of variance

indicates that there is a significant effect of age on weekday sleep onset ( $p = 0.0008$ ) and weekend sleep onset ( $p > 0.0001$ ), sleep offset on both weekdays ( $p > 0.0001$ ) and weekends ( $p = 0.0008$ ), and a trend toward significance for sleep duration weekday ( $p = 0.06$ ).

**Conclusions:** In summary, sleep onset and offset times are later among older youth entering detention, while there is no significant difference in sleep duration between age groups. In comparison to previous data (1) the juvenile detainees in the current study have later sleep onsets and wake times on both weekdays and weekends, while sleep durations appear to be longer and do not vary significantly with age. Although these juveniles are sleeping an average of 8.5-9.5 hours a night almost half experience significant daytime sleepiness. Further analysis of these data may reveal relationships between sleep times and other measures of mental health, criminal behavior and school performance.

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**613.G**

**PRELIMINARY EVIDENCE OF THE NEUROCOGNITIVE SEQUELAE OF A SLEEP RESTRICTION PROTOCOL IN PRE-ADOLESCENTS**

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**Introduction:** There is increasing evidence that insufficient sleep causes specific decrements in cognitive abilities. A few studies have evaluated the impact of insufficient sleep on adolescents and have also identified similar problems. To date, there are few data addressing the impact of insufficient sleep in pre-adolescent children. Some evidence comes from studies that have evaluated behavior problems and psychiatric disorders that are associated with sleep disorders. For example 18% of children with learning disabilities and behavioral problems were found to have sleep disordered breathing (1). Pichetti (2) and Chervin (3) have suggested that a significant percentage of children with ADHD have an underlying sleep disorder. This report presents preliminary findings of neurocognitive sequelae of experimental sleep restriction (SR) in a 9-year-old child.

**Methods:** A 9-year-old boy completed a baseline neurocognitive battery and a nearly identical follow-up battery immediately following a lab-based SR challenge involving 4 hours of sleep. Both assessments were conducted at approximately 9:00 am on a weekend morning. Baseline PSG was used to rule out the presence of sleep disorders. The neurocognitive batteries consisted of measures of attention, verbal expressive and receptive abilities, short-term memory, and executive function.

**Results:** The subject was free of medical, psychiatric and sleep, disorders. Results of selected measures from the baseline and SR neurocognitive batteries are presented in Table 1. On two measures of verbal ability, Wechsler's Vocabulary and Similarities subtests, raw scores fell by 24% and 47% respectively. On the Meshulam Cancellation task, time to completion dropped by 25% from the baseline to SR condition, while omission rates increased by 44%. On the Wide Range Assessment of Memory and Learning (WRAML), Story recall task there was a 42% drop in recall rates following SR. There were no notable differences in performance on a timed word production task and on a measure of executive functioning (The Wisconsin Card Sort Task, score range from the 79th to 95th percentile).

**Table 1**

Measure	Baseline	Sleep Restriction
WISC* and WASI**		
Vocabulary (raw score)	33	25
Similarities (raw score)	30	16
FAS/PRW (timed word production task)	6	5.3
Mean # of words	0.7	2.3
Mean # of errors		
Wisconsin Card Sort		
Errors		94th percentile
Perseverative Responses		86th percentile
WRAML Story Memory (percentage recalled)	57%	29%

\*Wechsler Intelligence Scale for Children - III;  
 \*\*Wechsler Abbreviated Scale of Intelligence

**Conclusions:** While these descriptive findings involve only one subject and are therefore preliminary, they provide evidence that acute sleep loss can produce measurable decrements in cognitive performance in healthy children. While no significant decrements were noted on a non-verbal measure of executive functioning, a large decrement in verbal abilities requiring a relatively high level of comprehension, expressive ability, and abstract reasoning was noted. The ability to attend to and recall a short story was also affected by SR. On a rote cancellation task the subject's speed and accuracy both dropped suggesting that motivation to perform well and/or ability to attend to a repetitive low demand task were impaired. Studies with additional subjects using this protocol are in progress that will permit examining individual differences in the pattern of cognitive and behavioral deficits in response to acute sleep restriction. These preliminary results suggest that further assessment of cognitive and behavioral deficits in response to acute sleep restriction in children is warranted. Chronic and acute sleep disruption associated with sleep disorders or poor sleep habits may have a particularly negative effect on young children whose cognitive abilities, regulation of affect and attention and adaptive skills are less well established.

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**614.G**

**PERIODIC LIMB MOVEMENTS IN YOUNG CHILDREN: PRELIMINARY ACTIGRAPHY DATA**

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**Introduction:** Studies in adults have suggested that actigraphy may have utility in corroborating and quantifying Periodic Limb Movement Disorder (PLMD) subjective symptoms (1), but little similar data on actigraphic assessment of periodic limb movements in children exist. The purpose of this study, part of a larger examination of RLS/PLMD in young children, was to compare arm and leg actigraphic data in children meeting criteria for significant symptoms of PLMD with those of an asymptomatic comparison group.

**Methods:** Methods: The original sample consisted of 162 consecutive patients between the ages of 3 and 7 years inclusive (mean age 65.7 months, SD 16.5) presenting for well child or acute care at a pediatric primary care clinic located in a pediatric teaching hospital. As part of the initial study evaluation, parents completed the 12 item RLS/PLMD Pediatric Screening Questionnaire (RPSQ) and subjects scoring above a pre-determined threshold score using selected items from the RPSQ were defined as meeting symptomatic criteria for PLMD. Thirteen PLMD children (mean age = 64.5 months SD 16.2; 5 girls) and eight control children (mean age = 64.1 months SD 24.5; 3 girls) wore actigraphs on the non-dominant wrist and corresponding leg for one night. Nocturnal sleep period was determined from the actigraphy record using corroborative behavioral data (2). Difference scores for leg and wrist activity counts were calculated for each 1-minute epoch of the nocturnal sleep period and averaged for each child.

**Results:** Results: We examined mean difference scores (L-W), percent of epochs when leg activity exceeded wrist activity (% L>W), and maximum leg activity count for the nocturnal sleep period (Table 1). Group differences were in the expected direction for all three variables but failed to reach statistical significance with t-tests, although difference in maximum leg activity approached significance (p=.08).

**Table 1**

Actigraphy variables	RLS/PLMD Mean (SD)	Control Mean (SD)
Sleep period	494 (105)	526 (53)
Avg. leg-wrist activity	1 (6)	-2 (3)
% epochs L > W	26% (14)	21% (12)
Max leg activity count	245 (39)	207 (55)

**Conclusions:** Preliminary results from this small

sample suggest that children with symptoms suggestive of PLMD may have actigraphic findings consistent with increased nocturnal leg movements. Further study, including corroboration with polysomnographic data, is needed.

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**Research supported by Restless Legs Syndrome Foundation**

### 615.G

#### SALIVARY MELATONIN AND TEMPERATURE AS BIOPHYSICAL FACTORS OF SLEEP DISTURBANCE IN YOUNG CHILDREN: A PILOT STUDY

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**Introduction:** Sleep disturbances in young children can adversely affect brain development (1) and may contribute to behavioral problems when children are older (2). The circadian rhythms of temperature and melatonin are closely linked to efficient sleep. There is very little literature reporting the characteristics of biological rhythms in young children and their possible contribution to sleep disturbance in this age group. The purpose of this pilot study was to test the methods for determining variations in melatonin and body temperature patterns and their association with the measurement of sleep efficiency and a score on the Toddler and Preschool Sleep Problems Screening Tool (TPSPST), a 14 item forced choice questionnaire developed by this researcher to classify the severity of sleep disturbance in young children. The specific aims of the study are 1) describe the rhythms of melatonin and temperature in young children. 2) determine if a relationship exists among the rhythms of melatonin and body temperature, sleep efficiency, and the TPSPST.

**Methods:** This research used a descriptive, repeated measures design to make observations over four 24-hour periods. Serial correlations of period and phase of the circadian rhythms of temperature and melatonin were obtained through time series observations. A convenience sample (n=6) of children (12 months to 4 years) was recruited for the study. The presence and severity of sleep disturbance was determined using the TPSPST. During the first 48 hours, temperature was measured by a tympanic thermometer at the predetermined circadian temperature times of 0700, 1000, 1400, 1700, and 2200. Sleep efficiency was obtained by actigraph (a computerized activity monitor) (Actiwatch, Mini-Mitter, Sunriver, OR). During the second 48 hours, saliva samples were collected every 4 hours and melatonin concentration determined using ELISA. Cosinor analysis was used to identify the mesor, amplitude, period, and phase of melatonin and temperature data. Sleep Efficiency

was calculated using the sleep watch software provided by the manufacturer. A composite score indicating the presence and severity of sleep disturbance was calculated from the TPSPST. Regression analysis was used to determine if a significant correlation existed among the parameters measured.

**Results:** Preliminary analysis indicates a significant correlation between higher scores on the TPSPST and melatonin periods that vary from the expected 24-hour circadian period. Additional results on the remaining parameters are pending.

**Conclusions:** Salivary melatonin and tympanic body temperature are noninvasive methods for determine circadian rhythms in young children and may prove to be associated with sleep disturbances in this age group. Larger studies are warranted to determine the true statistical significance of the association among the parameters measured in this study.

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**Research supported by a grant from the Delta Alpha Chapter of Sigma Theta Tau International, The University of Texas Health Science Center at San Antonio.**

### 616.G

#### SLEEP ABNORMALITIES RELATED TO PATIENT GENOTYPES AND OBESITY IN PRADER-WILLI SYNDROME

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**Introduction:** Sleep problems, including sleep apnoea and excessive daytime sleepiness (EDS) are common features in Prader-Willi Syndrome (PWS). The aim of this study was to assess whether sleep abnormalities are related to the genetic characteristics or to being overweight.

**Methods:** We performed Polysomnographic studies, Multiple Sleep Latency Test (MSLT) and determined the chromosome 15 genotypes in 65 patients with PWS, 32 males and 33 females, age ranges: 4 months to 19 years, compared with 65 obese control patients matched for age and gender. Fifty seven patients underwent MSLT, and all of them showed EDS. Twenty two patients with EDS displayed deletion of chromosome 15q11-q13, paternally derived, and all of them had maternal uniparental heterodisomy (UPD) in the same chromosomal region.

**Results:** Obstructive and central apnoeas were found in 6 % of the patients but REM related hypoventilation occurred in 44 out of 65 PWS subjects, significantly correlated with obesity. EDS was found in 57 patients and was correlated to decreased sleep efficiency. Not consistently relationship was found between sleep disorders (apnoeas and hypoventilation) and the patient genotypes.

**Conclusions:** EDS in PWS is independent of sleep apnoea and obesity. No relationship of sleep abnormalities to PWS genetic characteristics were found. REM related disturbances were significantly correlated with obesity and hypoventilation.

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**617.G****DEVELOPMENT OF THE TODDLER AND PRESCHOOL SLEEP PROBLEMS SCREENING TOOL**

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**Introduction:** Sleep problems among children are the most common complaint voiced to health care providers. Practitioners, particularly nurses, are in a position to screen and identify sleep disturbances in children and implement education and intervention. Currently there are no tools available for such screening and what tools are available are too complex for use by practitioners in the clinical setting. The purpose of this presentation is to outline the steps in the development a tool to be used by health care practitioners to accurately identify sleep problems in toddlers and preschool children.

**Methods:** A widely cited definition of sleep disturbance was developed by Richman (1981) [3] who defines severe sleep disturbance as a condition that has existed for greater than three months whereby the child awakens five or more nights a week in combination with at least one of the following: waking three or more times a night, awakening for more than 20 minutes, and/or going into the parent's bed. More current criteria for defining sleep problems in young children are described by Gaylor and colleagues (2001) [1]. They describe a classification scheme that relates to the DSM-IV [2] criteria for the diagnosis of dyssomnias, a group of disorders characterized by problems falling asleep or maintaining sleep. The Toddler and Preschool Sleep Problems Screening Tool (TPSPST) is a 14 item forced choice questionnaire that was initially developed using Richman's criteria. Modifications were made to reflect the more current classification scheme described by Gaylor and colleagues.

**Results:** Each answer to the 14 questions in the TPSPST is valued from 0 to 3 with the total falling into one of 4 categories: no sleep problem, mild, moderate, or severe sleep problem. The content validity of the tool was established by sending the questionnaire to 4 experts in the area of pediatric sleep medicine. The tool was then revised according to the comments obtained from the experts. The questionnaire was then sent out to same 4 experts for comments on the revisions. Additional changes were made and the final questionnaire was piloted on 10 parents for feedback on readability and understanding. Now that the instrument has been developed it is important to test the reliability and validity of the tool prior to publishing the questionnaire for widespread use.

**Conclusions:** A high prevalence of sleep disturbance in children is reported in the literature. Sleep disturbance has been

examined in a variety of ways but there are still no up to date empirically tested tools available to practitioners to quantify sleep disturbances. Gaylor and colleagues have taken the first steps in developing an age-appropriate classification scheme however, their approach maybe somewhat cumbersome for the everyday clinician. There is a definite need for the development of a simple to use tool that can aid practitioners in identifying sleep disturbances in children.

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**618.H****SLEEP DISTURBANCES IN THE ELDERLY: AN EPIDEMIOLOGICAL STUDY IN A MUNICIPALITY OF THE CITY OF UDINE**

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**Introduction:** Aging processes cause progressive changes in the sleep patterns of elderly people. Quantitative and qualitative alterations are described in medical literature: changes of sleep/wake rhythm, modifications in duration and disruption in sleep architecture.

**Methods:** The aim of our study is to find a method to evaluate sleep disturbances with a questionnaire, in elderly people with and without cognitive impairment. Our population included 1000 subjects, over 65 years of age, randomly selected among residents in the seventh district of the City of Udine, stratified for sex and age. The first 426 interviews are included in this report. All patients underwent a Mini Mental State Examination (MMSE) and a sleep questionnaire particularly concerning excessive daytime sleepiness. A statistical analysis was performed for subjects with and without cognitive impairment, using the analysis of the variance with diagnosis as independent variable and the answers of the questionnaire as categorical variables.

**Results:** In our total sample, we found a high prevalence of excessive daytime sleepiness, insomnia, night-time awakenings, snoring, restlessness and periodic legs movements during sleep. Compared to healthy subjects, patients with cognitive dysfunction showed less difficulty to falling asleep and fewer night-time awakenings; they snored less frequently and they were the only ones to present enuresis and to fall off the bed

(Table 1). Moreover patients with cognitive impairment present excessive daytime sleepiness with variable intensity and frequency (Table 2).

Table 1

Sleep disorders			
SLEEP DISORDERS	COGNITIVE IMPAIRED	HEALTHY SUBJECTS	STATISTICAL SIGNIFICANCE
Un-refreshing sleep	17%	33%	P<0.064
Difficulty to falling asleep	27%	45%	P<0.024
Frequent night-time awakenings	73%	91%	P<0.009
Early-morning awakenings	35%	49%	N.S.
Sleep inducing drugs	36%	37%	N.S.
Tiredness on waking	24%	31%	N.S.
Mood disorders after sleep deprivation	33%	28%	N.S.
Snoring	60%	78%	P<0.001
Restlessness and legs movements during sleep	25%	26%	N.S.
Sleep walking	0%	0.76%	N.S.
Nightmares	9.6%	6.3%	N.S.
Enuresis	2.2%	0.5%	P<0.001
Falling off the bed	9.6%	0.25%	P<0.000

Table 2

Excessive Daytime Sleepiness			
SLEEP DISORDERS	COGNITIVE IMPAIRED	HEALTHY SUBJECTS	STATISTICAL SIGNIFICANCE
Difficukty to maintaing attention and concentration	60%	39%	P<0.019
Resistible excessive daytime sleepiness	55%	59%	N.S.
Irresistible excessive daytime sleepiness	56%	42%	P<0.008
Sleep attacks	9.6%	0.5%	P<0.000

**Conclusions:** The administration of a questionnaire, divided into several specific areas, showed significant differences in sleep disturbances between healthy subjects and patients cognitively impaired. This form of subjective evaluation seems to be a useful method for performing an assessment of sleep disturbances in elderly people.

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**619.H**

**BRIGHT LIGHT IMPROVES SLEEP BUT MELATONIN DOES NOT IN SEVERE ALZHEIMER'S DISEASE**

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**Introduction:** Patients with Alzheimer's Disease (AD) have highly fragmented sleep, which is one of the primary reasons for institutionalization. Treatments are needed that consolidate sleep during the night and increase wakefulness during the day. This study examined the effects of light therapy and melatonin on sleep in patients with AD.

**Methods:** A total of 92 subjects participated in light treatment (mean age 82.3, SD 7.6; mean MMSE 5.7, SD 5.6) and 41 subjects received melatonin (mean age 82.7, SD 6.8; mean MMSE 5.7, SD 5.5). 29 of these subjects received both consecutively. Protocols lasted for 18 days and consisted of 3 days of baseline, 10 days of treatment, and 5 days of follow-up. In the light study, subjects were randomized into morning bright (>2500 lux) or red (<300 lux) light from 9:30 to 11:30h, or evening bright (>2500 lux) light from 17:30 to 19:30h PM. In the melatonin study, subjects were randomized into either placebo or 10 mg of melatonin (8.5 mg immediate release and 1.5 mg sustained release) which was administered by nursing staff at 22:00h. Activity was continuously recorded throughout the protocol with an Actillum (Ambulatory Monitoring, Inc.). Traditional sleep variables were computed: total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency (SE). In addition, bouts of sleep and wake at night were tallied to examine whether sleep was consolidated. Statistics of the distributions of sleep and wake bouts were computed (mean, median, standard deviation, maximum, minimum, and the 10th, 25th, 75th, and 90th percentiles.) Differences in sleep among treatment groups were computed using MANOVA, treating traditional measures of sleep and statistics of the sleep/wake bouts as separate groups of dependent variables and the treatment group as the independent variable.

**Results:** LIGHT: The light therapy had no effect on TST, WASO or SE. There was an overall treatment effect on the sleep bouts (F(12,128)=1.9, p=0.04) but not on the wake bouts. Follow-up tests demonstrated that both morning and evening bright light groups produced an increase in the length of the maximum sleep bout but morning red light led to a decrease of the maximum. MELATONIN: Melatonin had no statistical effect on any measures of sleep.

Table 1

Length in minutes of the maximum bout of sleep at night	Baseline	Treatment
	Moming red light	107.4
Moming bright light	64.9	92.7*
Evening bright light	71.4	91.8*

\*p<0.05 when compared to baseline

**Conclusions:** Although there was no increase in overall TST, light therapy produced longer periods of uninterrupted sleep which may have allowed subjects to have more restorative sleep. In other words, although the quantity of sleep did not change, the quality did. As expected, the improvements were seen in the groups that received bright light therapy and not in those that were exposed to dim red light. Surprisingly, melatonin administration did not lead to any improvements in sleep quantity or quality. This patient sample was severely demented, so there may have been a reduced ability of the circadian system to respond to exogenous melatonin. Melatonin treatment may be more effective in patients with less severe dementia. Overall, these results support the use of bright light therapy, but not melatonin, for improving sleep in patients with severe AD.

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## 620.H

### EVOKED K-COMPLEX PRODUCTION DURING STAGE 2 SLEEP IN RECOVERING LONG-TERM ALCOHOLICS

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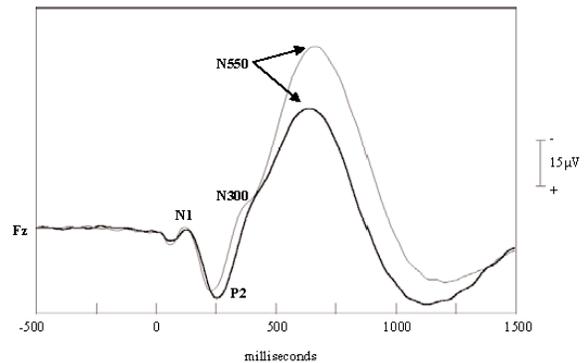
**Introduction:** Recent studies have shown that normal aging is associated with a reduction in the probability that an auditory stimulus will evoke a K-complex (KC) during sleep. There is also a reduction in the amplitude of the KC-related N550, an augmentation of the P2 component and the appearance of a long-lasting positivity (LLP) in the auditory evoked potential (EP), particularly prominent in trials in which KC's are not elicited (1). Normal aging is also associated with reduction in delta EEG and SWS during sleep (2) and in the volume of cortical gray matter, particularly in the frontal and pre-frontal regions of the brain (3). It has been suggested that the reduction in gray matter is the major mechanism responsible for the evoked potential changes observed during sleep. This hypothesis predicts that alcoholics would show similar evoked potential changes to those seen in ageing, as they have a similar pattern of SWS and reduction in cortical gray matter.

**Methods:** Seven abstinent long-term alcoholics (total lifetime alcohol consumption, mean  $\pm$  SD: 1485.7  $\pm$  1456.3 kg) and eight normal controls (total lifetime alcohol consumption 88.2  $\pm$  101.4 kg) participated in the study. The alcoholic and control groups were matched for age 59.3  $\pm$  7.0 yrs (mean  $\pm$  SD) and 63.0  $\pm$  7.4 yrs, years of education 17.4  $\pm$  2.1 yrs and 17.2  $\pm$  2.5 yrs, and pre-morbid IQ measured by the National Adult Reading Test 115.3  $\pm$  5.31 and 115.0  $\pm$  6.8 respectively. Participants were screened for general health and were excluded for sleep or auditory disorders. Each subject spent one night in the laboratory. EEG was recorded from 6 midline scalp sites

adapted from the international 10/20 system (Fz, FCz, Cz, CPz, Pz, O2) referenced to linked ears. EOG and EMG were also recorded. The protocol involved the presentation of auditory stimuli (50msec duration, 1000Hz, 80dBA, ISI 15-30sec). Stimulus locked averages of tone trials that elicited a KC and those that did not produce a KC were computed to produce the averaged evoked potentials for each subject in each group. The amplitude and latency of the N1, P2, N300 and N550 components of the EP were compared between the groups as was the proportion of the elicited KC's.

**Results:** N550 amplitude at Fz (maximum amplitude) was reduced in the alcoholics (-46 mV) relative to controls (-68 mV),  $t(13) = 2.48$ ,  $p < .05$  (figure 1). Alcoholics (51%) also showed a reduced likelihood of KC production relative to controls (67%)  $t(13) = 1.99$ ,  $p < .05$ . No differences were noted in either amplitude or latency of the N1 or N300 components. There was no difference in P2 amplitude (maximal at Cz in both groups), and both groups displayed a prominent LLP potential of approximately 15mV at Cz.

Figure 1



Grand mean wave forms for tone trials that elicited KC's at Fz (thick line – alcoholics; thin line – controls).

**Conclusions:** Alcoholics showed diminished KC activity compared to matched controls. In contrast, EEG components seen more prominently in non-frontal scalp regions (P2 and LLP) appear to be unaffected by alcoholism, and show similar age-related effects to those reported by Crowley, Trinder and Colrain (1). This dissociation of EP measures to that seen in ageing showing reduced KC production and N550 amplitude with the lack of an additional effect on the P2 and LLP potential from long term alcohol exposure indicate that the evoked K-complex may be a sensitive measure of alcohol related reductions in SWS and cortical gray matter volume. This interpretation would be consistent with their previously reported loss of prefrontal and frontal cortical mass (3).

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621.H

FIRST NIGHT EFFECT IN PATIENTS WITH ALZHEIMER'S DISEASE AND CONTROLS – PRELIMINARY DATA

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**Introduction:** First night effect on polysomnography (PSG) is characterized by alteration of the sleep structure. Alterations may include increase in REM sleep latency combined with decrease in REM sleep and Slow Wave Sleep percentage (1). First night effects have been demonstrated in elderly (2). If habituation to PSG is secondary to a learning process, it may be altered in patients with Alzheimer's disease. There are no data up to date on this subject. The purpose of this study is to compare the first night effect in Alzheimer's Disease (AD) patients with age matched normal control subjects.

**Methods:** Six patients (4 female and 2 male) with mild and moderate AD followed in the Federal University of São Paulo, whose ages ranged from 65 to 85 years were included in this study. Control group consisted of 9 age matched subjects (5 male and 4 female). All had body mass index < 35 kg/m<sup>2</sup>. They underwent PSG monitoring in two subsequent nights. Different PSG parameters were studied, as presented in the results. Data were analyzed using a two-way ANOVA.

**Results:**

Table 1

	Alzheimer		Controls	
	Night 1	Night 2	Night 1	Night 2
S Ef %	80.9±14.0	75.9±16.7	69.0±13.5	75.9±8.8
S Lat	6.3±7.4	10.2±12.3	25.1±25.1	18.1±18.6
REMLat	63.5±63.3	133.3±77.9	134.0±78.0	93.0±75.5
WASO	53.5±43.6	98.5±72.7	27.2±11.9	21.0±6.8
S1 %	13.0±11.5	7.1±8.3	13.8±8.6	12.1±9.6
S2 %	64.0±8.9	63.3±8.5	48.7±15.3	50.6±10.2
SWS %	13.7±10.0	25.0±14.1	17.1±10.9	23.3±10.2
REM %	9.1±5.5	4.5±3.5	11.4±4.6	13.8±2.8

S Lat= sleep latency (min), REMLat = REM latency (min)  
S Ef= sleep efficiency S1= stage 1 S2 = stage 2  
SWS = slow wave sleep percentage

Table 2

	disease	night	int
F (1,13); p level			
S Ef %	ns	ns	ns
S Lat	ns	ns	ns
REMLat	ns	ns	4.8; 0.04
WASO	9.8; 0.00	ns	5.1; 0.04
S1 %	ns	ns	ns
S2 %	7.2; 0.01	ns	ns
SWS %	9.3; 0.00	ns	ns
REM %	11.9; 0.00	ns	5.4; 0.04

int = interaction

**Conclusions:** Sleep latency was consistently increased in normal subjects, however there was no significant interaction factor. REM latency and percentage showed habituation only in normal controls. Conversely, in AD patients an increase in REM latency was observed during night 2. WASO decreased in night 2 only in normal controls. In the same fashion it presented a significant increase in night 2 of AD patients. Normal controls also had consistently increased stage 2 NREM sleep compared to AD patients during the 2 PSG nights. Interestingly, SWS % increased in both conditions during night 2 suggesting homeostatic "habituation". Lack of REM sleep changes towards habituation to the sleep laboratory was found in AD patients. However, they were able to show some SWS homeostatic increase in night 2. Further EEG spectral analysis is needed to demonstrate that homeostatic delta power regulation is also present in these patients.

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622.H

EFFECTS OF LIGHT AND DARK ON REST AND ACTIVITY IN DROSOPHILA MELANOGASTER

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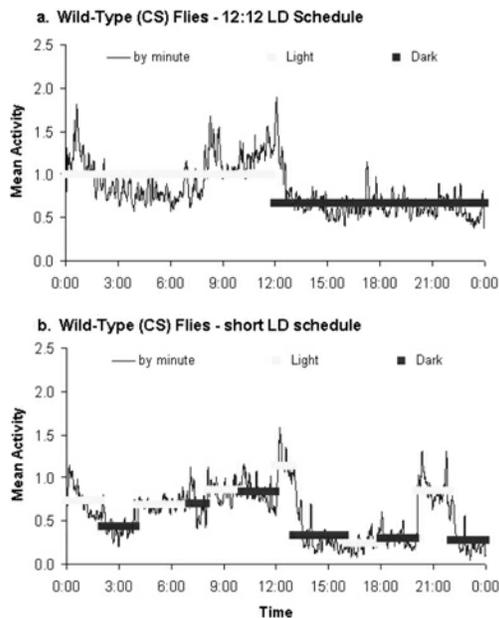
**Introduction:** The light-dark cycle is an important regulator of the sleep-wake behavior and neuroendocrine function, through its effects on the circadian pacemaker as well as direct effects on behavior. Although significant progress has been made in understanding the molecular mechanisms for circadian rhythms, relatively little is known about mechanisms underlying acute behavioral responses to lighting changes. The presence of a sleep-like state has recently been demonstrated in the fruit fly, *Drosophila melanogaster*<sup>1,2</sup>. The goal of this study is to characterize behavioral responses to acute changes in lighting in flies as a prelude to studies of molecular mechanisms for acute responses to light.

**Methods:** Wild type (Canton-S; 7-11 day old virgin females, n=94) flies were individually housed in glass tubes. Each tube was monitored with infrared beams (Drosophila Activity Monitoring System, Trikinetics). The number of beam crossings was recorded every minute for each fly. The testing enclosure was maintained on a 12:12 LD schedule at 23° C for four days. Flies were then exposed to 24h of short LD cycles, such that total amount of light in 24 hours remained the same at 12 h. The schedule, starting at the normal lights-on time was as follows: 2L:2D:2L:3D:1L:2D:2L:1D:3L:2D:2L:2D.

**Results:** During a 12:12 LD cycle, flies exhibited a diurnal rest-activity pattern (see figure). During a day of short LD cycles, flies were more active in the light than in the dark. Some, but not all, periods of light during subjective night and dark during subjective day had a dramatic effect on activity.

Average activity during the subjective day was greater than activity during subjective night, consistent with the expected circadian influences. Overall activity for the 24h of the short LD cycles was somewhat lower than for the preceding day.

Figure 1



**Conclusions:** The results suggest that activity in flies is controlled by light as well as by homeostatic and circadian influences, similar to rodents and other mammals. Systems mediating acute behavioral responses to light are present in flies, thus providing a model to study the genetic and molecular mechanisms for these responses.

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### 623.I

#### THE EFFECTS OF SLEEP LOSS AND FATIGUE IN GRADUATE MEDICAL EDUCATION: A MULTI-INSTITUTIONAL FOCUS GROUP STUDY

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**Introduction:** Sleep is a fundamental human need. The consequences of work-related sleep loss for physicians-in-training

are potentially serious. The research in this area has yielded inconsistent findings, is poorly controlled, and lacks adequate assessment of sleep loss or related effects on performance. The purpose of this study is to assess sleep loss and fatigue (SL&F) from residents' perspectives, specifically our goal was to: 1) ascertain the areas of medical residents' professional and personal life affected by sleep loss and fatigue, 2) enumerate effective countermeasures, and 3) identify institutional strategies that they suggest to remedy the situation.

**Methods:** Study protocol was developed collaboratively by six schools. Each school was assigned three specialties and asked to conduct separate focus groups each consisting of 6-8 participants for interns and senior residents. Six specialties studied were as follows: Family Medicine, Internal Medicine, Emergency Medicine, Surgery, Obstetrics and Gynecology, and Pediatrics. Focus group discussions were audiotaped, transcribed, coded, and analyzed using NVivo Software. Focus group participants completed a 30-item questionnaire at the end of the session. Surveys were analyzed using SPSS.

**Results:** Fourteen focus groups are completed to date. Responses were classified into the following general categories: personal direct experiences, directly observed or heard about happening to someone else, and part of the lore or culture of the institution. Categories of job performance coded are: physical harm, objectification of patients, communication violation, role resistance, cognitive deficits; interpersonal issues are: losing friends and interests, distortion of time, inability to perform activities of daily living; professional development issues are: inability to read or focus, fall asleep at conferences, or miss opportunities to interact with colleagues. Effective countermeasures listed include participating in vigorous exercise, eating, napping, and consuming caffeine products. Residents speak about making frequent "medical mistakes" instead of "errors." Residents identified institutional countermeasures. Some suggestions made were: hiring additional staff for routine tasks, setting criteria for physical space and conditions of "on-call" rooms, scheduling changes, and allowing nap time. Of the 108 residents who completed the survey, overall 86% agreed or strongly agreed that SL&F has a major impact on my personal life, 57% agreed that SL&F have major impact on my work. About 58% agreed that they have written incorrect orders and 86% agreed that they heard about others making medical errors due to SL&F.

**Conclusions:** Sleep loss and fatigue is a major issue for physicians in graduate education judging from the themes that emerged in this focus group study. Professional and personal areas of life were profoundly affected. Simple institutional countermeasures, if implemented, could significantly improve residents' quality of life during these important years of medical education and training.

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## 624.I

### PROLONGED TOTAL SLEEP DEPRIVATION AND OXIDATIVE STRESS

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**Introduction:** Prolonged total sleep deprivation in animals results in increased eating, altered thermoregulation and eventually death (1). It has been proposed that reactive oxygen species (ROS), which accumulate during waking as a result of enhanced cerebral metabolism, may be responsible for some of these effects. The accumulation of ROS is determined by the rate of its production by prooxidants such as superoxide (O<sub>2</sub><sup>-</sup>) and nitric oxide (NO), and the rate of its removal by antioxidative enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). Heat shock proteins (HSPs) also provide protection under nitrosative and oxidative stress. Furthermore, nitric oxide, produced by the enzyme nitric oxide synthase (NOS) reacts rapidly with superoxide produced by oxidative phosphorylation to form peroxynitrite (ONOO) which decomposes to nitrotyrosine (NT). In this study we investigated changes in the activity of hypothalamic Cu/Zn-SOD as well as changes in the levels of hypothalamic Hsp70, nNOS (neuronal NOS) and NT.

**Methods:** Male Sprague Dawley rats (350-450 g) were subjected to total sleep deprivation by the disk-over-water method as previously described (2,3). The animals were killed by decapitation and the hypothalamus was dissected and stored at -80°C prior to performing biochemical assays (for Cu/Zn-SOD) and Western blots (for Hsp70, nNOS and NT). The paired students t-test was used to determine statistical significance.

**Results:** Sleep deprived (SD) rats had significantly higher levels of expression of hypothalamic nNOS than yoked control (YC) rats (175% of YC,  $t = 3.9$ ,  $df = 3$ ,  $p = 0.03$ ). However, there was no significant change in the level of expression of NT or Hsp70 between SD and YC rats. Also, no change in the activity of Cu/Zn-SOD was observed between SD and YC rats.

**Conclusions:** We previously reported that prolonged total sleep deprivation results in oxidative stress, as assessed by changes in the activity of Cu/Zn-SOD (in the cortex and hippocampus) and GPx (in the hippocampus) (2,3). Here we report no significant change in the activity of hypothalamic Cu/Zn-SOD. We went on to investigate other markers of oxidative stress by measuring the level of expression of Hsp70, nNOS and NT. We did not find any change in the level of expression of NT or Hsp70. However, we did observe a significant increase in the level of expression of nNOS. An increase in NOS levels leads to an increase in the level of nitric oxide. Several studies have shown that brain nitric oxide has a stimulatory role on non-REM sleep. Oxidative stress can be assessed by alterations in several markers including changes in the activity of SOD or GPx or changes in the expression of nNOS. Based on our findings, we can conclude that prolonged

total sleep deprivation results in oxidative stress.

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## 625.I

### EFFECTS OF CHRONIC SLEEP DOSE AND CIRCADI-AN PHASE ON SLEEP PHYSIOLOGY

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**Introduction:** Changes in sleep physiology during chronic partial sleep deprivation have been reported (1,3). However, in most studies the duration of partial sleep deprivation has been relatively short (< 4 days), with sleep placed only nocturnally. The aim of the present study was to compare the dynamic changes in sleep architecture when sleep was restricted chronically (10-14 days) at a nocturnal versus a diurnal circadian phase.

**Methods:** In Study 1 (nocturnal sleep),  $n = 16$  subjects were randomized to either 8h (23:30-07:30) or 4h (03:30-07:30) time in bed for 14 nights following 3 baseline nights of 8h TIB. In Study 2 (diurnal sleep),  $n = 16$  subjects were randomized to either 8h TIB (11:30-19:30) or 4h TIB (15:30-19:30) for 10 days. In both studies, PSG was recorded on all baseline days, and on approximately 2 out of every 3 days throughout the restriction period. More than 350 PSG records were generated, of which 210 have been visually scored using standardized criteria.

**Results:** For Study 1, analyses indicated decreased sleep latency in the nocturnal 4h condition ( $p = .004$ ), decreased stage 2 sleep ( $p < .001$ ), decreased latency to REM ( $p = .038$ ), and decreased REM sleep ( $p = .001$ ), relative to baseline sleep. A significant decrease in sleep latency ( $p = .013$ ), the amount of stage 2 sleep ( $p = .002$ ), and REM sleep ( $p = .020$ ) between the 4h and 8h nocturnal conditions was also observed. SWS, however, was conserved in the 4h condition relative to the 8h condition and to baseline sleep. Average sleep efficiencies were also higher in the 4h condition relative to the 8h condition ( $p = .008$ ), and increased across days ( $p = .027$ ). WASO was significantly different between the conditions, being higher ( $p < .001$ ) and more variable night to night in the 8h condition. Further sleep scoring and analysis of Study 2 (4h vs. 8h diurnal sleep) is continuing.

**Conclusions:** The results of Study 1 (4h vs. 8h nocturnal sleep) are consistent with expected changes in sleep physiology associated with chronic partial sleep deprivation, particularly a maintenance of SWS at the loss of stage 2 and REM

sleep (2). Despite this loss of stage 2 and REM as a result of truncated sleep time, reduced REM sleep latency in the nocturnal condition suggested increasing REM pressure when sleep was restricted to 4h. The increase in sleep efficiency in the 4h condition reflected increased pressure of the homeostatic drive. Completion of PSG scoring for Study 2 will permit comparisons between diurnal and nocturnal sleep conditions, which should help determine the relative importance of circadian influences with respect to homeostatic forces when sleep time is chronically restricted (4h) relative to chronically unrestricted (8h).

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### 626.I

#### STABILITY OF BEHAVIORAL ALERTNESS IN PILOTS REPEATING SIMULATED NIGHT FLIGHTS

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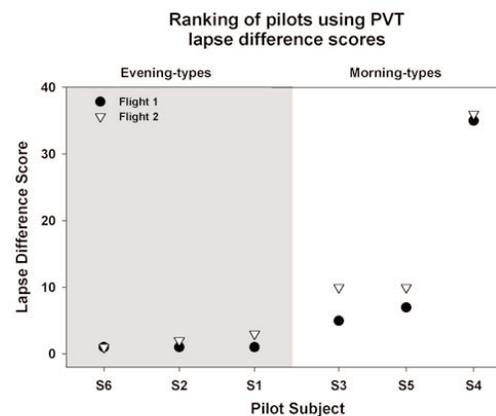
**Introduction:** Long-haul pilots are faced with the requirement to remain vigilant in highly automated cockpits throughout night flights. Sleepiness and its associated performance degradation have been documented in flight crews at night, but there are also indications of large inter-individual differences in behavioral alertness and sleepiness when crews remain awake in the cockpit through the circadian nadir.<sup>1</sup> The stability of individual differences in behavioral alertness and sleepiness was examined in pilots flying 6-hr simulated night flights in a Boeing 747-400 flight simulator.

**Methods:** Using a within-subjects design, n = 6 healthy adult pilots (M = 52.9 yr), with active flight schedules, participated twice in a night flight simulator protocol (~0200h - 0800h) from Seattle to Honolulu. Each episode of their participation was separated by one year. Pilots completed travel logs and sleep/wake diaries up to 3 days prior to the simulated flights. Upon enrollment, data were collected on age, home time zone, morning-eveningness, caffeine use and alcohol consumption. At four points during the flight, data were collected on psychomotor vigilance task (PVT) performance. The difference in PVT lapses at 0200h and 0600h provided a measure of in-flight changes in alertness, and background variables were examined in an effort to explain inter-subject differences between the two flights.

**Results:** A paired-sample t-test revealed a greater overall lapse increase during the second flight relative to the first flight ( $p < 0.05$ ). However, individual differences in the increase in performance lapses across night flights were remarkably stable.

This was evident when pilots were ranked by average lapse difference scores for the two night flights (Figure 1). A strong correlation was found between flights 1 and 2 for lapse difference scores ( $r = 0.99$ ) and mean raw lapsing ( $r = 0.99$ ). The inter-subject difference was very large between the lowest lapsing pilot (S6 with an increase of only 1 lapse across the night) and the highest lapsing pilot (S4 with an increase of 35 lapses across the night). Pilots who tended to lapse more at night (S3, S5, S4) tended to be more morning types (see shading on graph), as determined by a self-reported global morningness-eveningness questionnaire.

**Figure 1**



**Conclusions:** The high correlations indicate the stability of inter-pilot variability in behavioral alertness during simulated night flight experiments conducted one year apart. Such stability suggests these are trait-like responses, which may in part be determined by endogenous circadian phase preference. The significant difference in mean lapsing between the two flights suggests that it was likely due to the loss of novelty during the second flight. It remains to be determined what factors contributed to the severe effects the simulated night flights had on the behavioral alertness of S4. This type of severe impairment at night has been seen on a subset of pilots in other studies. There is indirect indication that it is associated with an elevated likelihood of sleep disorders.

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## 627.I

### COMPARING THE EFFECTS OF TOTAL SLEEP DEPRIVATION AND CHRONICALLY RESTRICTED DIURNAL SLEEP ON PREFRONTAL NEUROPSYCHOLOGICAL FUNCTIONING

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**Introduction:** Studies have found that performance deficits attributed to the prefrontal cortex (PFC) can be induced by periods of acute total sleep deprivation (TSD).<sup>1,2</sup> The aim of the current study was to compare the effects of TSD to those of chronically restricted sleep placed at a diurnal circadian phase on tasks putatively subserved by the PFC. PFC functioning was measured using the Hayling Sentence Completion Test (HSC), developed for use in assessment of frontal lobe damage.<sup>3</sup> This test consists of 2 conditions: (1) response generation, in which the sentence must be completed sensibly; and (2) response suppression, in which the sentence must be completed with a totally unrelated word.

**Methods:** Data from three experiments were compared (total N=86, 59m, 27f, aged 21-44y). In study 1, a control group completed the HSC after a nocturnal sleep opportunity of 8.2h. In study 2, subjects received a diurnal (i.e. adverse circadian time) 4h, 6h or 8h sleep opportunity for 10 consecutive days, with HSC administered after 4 days of diurnal sleep. In study 3, subjects underwent 3.7 days (88h) of total sleep deprivation, with HSC measured after approximately 3.2 days of waking (77h). Beginning at 22-hours of sustained wakefulness, subjects received an hourly pill containing either low-dose caffeine (0.3mg/kg) or placebo. Mann-Whitney U statistics revealed no significant effect of caffeine on HSC performance. Therefore, HSC scores for placebo and caffeine conditions were collapsed into a single group for analysis of data from study 3.

**Results:** Kruskal-Wallis Analysis (p-values corrected for ties) indicated no significant differences between the control group (study 1), the TSD group (study 3) and the 3 diurnal sleep groups (study 2- 4h, 6h, 8h) for response generation or suppression latencies. However, when the number of response suppression errors was examined, a significant effect of group was observed (p<0.01). Mann-Whitney U Statistics revealed that while error scores for all experimental groups were significantly poorer (p<0.05) than those of the control group, no significant differences were found among experimental groups (TSD and all 3 circadian-displaced sleep conditions - 4h, 6h, 8h). In addition, analysis of overall HSC scores (calculated using a standardized formula to sum response generation, suppression and error scores), yielded no significant differences between groups.

**Conclusions:** Taken together, results indicate that TSD and chronically restricted daytime sleep of varying duration may produce similar, limited effects on PFC functioning as measured by the HSC. Although effects were observed for response suppression errors, response latencies and overall HSC scores were not changed. Such results are intriguing given that previous studies have found that, in addition to errors, TSD was associated with significantly elevated response suppression

latencies.<sup>1,2</sup>

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## 628.I

### DYNAMICS OF WAKING EEG FREQUENCY BANDS DURING CHRONICALLY RESTRICTED SLEEP

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**Introduction:** Daytime sleepiness and neurobehavioral performance impairment are documented to increase across days of chronic partial sleep deprivation (PSD) [1]. We previously observed that the temporal profile of delta power during sleep across days of PSD was consistent with the two-process model of sleep-wake regulation, which predicts that the homeostatic pressure for sleep saturates at approximately 130% of baseline after only a few days of PSD. However, delta power during sleep did not track the changes in performance during wakefulness [2]. In this study, we investigated the time course of power in the frequency bands conventionally computed for the waking EEG.

**Methods:** In this study, n=22 subjects spent 20 days inside a laboratory undergoing a strict schedule of performance testing and restricted sleep. After 3 baseline days, subjects underwent 14 days of PSD (4h TIB; 03:30-07:30; n=13), or they remained on the baseline schedule (8h TIB; 23:30-07:30; n=9). Waking EEG (C3) was recorded during a Karolinska Drowsiness Test (a 5min period of staring at a dot) at 11:45 each day. The data were placed in 2s bins, artifacts were removed, and the 5min average powers in the delta (0.5-4Hz), theta (4-8Hz), alpha (8-12Hz) and beta (12-25Hz) frequency bands were computed. These were expressed as percentage of baseline and subjected to mixed-model regression to determine the immediate response on the first condition day as well as changes over days of PSD. These parameters and their between-conditions differences were compared to zero using t-tests. Linear regression was applied to detect deviations from the two-process model predictions for the homeostatic pressure for sleep.

**Results:** Thus far, data have been analyzed for n=4 subjects (2 in each condition). In the 4h TIB condition, an immediate decrease of delta power on the first day of sleep restriction was found (t[11]=1.80; P=0.002). However, power in the delta,

theta and alpha frequency bands did not deviate significantly from the temporal profile for homeostatic pressure predicted by the two-process model. The beta frequency band in the 8h TIB condition yielded less power than baseline during the first few days of PSD ( $P < 0.05$ ). There was a significant increase over days in the number of artifacts in the 5min EEG records ( $t[11] = 2.74$ ;  $P = 0.019$ ), which was not significantly different between conditions ( $t[11] = 1.39$ ;  $P = 0.19$ ).

**Conclusions:** Considering the increasing neurobehavioral performance deficits across days of PSD [1], a concomitant intensification of theta and/or delta power in the waking EEG was expected. However, the temporal profile of power in all waking EEG frequency bands appeared to saturate rapidly, as consistent with the two-process model of sleep-wake regulation. The current findings match the profile for delta power during sleep in the same experiment [2]. Waking EEG spectral analysis will be completed for the remaining subjects to establish the generalizability of these findings.

**References:**

- (1) Dinges DF, Maislin G, et al.: Chronic sleep restriction: Neurobehavioral effects of 4hr, 6hr and 8hr TIB. Sleep 1999;22S:S115-S116.
- (2) Shah AD, Van Dongen HPA, et al.: Dynamics of slow-wave activity during chronically restricted sleep. Sleep 2001;24S:A247.

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**629.I**

**HEALTHY YOUNG MALE ADULTS ARE RESISTANT TO SLEEP-DEPRIVATION INDUCED DEFICITS IN VENTROMEDIAL/ORBITAL PREFRONTAL FUNCTION**

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**Introduction:** To help identify sleep effects on cognition relevant to cognitive deficits of chronic cocaine use, we here investigate the effects of acute 37-39 hr total sleep deprivation (TSD) on neurocognitive probes of ventromedial and orbital prefrontal (VMPFC) performance. Neurocognitive deficits resulting from chronic cocaine use may specifically impact VMPFC areas controlling behavioral inhibition and decision making (Bolla et al. 1998) while Harrison et al. (2000) report that one night's TSD also degrades prefrontal performance including a measure of behavioral inhibition (Haylings Sentence Completion task).

**Methods:** Participants were 20 right handed, English-as-first-language males, aged 19-25 who had completed of at least one semester at a competitive admissions 4-year liberal arts college. In this IRB-approved study, paid subjects were recruited by newspaper and word of mouth and signed informed consent. Subjects had good health, normal vision, audition and olfaction, no history of major mental, sleep or substance abuse disorders nor brain injury. A total of ten subjects each were

assigned as recruited, in groups of 2 to 3, alternately to a TSD and control (CTL) group. Subjects were monitored for one week using the Nightcap (Ajilore et al. Psychophysiology 32:92) and diaries. TSD subjects underwent sleep deprivation from their arising on Day 4 until about Midnight Day 5 and were under staff supervision in small groups of 2-3 after 7 pm on Day 4. Subjects were tested from approximately 6:30 to 11 pm on Day 5 and again on Day 8. Tasks were always presented by the same of 3 examiners and were counterbalanced by 2 anatomical PFC groupings and, within each grouping, by order of presentation. VMPFC tasks were a (computerized) modified Bechara Gambling task (Bechara et al. Cognition 50:7); a (computerized) Object Alternation Task or OAT (Freedman, Brain and Cognition 14:134); the Haylings Sentence Completion Task (Harrison et al. 2000); the Stroop Color Word Task (Golden, Stoelting Company); and the Smell Identification Test or SIT (Doty, Sensonics, Inc.). Results for all tasks except the Haylings Sentence Completion task (analysis in progress) are reported here. For each variable, TSD and CTL variable group means were compared using unpaired t-tests. If t-tests of Day 5 vs. 8 in CTL's showed no learning effects for a variable, paired t-tests were also used to compare Days 5 (sleep deprived) and 8 (after recovery sleep) in TSD subjects.

**Results:** Using unpaired t-tests, there were no significant group difference between TSD and CTL groups following TSD (Day 5) or after the recovery sleep of the TSD group (Day 8). The Gambling, Stroop and SIT tasks showed no learning effects in paired t-tests of Day 5 versus Day 8 in the CTL group. However, these tasks also showed no improvement following recovery sleep in paired t-tests of Day 5 versus Day 8 in the TSD group.

**Table 1**

Task	Day 5 (TSD sleep deprived)			Day 8 (after recovery sleep)		
	TSD (SD)	CTL (SD)	p	TSD (SD)	CTL (SD)	p
GAMBLING %advantageous ( $\sqrt{n.s.}$ )	60.20 (16.19)	52.6 (9.14)*	.22 9	64.0 (21.21)	62.3 (16.67)*	.852
OAT #trials before 12 right (=criterion)	23.3 (15.67)	29.9 (19.41)	.41 4	5.6 (9.25)	15.6 (14.97)	.089
SIT #correct( $\sqrt{n.s.}$ )	35.5 (2.55)	36.4 (2.12)	.40 2	36.1 (1.72)	36.7 (1.83)	.468
STROOP interference ( $\sqrt{n.s.}$ )	4.54 (11.19)	5.05 (5.13)	.89 7	3.07 (7.07)	7.46 (5.52)	.139

( $\sqrt{}$ )-unpaired and paired t-tests of CTL show no learning effects.

**Conclusions:** As found by Binks et al (1999) for the Stroop task, young healthy American undergraduates are remarkably resistant to the VMPFC effects of one-night's total sleep deprivation.

**References:**

- (1) Binks PG, Waters WF, Hurry, M. Short-term total sleep deprivation does not selectively impair higher cortical functioning. Sleep 1999;22:328-334.
- (2) Bolla KI, Cadet JL, London ED. The neuropsychiatry of chronic cocaine abuse. Journal of Neuropsychiatry and Clinical Neurosciences 1998;10:280-289.

(3) Harrison Y, Horne J, Rothwell, A. () Prefrontal neuropsychological effects of sleep deprivation in young adults-A model for healthy aging? Sleep 2000;23:1067-1073.

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630.I

HEALTHY YOUNG MALE ADULTS ARE RESISTANT TO SLEEP-DEPRIVATION INDUCED DEFICITS IN DORSOLATERAL PREFRONTAL FUNCTION.

Pace-Schott EF,<sup>1</sup> Hutcherson CA,<sup>1</sup> Bemporad B,<sup>1</sup> Stickgold R,<sup>1</sup> Kumar A,<sup>1</sup> Hobson JA<sup>1</sup>

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**Introduction:** To help identify sleep effects on cognition relevant to cognitive deficits of chronic cocaine use, we here investigate the effects of acute 37-39 hr total sleep deprivation (TSD) on neurocognitive probes of dorsolateral prefrontal (DLPFC) performance. Neurocognitive deficits resulting from chronic cocaine use may impact prefrontal (PFC) areas especially areas controlling behavioral inhibition and decision making (Bolla et al. 1998). Similarly, one night's acute TSD has also been reported to degrade prefrontal performance (Harrison et al. 2000).

**Methods:** Participants were 20 right handed, English-as-first-language males, aged 19-25 who had completed of at least one semester at a competitive admissions 4-year liberal arts college. In this IRB-approved study, paid subjects were recruited by newspaper and word of mouth and signed informed consent. Subjects had good health, normal vision, audition and olfaction, no history of major mental, sleep or substance abuse disorders nor brain injury. A total of ten subjects each were assigned as recruited, in groups of 2 to 3, alternately to a TSD and control (CTL) group. Subjects were monitored for one week using the Nightcap (Ajilore et al. Psychophysiology 32:92) and diaries. TSD subjects underwent sleep deprivation from their arising on Day 4 until about Midnight Day 5 and were under staff supervision in small groups of 2-3 after 7 pm on Day 4. Subjects were tested from approximately 6:30 to 11 pm on Day 5 and again on Day 8. Tasks were always presented by the same of 3 examiners and were counterbalanced by 2 anatomical PFC groupings and, within each grouping, by order of presentation. DLPFC tasks were combined verbal and category fluency (FAS/animals Day 5, BCT/vegetables Day 8), modified Baddely Logical Reasoning (Blagrove et al. Appl. Cog. Psychol. 9:21), Tower of London or TOL (Culbertson & Zillmer, MHS), Parkin Temporal Memory for Faces (Harrison et al. 2000), and a combined Digit Span (WAISR) and (computerized) 2-back (courtesy L. Seidman). For each variable, TSD and CTL variable group means were compared using unpaired t-tests. If t-tests of Day 5 vs.8 in CTL's showed no learning effects for a variable, paired t-tests were also used to compare Days 5 (sleep deprived) and 8 (after recovery sleep) in TSD subjects.

**Results:** Using unpaired t-tests, the only significant group difference between TSD and CTL groups following TSD was for false recognitions on the Parkin Temporal Memory task. How-

ever, within TSD subjects, paired t-tests of digits forward showed a increase following recovery sleep while digits backwards showed a similar trend. CTL subjects outperformed TSD subjects as a group in the second presentation of the TOL on "number of correct trials" suggesting that TSD may impact the encoding of new learning

Table 1

Task	Day 5			Day 8		
	TSD (SD)	CTL (SD)	p	TSD (SD)	CTL (SD)	p
TOL: total moves	18.3 (14.00)	20.2 (15.62)	.778	17.0 (11.99)	10.6 (11.62)	.241
TOL: #correct	5.7 (2.75)	6.4 (1.90)	.516	6.50 (2.17)	8.30 (1.77)	.057
LOGIC: #correct	43.2 (13.68)	39.6 (11.73)	.536	54.8 (13.81)	51.8 (11.89)	.609
LOGIC: #attempted	47.0 (13.44)	47.0 (10.48)	1.00	56.9 (13.67)	55.7 (12.06)	.837
DIGITS forward (√, p=0.32)	10.7 (1.64)	10.9 (1.85)	.801	11.8 (1.23)	11.2 (1.75)	.387
DIGITS back (√, p=0.96)	9.6 (2.37)	9.2 (2.47)	.717	10.8 (2.25)	10.0 (2.45)	.457
2-BCK: %correct (√, n.s.)	56.9 (5.09)	58.6 (4.17)	.424	58.5 (4.12)	58.7 (5.66)	.929
PARKIN: % in correct order (√, n.s.)	81.3 (4.1)*	81.6 (10.7)	.925	84.2 (15.1)*	92.5 (5.9)*	.141
false recognition (√, p=0.49)	4.33 (3.74)*	0.90 (1.20)	.014	1.78 (2.86)*	0.22 (0.67)*	.132
FLUENCY: fas (Day 5); bct (D8) (√, n.s.)	46.6 (12.08)	46.4 (10.08)	.968	51.4 (10.99)	49.6 (8.20)	.623
animals(D5); vegetables(D8)	23.6 (4.08)	24.80 (5.45)	.585	14.6 (2.80)	13.8 (3.58)	.585

N=10 (\*N=9), (√)-unpaired and paired t-tests of CTL show no learning.

**Conclusions:** As found by Binks et al (1999), young healthy American undergraduates are remarkably resistant to the DLPFC effects of one-night's total sleep deprivation reported in British studies (Harrison et al. 2000). Deficits, however, may begin to emerge using within-subject measures.

References:

- (1) Binks PG, Waters WF, Hurry, M. Short-term total sleep deprivation does not selectively impair higher cortical functioning. Sleep 1999;22:328-334.
- (2) Bolla KI, Cadet JL, London ED. The neuropsychiatry of chronic cocaine abuse. Journal of Neuropsychiatry and Clinical Neurosciences 1998;10:280-289.
- (3) Harrison Y, Horne J, Rothwell, A. () Prefrontal neuropsychological effects of sleep deprivation in young adults-A model for healthy ageing? Sleep 2000;23:1067-1073.

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631.I

DEVELOPMENT OF A REPEATABLE BATTERY OF TESTS OF PREFRONTAL FUNCTION FOR SLEEP DEPRIVATION STUDIES

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**Introduction:** Tasks that engage the prefrontal cortex generally require flexible problem solving strategies. Because novelty is a key component, these kinds of tasks may cease to be a good indication of prefrontal function following repeated

administration (Harrison, Horne, & Rothwell, 2000). This makes within-subject comparisons difficult. Reported here are several tests of prefrontal function that showed little effect of repeated administration, and may thus represent a battery of neuropsychological tests potentially useful in within-subject, repeated-measure designs for assessing dorsolateral (DLPFC) and ventromedial (VMPFC) prefrontal function. The battery was developed in order to examine sleep effects on cognition relevant to cognitive deficits in chronic cocaine users.

**Methods:** Participants were 10 right handed, English-as-first-language males, aged 19-25 who had completed of at least one semester at a competitive admissions 4-year liberal arts college. In this IRB-approved study, paid subjects were recruited by newspaper and word of mouth and signed informed consent. Subjects had good health, normal vision, audition and olfaction, no history of major mental, sleep or substance abuse disorders nor brain injury. Subjects were recruited in groups of 2-3, and sleep patterns were monitored for one week using the Nightcap (Ajilore et al. *Psychophysiology* 32:92) and diaries. Subjects were tested from approximately 6:30 to 11 pm on Day 5 and again on Day 8. Tasks were always presented by the same 3 examiners and were counterbalanced by 2 anatomical PFC groupings and, within each grouping, by order of presentation. DLPFC tasks were combined verbal and category fluency (FAS/animals Day 5, BCT/vegetables Day 8), modified Baddely Logical Reasoning (Blagrove et al. *Appl. Cog.Psychol.* 9:21), Tower of London or TOL (Culbertson & Zillmer, MHS), Parkin Temporal Memory for Faces (Harrison et al. 2000), and a combined Digit Span (WAISR) and (computerized) 2-back (courtesy L. Seidman). VMPFC tasks were a (computerized) modified Bechara Gambling task (Bechara et al. *Cognition* 50:7); a computerized Object Alternation Task (OAT) (Freedman et al., 1990); the Stroop Color Word Task (Golden, Stoelting Company); and the Smell Identification Test (Doty, Sensonics, Inc.). Posterior cortical tasks were (computerized) Shepard Mental Rotation Task (courtesy S. Kosslyn) and the recognition portion of the Parkin Temporal Memory for Faces (Harrison et al. 2000). For each variable, group means were compared using unpaired and paired t-tests.

**Results:** Tests of DLPFC function which showed no effects of repeated administration, for either unpaired or paired comparisons, included fluency, combined Digit Span, 2-back, and the false recognition portion of the Parkin Memory Task. VMPFC tasks that showed no effect included the Bechara gambling task, Stroop task, and Smell Identification Task. The Logical Reasoning, the TOL, the recognition portion of the Parkin Temporal Memory task, OAT, and the Mental Rotation Task revealed higher performance on Day 8.

**Conclusions:** Compiling a battery of prefrontal tasks that do not show an effect of repeated administration has potential uses for investigating frontal function using a within-subjects design in several settings, including but not limited to sleep deprivation and drug-addiction.

#### References:

(1) Harrison, Y, Horne, J. & Rothwell, A. (2000) Prefrontal neuropsychological effects of sleep deprivation in young adults-A model for healthy aging?. *Sleep* 23:1067-1073.

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## 632.I

### THE EFFECT OF MILD SLEEP DEPRIVATION ON FOOD CONSUMPTION IN RATS

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**Introduction:** Anecdotal evidence about the link between sleep and eating abounds. Sleep deprivation-induced "munchies" and the desire for sleep after a large meal seem nearly universal. More systematic evidence of a link was seen in studies of rat sleep deprivation that used the "disk-over-water" method; rats deprived of sleep show robust increases in food intake, presumably in response to increased energy expenditure. Nevertheless, the neural mechanism(s) whereby sleep and eating interact is unknown. In this experiment, we sought to see whether moderate REM sleep deprivation produced by the "flower-pot" method was sufficient to induce increased feeding behavior in rats.

**Methods:** Nine animals were randomly assigned to one of three groups: a REM sleep deprived group (D), an apparatus control group (C), and a home cage control group (H). A liquid diet was used to minimize spillage and to improve measurement accuracy. All animals were accustomed to a liquid diet for rodents (caloric content was 20.8% protein, 11.9% fat, 67.3% carbohydrate; AIN-76, Bio-Serv, Frenchtown, NJ). Both D and C animals were placed on platforms in an enclosure filled with water to approximately 3 cm below the crown of the platforms. Enclosures for the deprived animals contained three platforms 6.5 cm in diameter whereas control enclosures had two platforms 12 cm in diameter. The platforms were placed so that a rat could move freely among the platforms, yet could not span the distance between them in a resting posture. In each enclosure one of the platforms was placed so that the rat had easy unimpeded access to both food and water. Home Cage controls were singly housed in a colony room with no alteration in their care. All rats were monitored in the testing conditions for 120 hours, during which time food intake was measured approximately every twelve hours.

**Results:** Although feeding behavior was similar among groups, the H group was the only group that continually gained weight. The C group maintained the same weight with little fluctuation while the D animals lost weight throughout the testing period.

Table 1

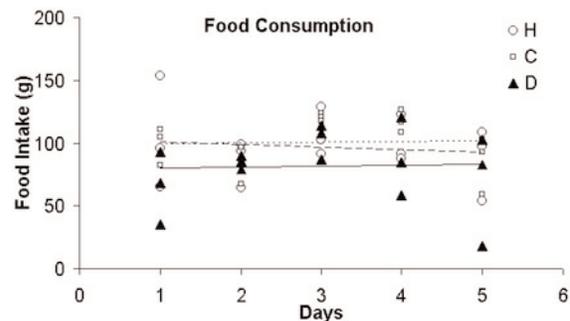
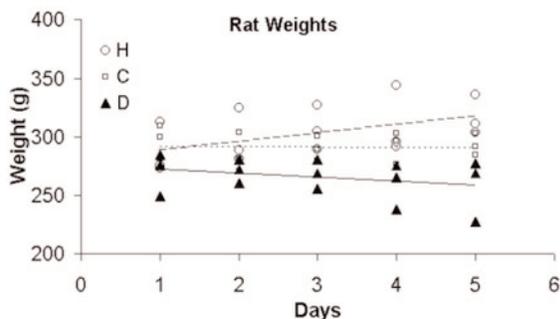


Table 2



**Conclusions:** The results suggest that REM sleep deprivation for five days by the flower-pot technique is not sufficient to achieve an increased feeding response seen in chronically sleep deprived animals. Nonetheless, mild sleep deprivation does seem to elicit increased metabolic resting rates in these animals, as suggested by weight loss despite normal food intake in comparison to control groups.

### 633.I

#### SUBJECTIVE AND OBJECTIVE INDICES OF SLEEP LOSS: EFFECTS OF CHRONIC PARTIAL SLEEP RESTRICTION

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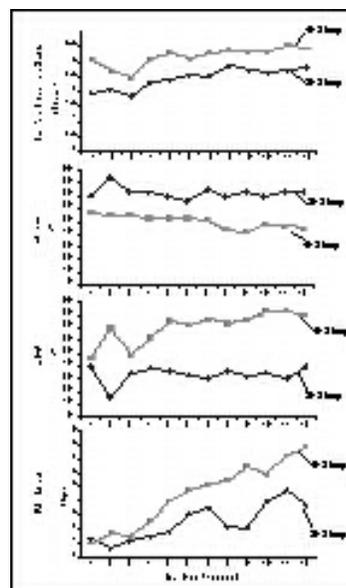
**Introduction:** Chronic undersleeping is a frequent problem in modern living. Shift work and emergency operations frequently require individuals to curtail nocturnal sleep for prolonged periods. The current study was part of an ongoing larger study to investigate the effects of sleep loss on human host response. We describe here the subjective estimations of effort, motivation, sleepiness. In addition, we present an objective performance measure derived from the psychomotor vigilance test (PVT).

**Methods:** Healthy volunteers, between the ages of 21-40, lived in a controlled Clinical Research facility for 16 days. All subjects were allowed to sleep for 8 hours on the first two nights of the study, and were then randomized to either a 4 or 8 hour (nocturnal) sleep condition. For 12 days, subjects slept either between 2300-0300h, or 2300-0700h, depending on experimental group assignment. All subjects were allowed one night of recovery sleep at the end of the study. Performance testing was done at two-hour intervals throughout waking periods. These tests consisted of (U Penn's) ten minute Psychomotor Vigilance Test (PVT), a logical reasoning test, the Stanford Sleepiness Scale (SSS), as well as subjective indices of motivation and effort.

**Results:** These data are part of a larger on-going study of >40 subjects. We report here preliminary data on the first 8 subjects run, 4 subjects in each condition. This data measures lapse performance using the PVT (a lapse is a reaction time  $\geq$  500 ms). We also examined subjective indices of motivation and

effort relating to the participant's performance in each PVT session and their global subjective measures of sleepiness. Performance decrements on the PVT increased linearly across days in the study. Interestingly, in the few control subjects run so far, we also see a modest increase in performance decrement, through the CRC stay. We found that while all participants showed increases in subjective sleepiness over the course of the study, those in the 4hr group showed more subjective sleepiness. When asked to rate how hard it was to maintain fast reaction times during the PVT, the 4hr group estimated greater difficulty in sustaining effort. The 8hr group showed very little change on this measure. In addition, when asked how motivated they were during the PVT, the 4hr group showed a gradual decline in motivation as the study went on, while the 8hr group remained quite stable.

Figure 1



**Conclusions:** As has been described by the Dinges group at the University of Pennsylvania (1), PVT performance decrements (lapses) accrue in a linear manner across days of prolonged partial sleep restriction to 4 hours per night. Moreover, chronic sleep restriction leads to a higher level of perceived difficulty.

#### References:

(1) Kuo A, Carlin M, Powell J, Dinges D: Chronic restriction of sleep to 4 hours per night for 14 nights changes performance linearly but not subjective sleepiness. Sleep 21:241, 1998.

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## 634.J

**THE RELATIONSHIP BETWEEN MARKERS OF SLEEP FRAGMENTATION IN PATIENTS WITH OSAS AND THEIR FUNCTIONING DURING THE DAY**Van Son B,<sup>1</sup> Hofman W,<sup>1</sup> Van Uffelen R<sup>1</sup>

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**Introduction:** Sleep fragmentation in OSAS may lead to daytime sleepiness and cognitive problems. The severity of OSAS is normally quantified by the apnoea/hypopnoea index (AHI), oxygen desaturation index (ODI) or the arousal index (AI). An alternative is to look at blood pressure (BP) changes measured by PTT (pulse transit time). The goal of this paper is to study the relationship between the different markers of sleep fragmentation and functioning during the day measured by questionnaires and performance tests.

**Methods:** Patients (15) with an AHI of 10 or more at the time they were screened at home were included. Control subjects (10) were recruited among the hospital staff. All subjects were between 30 and 55 years old. All subjects got a night of full polysomnography. The next morning they filled in three questionnaires and did two performance tests on a computer. Sleepiness was measured with the Epworth Sleepiness Scale (ESS), sleep quality with the Dutch Specific Sleep quality Scale (SSS) and mood with the profile of mood states (POMS). The two performance tests were the Parasuraman vigilance task and a N-back attention task with memory load. EEG arousals of 3 seconds or more, apnoea/hypopnea and saturation dips (of 3% or more) were scored and indexed. PTT dips were scored if the averaged (moving window of 10 samples) PTT trace dropped for 15 ms for at least 5 seconds but no more than 45 seconds.

**Results:** Patients had a higher AHI ( $p=.009$ ), AI ( $p=.029$ ), mean ( $p=.040$ ) and minimum ( $p=.001$ ) desaturation level. They were sleepier ( $p=.001$ ), had a worse sleep quality ( $p=.002$ ) and scored higher on the POMS dimensions Fatigue ( $p=.001$ ), Vigor ( $p=.000$ ) and Tension ( $p=.049$ ) than controls. All presented correlations were significant ( $p<.05$ ). The SSS correlated with the ODI ( $r=-.469$ ) and the AHI ( $r=-.509$ ). The ESS showed correlations with the AI ( $r=.645$ ), ODI ( $r=.607$ ) and the AHI ( $r=.656$ ), but not with PTT arousals. The POMS dimension Vigor correlated with all the markers (PTT arousals,  $r=-.638$ ; AI,  $r=-.629$ ; ODI,  $r=-.54$ ; AHI,  $r=-.516$ ). The expected difference in results on the performance tests between the groups was not found.

**Conclusions:** There seemed to be a difference in sleepiness and sleep quality between the patient and the control group, but not in the performance test results. From the physiological data, it became clear that the patient group was not as uniform as expected. Not all patients had an A/H index of 10 or more. The overall relationships between the sleep fragmentation markers were good. Only the A/H index did not show any significant correlations with other markers. Contrary to the findings of Pitson and Stradling (1998) the subjective sleepiness measurements showed a fairly good relationship with the sleep fragmentation markers.

**References:**

(1) Pitson, D.J. and Stradling, J.R. Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnoea, their relationship to EEG arousals, respiratory events and subjective sleepiness. *J. Sleep Res.* 1998; 7:53-59

## 635.J

**IMPROVEMENT OF CPAP TITRATION BY CARDIO-VASCULAR PROFILING**Kumar A,<sup>1</sup> Van Son B,<sup>1</sup> Hofman WF<sup>2</sup>

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**Introduction:** The recurrent transient arousals at the termination of a disturbed-breathing event fragment sleep. These transient arousals elicit a reflex in sympathetic activity, that triggers an autonomic reaction manifesting itself in a rise in blood pressure (BP) or in vasoconstriction. Elimination or reduction of apneas/hyponeas by CPAP is one of the measures for determining optimal pressure. Can the CPAP pressure be further optimized to eliminate vasoconstriction? To find an answer to this question, we present results of two clinical cases of OSAS patients during a CPAP titration night.

**Methods:** Data from two OSAS patients were used during a split night recording with multiple CPAP levels. The CPAP titration was performed by an expert PSG technician. The conventional markers, AHI, ODI, and AI were analyzed for each CPAP level. In addition, autonomic arousal in vasoconstriction was scored by evaluating the plethysmogram signal. Two levels of vasoconstriction in the plethysmogram signal (a reduction of 10% or 20% in the peak-peak level) lasting at least 5 seconds was scored separately as Peripheral Vasoconstriction (PV) events. The number of PV's were indexed per CPAP level resulting in PVI(10%) or PVI(20%). All analyses were done by an experienced human scorer. Non-parametric correlations were calculated.

**Results:** PVI values of two sensitivities were evaluated to determine the usable criterion for PV. The PVI for a reduction by 20% (PVI(20%)) discriminated CPAP levels and the pattern was systematic. In the first patient the PVI showed a good relation with all conventional indices. In the second patient the PVI(20%) showed a relation with AHI and AI but not with ODI.

**Conclusions:** The less restrictive criterion for PV(10% decrease) captures spontaneous and epiphenomenological changes partially explained by vasoconstriction during REM sleep. PVI(40%) discriminated different CPAP levels better. To our knowledge it is one of the first efforts to determine criteria for defining the clinically useful PV. More research is needed to determine recommended values of reduction in PV. PV gives more information about cardio-vascular distress at higher CPAP levels than the conventional indices of sleep fragmentation like AHI or AI. The autonomic arousals associated with disturbed breathing result in a higher overall BP during sleep. With the presumed higher sensitivity of autonomic arousals, PVI might be a good tool for fine-tuning the CPAP. If all visible apneas/hypopneas are gone but PV are still present then it is plausible that the higher CPAP-pressure is better.

If the CPAP gets too high the PVI should increase again. The PVI might also be useful as an indicator for cardiovascular reactivity during sleep. Cardiovascular problems are frequent in respiratory disturbances and a non-invasive indication of autonomic reactivity like PVI could be valuable.

### 636.J

#### ESOPHAGEAL PRESSURE MONITORING IN CHILDREN: WHAT FACTORS DETERMINE SUCCESS OR FAILURE?

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**Introduction:** Esophageal pressure monitoring (Pes) is a gold standard in polysomnographic evaluations of adults and children for sleep-disordered breathing. However, Pes monitoring often is not used in children, in part because of concern that it may not be tolerated well. Little information has been published on children's acceptance or tolerance of Pes monitoring. **Methods:** We recruited 50 children (23 girls) aged 5 to 12 years (M=7.9, SD=1.9) to participate in an ongoing study of sleep-disordered breathing: 42 subjects had been scheduled for adenotonsillectomy (AT) and 8 had been seen at a general surgery clinic (and most scheduled for hernia repair). Children underwent pre-operative behavioral assessment by a board certified child psychiatrist and laboratory-based nocturnal polysomnography that included Pes monitoring using a thin water-filled catheter connected to a transducer. Tolerance of Pes monitoring was assessed by technicians' reports and total Pes monitoring time. Parents of potential subjects who declined participation were asked to provide the primary reason for their decision.

**Results:** Among 140 subjects who were referred for possible enrollment and ultimately declined participation, nearly 23% reported Pes monitoring as a major factor in their decision. Virtually all enrolled parents and children expressed some concern about Pes monitoring. All enrolled subjects attempted Pes insertion, as required to be eligible for the study; 39 (78%) had 2 or more hours of Pes monitoring and 34 (68%) tolerated Pes monitoring for the entire night. No significant differences in overall Pes tolerability were identified for general surgery controls (75%) versus children scheduled for adenotonsillectomy (79%). Likewise, the presence of disruptive behavior disorders (ADHD, Oppositional Defiant Disorder, or Conduct Disorder) or obstructive sleep apnea were not predictive of Pes tolerance (all  $p \geq 0.5$ ). Trends suggested that fewer younger (ages 5-6) than older children (ages 7-12) and fewer girls than boys tolerated full-night Pes monitoring ( $p = 0.09$  and OR 0.33;  $p = 0.11$  and OR 0.37, respectively). Parent withdrawal of consent was the most-frequently reported reason for termination of Pes monitoring (11/16 cases). This was often, but not always, preceded by the child crying or screaming. Vomiting (5/16) and complaint of nasopharyngeal pain also prompted discontinuation of Pes monitoring.

**Conclusions:** Esophageal pressure monitoring most often is not a barrier for enrollment and participation in research protocols requiring polysomnographic evaluations. Successful full-night Pes monitoring was limited, however, by poor toler-

ance in a significant minority of children who volunteered for research studies. Although perceived as challenging subjects, children who meet DSM-IV criteria for disruptive behavior disorders do not appear predisposed to failure of Pes monitoring. Larger sample sizes are needed to determine whether female gender and younger age are risk factors for intolerance of Pes monitoring. Adverse reactions to Pes monitoring in some of our carefully observed research subjects suggest that similar experiences may occur in children forced to undergo Pes monitoring for clinical indications. The procedure should be performed, therefore, only when clinicians believe that anticipated medical benefit outweighs the risk.

Research supported by The National Institutes of Health grants R01 HD38461, K02 NS02009, and M01 RR00042

### 637.J

#### IS OBSTRUCTIVE SLEEP APNEA ASSOCIATED WITH CARDIOVASCULAR DISEASE IN A SOUTHWESTERN U.S. VETERAN POPULATION?

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**Introduction:** Obstructive sleep apnea (OSA) has been hypothesized as an independent risk factor for cardiovascular disease (CVD). A preponderance of OSA-related CVD studies, however, have used civilian samples and civilian hospitals. This study investigates relationships between OSA and CVD in VA veteran outpatients.

**Methods:** Male veterans over 54 years of age ( $n=195$ ; 44% Hispanic/56% non-Hispanic white; mean age  $68.3 \pm 8.0$  years) served as subjects. Participants completed the Southern Arizona VA Health Care System (SAVAHCS) Minority Vascular Registry questionnaire, including demographic information, health care provider diagnosed cardiovascular diseases, the Sleep Heart Health Study (SHHS) Sleep Habits Questionnaire, and a dichotomized question regarding physician diagnosed OSA. Height, weight and blood pressure were also obtained. Chi-square was used for nominal variables, and Relative Risk Ratios (RR) were provided for subjects with and without OSA. ANOVA was used to examine interval data between groups.

**Results:** The prevalence rate for OSA in this veteran population was 7.7%. Veterans with OSA were significantly more likely to be overweight (BMI=31.9 versus 27.5,  $p < 0.01$ ), and to report loud snoring (RR=3.2,  $p < 0.0001$ ), early morning awakening with difficulty returning to sleep (RR=2.2,  $p < 0.05$ ), insufficient sleep (RR=3.7,  $p < 0.001$ ), and daytime sleepiness (RR=2.5,  $p < 0.01$ ). Veterans with OSA were at greater risk for angina (RR=2.1,  $p < 0.05$ ), myocardial infarct (RR=3.6,  $p < 0.01$ ), and to have undergone coronary angiography (RR=2.8,  $p < 0.0001$ ). A borderline significant finding was noted for higher systolic blood pressure for veterans with OSA compared to veterans without OSA ( $140 \pm 19.5$  versus  $132 \pm 17.0$ ,  $p < 0.10$ ). No significant differences were noted between groups for age, ethnicity, education, income, smoking status, pack years, diastolic blood pressure, physician diagnosed congestive heart failure, peripheral vascular disease,

stroke, TIA, or to have undergone coronary artery bypass surgery.

**Conclusions:** The prevalence rate for OSA in this veteran population is higher compared to the rate reported for men in a civilian sample (1). Profiles of OSA with BMI, snoring and sleep complaints are consistent with diagnostic criteria reported in the sleep literature, and findings for OSA associated CVD risk complement findings emerging from the SHHS (2). Although substantial interest in sleep medicine exists in VA hospitals nationally, inconsistencies have been reported in sleep testing, referrals, and interventions (3). Because 80% of veterans with OSA in this study underwent coronary angiography, emphasis should be placed on early diagnosis of, and appropriate interventions for OSA to improve veterans' health and well being, and reduce health care costs.

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**638.J**

**HEALTH-RELATED QUALITY OF LIFE AND SLEEP APNEA IN AN ELDERLY CAUCASIAN SAMPLE**

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**Introduction:** The relationship between health-related quality of life and apnea has been described in both clinic populations and random community samples with the focus primarily on middle-aged adults. We had the opportunity to study the relationship between health-related quality of life in a non-clinic sample of Caucasian elderly who were selected based on the presence of symptoms of sleep-disordered breathing.

**Methods:** Seventy Caucasian elderly were screened for snoring and daytime sleepiness (40 women and 30 men). Sleep was recorded for two nights using the modified Resptrace/medilog portable recording system, which recorded thoracic and abdominal respiration, leg movements and wrist activity. Finger pulse oximetry was recorded on one of the nights. Health-related quality of life (QOL) was measured using the 116-item long version of the Medical Outcome Studies (MOS) Core Measures of Health-Related Quality of Life and the Quality of Well Being (QWB) scale. The MOS is comprised of subscales that allow the measurement of the physical, mental and general health of a population. Scale scores

range from 0 to 100, with 100 representing better health. This study examined the Physical and Mental Component Summary scales and the Sleep Problems and Vitality subscales. The QWB consists of a symptom/problem, and mobility, physical activity, and social activity scales. Scores from each scale are coupled with population-derived weights to yield one composite score ranging from 0 (death, or no functioning) to 1.0 (optimum functioning).

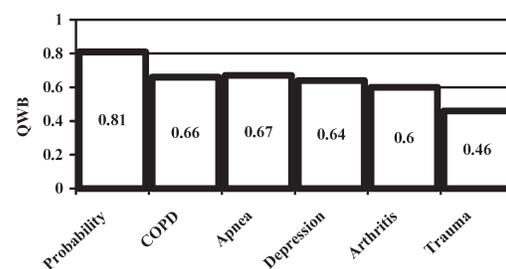
**Results:** The men had significantly worse apnea than the women; therefore, the men and women were studied separately (see Table 1). The men with higher AHI scores had lowered energy levels as measured by the Vitality subscale ( $r = -.38, p = .04$ ) and more Sleep Problems ( $r = -.48, p = .007$ ). No relationship was found between any measure of health-related quality of life and sleep apnea in the women. However, in women, the MOS Mental Summary Scale was negatively associated with WASO ( $r = -.45, p = .004$ ), such that the more wake, the worse their daytime QOL. There was no relationship between sleep variables and QOL in the men. Figure 1 shows that the mean QWB for men in this sample ( $.67 \pm .091$ ) is comparable to the QWB level for those with other significant medical conditions.

**Table 1**

(Mean ± SD)	Women	Men	p-value
Age	72.7 ± 6.1	74 ± 5.2	NS
BMI	28.0 ± 6.1	27.1 ± 3.6	NS
AHI	12.7 ± 11.7	23.9 ± 21.9	.002

**Figure 1**

**Quality of Life in Older Caucasian Men with SDB**



**Conclusions:** The results indicate that in elderly Caucasians men selected for symptoms of SDB, sleep-disordered breathing is associated with lowered energy levels, increased complaints of sleep problems, and QWB levels comparable with other significant medical conditions. These relationships were not seen in elderly Caucasian women, and might be explained by the low level of sleep-disordered breathing in this sample of women. However, in women, decreased energy (Vitality) was associated with increased wake measured objectively during the night.

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**DATA DRIVEN RESEARCH ILLUMINATES THE WEB OF VARIABLES ASSOCIATED WITH SLEEP DISORDERS**

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**Introduction:** An estimated 2-4% of the general population suffers from sleep disordered breathing, contributing to a number of adverse effects on health (1) and increased rates of chronic diseases (2). A major public health burden results from under-diagnosed obstructive sleep apnea – hypopnea (3) along with other sleep disorders such as narcolepsy, insomnia, and periodic limb movement disorder. Diagnosis is complicated by a multitude of intervening variables that range in effects from disguising the presence of sleep disorders to inadequate understanding of the relationships shared by other health problems and sleep disorders. Difficulty in acquiring valid data from patients whose diagnosis is based on a complete sleep study (polysomnography) further impedes investigations (2). Research in this area has the potential to advance knowledge about variables associated with sleep disorders, reveal patterns of symptomatology, illustrate effective treatment modalities, and ascertain covariances. To investigate these areas, we developed a comprehensive program of data driven research. This paper details three areas: 1. the foundation of a multi-disciplinary sleep disorder research team lead by pulmonologists and neurosurgeons, 2. the development of a comprehensive questionnaire and associated database created to track patients with sleep disorders in a detailed, consistent way from onset through diagnosis, treatment, and subsequent outcome, and 3. a sample of results derived from patients with sleep disorders during the first year of this data-driven research project.

**Methods:** We constructed an 80-item patient questionnaire to use in conjunction with nocturnal polysomnography studies, and medical chart reviews of patients with sleep disorders. The database includes 160 measures collected in the following 11 categories 1. general patient demographics, 2. sleep habits, 3. sleep observations, 4. daytime symptoms, 5. related complaints, 6. medical history, 7. medications, 8. sex specific information, 9. social history, 10. cognitive research measures, and 11. sleep study and scientific observations. An outpatient follow-up questionnaire is currently under development.

**Results:** This tool and method facilitates interdisciplinary investigations focused on achieving a complementary balance of basic and applied research. In our quest to reveal naturally occurring processes, we report quantitative and qualitative findings. Demographic, medical, cognitive, social, and sex specific variables associated with sleep disorders and their implications are discussed.

**Conclusions:** We believe our approach advances knowledge about the complex range of factors that affect sleep disorder compositions, diagnosis, treatment, and recovery. We hope to provide a more comprehensive perspective than would otherwise be observed and documented to help ameliorate the problems and resultant effects associated with under-diagnosed and misunderstood sleep disorders.

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640.J

**AN EVALUATION OF A NEW SELF TITRATING CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) DEVICE**

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**Introduction:** Automatically adjusted CPAP may be useful in reducing CPAP side effects and may increase the regularity of CPA use.

**Methods:** To evaluate the performance of a new automatically adjusted CPAP device (REMStar<sup>®</sup> Auto, Respironics, Inc., Murrysville PA), nine previously diagnosed, consenting adult subjects were recruited. There were eight males and one female. The mean age was 52.3 (13.7) ( $\pm$  SD) years. The mean BMI was 31.8  $\pm$  5.02 (SD). Patients were required to have been prescribed CPAP therapy for at least three months and to have been using CPAP an average of at least 4 hours per night. Patients were first treated with manually adjusted, fixed pressure CPAP. Manually adjusted, fixed pressure CPAP was adjusted to eliminate apneas, hypopneas, snoring, and arterial desaturation. Patients then used the REMStar Auto during polysomnography. The REMStar Auto was set in the automatically adjusting CPAP (Auto-CPAP) mode. The REMStar Auto identifies pressure requirements by optimizing the airflow pattern. Pressure is adjusted to identify the critical pressure required to prevent flow limitation and an upper pressure that does not result in improvement in the inspiratory flow pattern. Data from the optimally adjusted, fixed pressure CPAP setting were compared to data from the entire night on the REMStar Auto device.

**Results:** The mean, untreated Respiratory Disturbance Index (RDI) was 52.8  $\pm$  26 (SD) events per hour. There was significant improvement with both manual CPAP titration (mean RDI = 1.48  $\pm$  1.42 (SD)) and with the REMStar Auto (mean RDI = 1.6  $\pm$  0.84 (SD)) events per hour ( $p < 0.001$ , ANOVA). There was not a significant difference between manually titrated CPAP and Auto-CPAP with the REMStar Auto ( $p = 0.83$ , paired t-test). The mean manually titrated CPAP pressure was 10  $\pm$  3.08 (SD) cm H<sub>2</sub>O. The REMStar Auto 90% pressure (the calculated pressure provided for 90% of the night) was 10.17  $\pm$  3.4 (SD) cmH<sub>2</sub>O. The average pressure using the REMStar Auto device was 8.02  $\pm$  3.05 (SD) cmH<sub>2</sub>O. There was not a significant difference between the manually titrated CPAP pressure and the 90% pressure and the auto-CPAP average

pressure ( $p = 0.29$ , ANOVA). The mean, untreated minimum saturation was  $81 \pm 11.1$  (SD) percent compared to  $93 \pm 1.1$  (SD) percent while using the REMStar Auto ( $p = 0.04$ , paired t-Test).

**Conclusions:** The REMStar Auto treated severe OSAHS. The RDI was improved significantly with pressures that were not significantly different from manually adjusted, fixed pressure CPAP.

Research supported by Supported by Respironics, Inc.

## 641.J

### DIAGNOSIS OF SLEEP APNEA IN MEN AND IN WOMEN: IS IT PREVALENCE OR PRESENTATION THAT DIFFERS?

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**Introduction:** Sleep apnea, which increases with age, can seriously undermine quality of life in the short term and pose a risk for hypertension and heart disease in the long-term.<sup>1</sup> It is substantially under-diagnosed and is believed to affect men predominantly.<sup>2</sup> Here we evaluate the basis of the gender disparity and the extent of under-diagnosis.

**Methods:** Sixty-seven community-based older adults (age  $\geq 50$ ) comprised the sample. They responded to posters seeking participants experiencing excessive sleepiness or fatigue during the daytime or sleep problems at night. Posters were located in clinics and seniors' meeting places. Individuals were excluded if they had a medical condition or were taking medication known to cause the presenting complaints. Participants were evaluated by a sleep medicine specialist and by interview, questionnaire and one night of polysomnography. There were more women (58%) than men (42%) in the sample.

**Results:** Polysomnographic data indicate high rates of primary sleep disorders: 96% of men and 74% of women met diagnostic criteria for a breathing disorder, periodic limb movement disorder (PLMD), or both. Women were significantly more likely to present with only insomnia, 26% vs. 1%, ( $\chi^2$  (1) = 5.78,  $p < .05$ ). Table 1 contains the details. To explain the traditional gender bias in referring patients for sleep studies, we selected self-report and physiological data in the Apnea/Hypopnea group. A striking finding on physiological indices is that women had significantly lower RDI (respiratory disturbance index) than men ( $t(28) = 2.24$ ,  $p < .05$ ), suggesting less severe breathing obstruction. Yet, they experienced the same level of oxygen desaturation during sleep ( $t(28) = 0.78$ ,  $p > .05$ ). Presentation of the complaint also differed between men and women. While both reported significant daytime sleepiness, women were more likely to report daytime fatigue as well ( $\chi^2$  (1) = 5.78,  $p < .05$ ). Women also reported more sleep problems such as difficulty initiating sleep ( $\chi^2$  (1) = 5.43,  $p < .05$ ) and non-restorative sleep ( $\chi^2$  (1) = 3.9,  $p < .05$ ). They scored higher on various indexes of psychological distress as well.

Table 1

Age and Diagnosis for Women and Men.				
	Women		Men	
Age (Mean)	62.6		63.1	
Diagnosis	N	%	N	%
Apnea/Hypopnea	23	59	21	75
RLS/PLMD	3	8	1	4
Mixed Sleep Disorder	3	8	5	4
Insomnia Only	10	26	1	1
Total	39	100	28	100
RDI (Mean)	26.1		42.5	
SpO2 minimum (Mean)	87.3		88.8	

**Conclusions:** We conclude that of people suffering from sleep apnea/hypopnea syndrome, women present more diverse complaints than men. This can make it more difficult for a general practitioner to identify those women who could benefit from polysomnographic assessment. In view of the high percentage of treatable physiological sleep disorders found in both the men and women of our sample, we suggest that it would be prudent medical practice to refer to the sleep laboratory all those over 50 who complain of excessive sleepiness or fatigue during the day and/or sleep problems at night.

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## 642.J

### HEART RATE VARIABILITY: RELATION TO SLEEP APNEA AND SLEEP STAGE

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**Introduction:** Spectral analysis of Heart Rate Variability (HRV) is a measure of autonomic nervous system (ANS) functioning. Decreased HRV occurs with autonomic neuropathy (1) and aging (2). In apnea patients, the repeated hypoxic insults and arousals potentially impair ANS functioning. If correct, HRV should decrease as apnea severity increases. Alternatively, HRV could increase as apnea increases because of changes in sympathetic tone (3).

**Methods:** We analyzed HRV in 105 patients excluding those with frequent pre-ventricular contractions, heart transplant, and severe cardiomyopathy. For each patient, we selected an apnea free 3-6 minute sample from sleep stages 0, 2 and REM for analysis. Digitized ECG data were collected at a 128 Hz

sample rate using a Sandman polysomnographic system. We used the statistical software Systat to perform a multivariate repeated measures analysis looking at total HRV (beats/min<sup>2</sup>) in relation to the apnea hypopnea index (AHI), age, and BMI. We used a univariate F tests for follow-up comparisons.

**Results:** Because there were no statistical differences in HRV for those on cardiovascular medications (n = 12, p = 0.370) and those with diabetes (n = 11, p = 0.366) from other patients, they were included in the analysis. Total HRV was greatest in REM sleep followed by stage 0 and stage 2 sleep. Stage 0 and stage 2 sleep did not differ. With increasing age, HRV decreased in all stages: stage 0 (p = 0.002), stage 2 (p = 0.022) and REM sleep (p < 0.001). Unlike for age, HRV increased as AHI increased for samples from stage 0 (p < 0.001), stage 2 (p = 0.257, ns) and REM sleep (p = 0.026). BMI was related to HRV only in REM sleep where HRV decreased with increasing BMI (p = .021). The interactions with stage (table), reflect greater HRV in REM sleep.

Figure 1

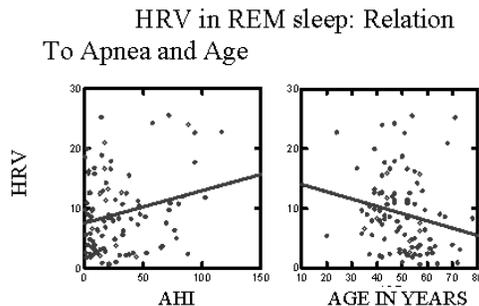


Table 1

Multivariate Repeated measures of HRV

Between Subjects					
Source	SS	df	MS	F	P
AHI	911.349	1	911.349	10.12	0.002
AGE	1571.704	1	1571.704	17.45	0.000
BMI	364.566	1	364.566	4.05	0.047
Error	9096.082	101	90.060		
Within Subjects					
Stage	703.285	2	351.643	11.13	0.000
Stage x AHI	183.430	2	91.715	2.90	0.057
Stage x AGE	338.649	2	169.325	5.36	0.005
Stage x BMI	244.482	2	122.241	3.87	0.022
Error	6384.476	202	31.606		

**Conclusions:** Apnea is associated with increasing HRV. Thus, the absence of blunted heart rate responsiveness suggests the absence of apnea induced autonomic neuropathy. The analysis did detect age related decreases. The elevated HRV with increasing apnea is compatible with increased sympathetic activity related to sleep apnea and perhaps subtle upper airway hypopnea events not otherwise detected during the scoring of the polysomnographic records. The differences among sleep stages indicates differences in autonomic balance and suggests that certain sleep stages may be more sensitive to change in the

innervation of the heart.

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643.J

MARKETING THEORY PREDICTION OF CPAP UTILIZATION

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**Introduction:** Continuous positive airway pressure (CPAP) is one of the preferred treatments for sleep related breathing disorders. For most patients, CPAP is extremely effective for reducing or eliminating episodes of apnea and hypopnea. However, the therapy is only beneficial when it is used; consequently, patients are instructed to use it nightly. Unfortunately, many patients either refuse treatment or use it for a while and then discontinue or reduce utilization. Attempts to predict utilization have mixed success. In general, apnea severity and comorbid sleepiness are correlated with greater adherence to therapy. Predicting utilization would be helpful to formulate therapeutic and follow-up strategy. Marketing theory posits that the two most important factors determining buying (or using) behavior are 1) the individual believes the product is beneficial and 2) the individual thinks they can use the product (change their behavior). The purpose of the present study was to determine if application of marketing theory could be used to predict CPAP.

**Methods:** All patients were evaluated using our standard clinical procedures. A post-CPAP evaluation questionnaire is administered the morning after titration. Therapy utilization was determined by meter reading 1-2 months after the patient had been given and instructed to use CPAP. Our standard clinical procedures include a physical examination, a thorough sleep history, a questionnaire battery, diagnostic polysomnography, positive airway pressure titration, and follow-up. Part of our testing includes a post-CPAP questionnaire that attempts to assess the positive and negative aspects of the patient's titration experience. The focus of this analysis is on two particular items on this questionnaire. These questions, their scoring, and acceptance classification are shown below.

**Results:** In our initial analysis, we compared CPAP utilization between patients with acceptance classifications of excellent (N=28) to those with classifications of poor and very poor (combined, N=23). At the time of analysis, patients in the excellent group used CPAP significantly more minutes per night than the comparison group (mean difference 162 min-

utes,  $p < 0.05$ ).

**Table 1.**

**RESPONSE CODING**

Q1= How hard do you think it will be to use CPAP nightly?  
Q2= How much did CPAP improve your sleep?

EXCELLENT:Q1=Not at All and Q2=Very Much

VERY GOOD:Q1=Not at All and Q2=Moderately -or- Q1=Somewhat and Q2=Very Much

GOOD:

Q1=Not at All and Q2=Somewhat -or- Q1=Somewhat and Q2=Moderately -or- Q1=Moderately and Q2=Very Much

ADEQUATE:Q1=Not at All and Q2=Not at All -or- Q1=Somewhat and Q2=Somewhat -or-Q1=Moderately and Q2=Moderately -or- Q1=Very Much and Q2=Very Much

MARGINAL:Q1=Somewhat and Q2= Not at All -or- Q1=Moderately and Q2=Somewhat -or-Q1=Very Much and Q2=Moderately

POOR:Q1=Moderately and Q2=Not at All -or- Q1=Very Much and Q2=Somewhat

VERY POOR:Q1=Very Much and Q2=Not at All

**Conclusions:** Marketing theory is useful for predicting CPAP utilization during the first 1-2 months of treatment. Having a reliable technique to gauge the effectiveness of therapeutic intervention can help in therapeutic management, resource allocation, and developing remediation programs. If patients can be identified as being AT RISK for therapeutic failure, strategies can be deployed to meet this challenge. Moreover, resource can be better managed by allocating them to produce the greatest benefit.

## 644.J

### DOES OBSTRUCTIVE SLEEP APNEA SYNDROME PROMOTE VEINUS THROMBOEMBOLISM ?

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**Introduction:** Obstructive sleep apnea syndrome (OSAS) is a risk factor for arterial cardiovascular diseases, partly through thrombophilia (1). Thrombophilia may predispose to venous thromboembolism (VTE). The impact of OSAS on VTE is unknown. The objective of the study is to determine OSAS frequency in patients with documented VTE.

**Methods:** Symptoms suggestive of OSAS (excessive daytime sleepiness with Epworth sleepiness scale, nycturia, fatigue, impaired cognitive performance, non-restorative sleep) and polysomnography were assessed in 68 consecutive patients with high probability VTE. They were referred to an university hospital chest department during 9 months for a doppler-proved deep venous thrombosis (n= 11), angioscan-proved pulmonary embolism (n= 47) and scintigraphy-suspected pulmonary embolism (n= 10).

**Results:** Forty-three patients (63 %) had a moderate to severe OSAS (apnea-hypopnea index, AHI >15). OSAS was as frequent in the 54 patients (79 %) with one or more identified risk factor for VTE as in the 14 (21%) without risk factor. The patients with moderate to severe OSAS were older than the patients with no or a mild OSAS ( $p < 0.01$ ).

**Table 1**

AHI	0-5	5.1-15	15.1-30	>30.1
Patients N (%)	7 (10%)	18 (26%)	21 (31%)	22 (32%)
Age (years)	55 ± 19	53 ± 16	64 ± 14	63 ± 13
Male %	29%	39%	33%	59%
Body mass index (Kg/m <sup>2</sup> )	22.0 ± 1.3	26.4 ± 6.8	25.1 ± 4.3	25.6 ± 5.5
Epworth score	8 ± 3	8 ± 4	6 ± 3	8 ± 5

**Conclusions:** The high (63 %) frequency of mildly symptomatic OSAS in patients with VTE suggests that OSAS may be a risk cofactor for VTE.

**References:**

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## 645.J

### DURATION OF SLEEP AT HOME IN CHILDREN, EFFECT OF SLEEP APNEA AND ADMISSION TO A SLEEP RESEARCH UNIT

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**Introduction:** Sleep restriction has been shown to impair cognitive and behavioral performance. We hypothesized that sleep duration at home in children would be shortened by sleep apnea and by impending admission to a sleep research laboratory.

**Methods:** We studied 26 children between the ages of 6 and 12 who were participating in a study of sleep apnea. Sixteen children had sleep disordered breathing with an apnea hypopnea index (AHI) > 1 (mean 7.4 ± 6.6 SD, range 1-24) and 10 had an AHI < 1. Sleep time was detected at home by actigraphy for 6 days before the research study and for a 7th night in the laboratory simultaneously with polysomnography. We used a Mini Motionlogger actigraph (Ambulatory Monitoring Inc.) with 1-minute recording bins, zero crossing mode and amplifier setting of 18. Sleep was detected using the Sadeh algorithm. Polysomnography was performed using standard methods including EEG, EOG and EMG, nasal flow with nasal pressure, chest and abdominal plethysmography and oximetry. **Results:** Sleep time at home was negatively correlated with AHI for all 6 nights ( $r = -0.38$ ,  $p < 0.05$ ) and for the night before admission ( $r = -0.47$ ,  $p < 0.02$ ). Children slept at home an average of 446 ± 51 SD minutes/night for the 6 days before admission and 407 ± 86 min the night before admission ( $p < 0.001$ ).

**Conclusions:** We conclude that sleep apnea decreases sleep time in children sleeping at home as does impending admission to a sleep research laboratory. Short sleep durations could adversely affect cognitive and behavioral performance.

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**646.J**

**CPAP COMPLIANCE IS POOR IN PATIENTS WITH COPD-OSA OVERLAP SYNDROME**

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**Introduction:** The COPD-OSA overlap syndrome is seen in as many as 11% of COPD patients. These patients tend to have worse blood gas and hemodynamics. Continuous positive airway pressure (CPAP) is the recommended treatment. Traditionally recommendation for treatment of COPD patients with BiLevel positive airway pressure is to maintain expiratory pressures on the lower side to avoid increase in expiratory work of breathing. In patients with OSAS, compliance rates of 65-90% have been reported when assessed by subjective means. As the CPAP pressures required for maintaining upper airway patency are often high in OSAS and there is paucity of data on compliance with CPAP in patients with overlap syndrome we examined the compliance in this group using a retrospective case control design.

**Methods:** From the database of patients who were prescribed CPAP therapy for OSAS from our sleep disorder center between 1/2001 and 9/2001, patients with COPD-OSAS overlap were identified. For each patient, two age and sex matched patients without COPD were identified as controls. All patients had a full night standard in hospital polysomnography followed by CPAP titration on another night. Standard criteria for scoring were used and OSAS was defined as RDI>5/hr. Compliance data were collected by self report on follow up visits. Patients reporting CPAP for at least 4 hours on 70% or more nights were deemed compliant.

**Results:** Optimal CPAP was reached in all patients during titration. All patients received heated humidifiers with the machines. The follow up duration was 5+2.6 months and was similar in both groups. Baseline characteristics were comparable in both groups but CPAP compliance was significantly worse in overlap syndrome patients (table 1).

**Table 1**

	RESULTS		
	COPD-OSA (n=13)	Controls (n=26)	p Value
Age	61±11	59±11	0.66
BMI (Kg/M <sup>2</sup> )	37.7±10.6	34.3±8.3	0.28
RDI (events/hr)	36.3±29.8	38.9±22.6	0.76
Lowest SpO <sub>2</sub>	75.3±15.4	81.1±11	0.18
Arousal Index	36.7±29.9	41.1±23	0.62
CPAP	9.6±1.2	10.3±1.6	0.53
FEV1 (L)	1.49±0.26		
Compliant	5 (38.40%)	16 (61.50%)	0.024

**Conclusions:** We conclude that in patients with COPD-OSA overlap syndrome, compliance with CPAP therapy is dismal. We speculate that lung mechanics affect CPAP tolerance in patients with COPD but more studies are needed to explore the

reasons for poor compliance and find way to improve it.

**647.J**

**THE VALUE OF A POST-CPAP TITRATION QUESTIONNAIRE IN PREDICTING CPAP COMPLIANCE**

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**Introduction:** Short-term (2 weeks to 3 months) compliance with CPAP has been associated with long-term compliance (1,2). There has been no report of the relationship between the patient's initial response immediately following split-night CPAP titration and compliance. We routinely ask patients to fill out a questionnaire immediately after a split-night polysomnogram. The aim of this study is to determine whether the initial response to CPAP with split-night polysomnography predicts subsequent use.

**Methods:** The medical records, polysomnographic results, and post-sleep questionnaire on consecutive patients who underwent split-night polysomnography with CPAP titration from January 1999 through February 1999 were reviewed. The two questions pertaining to CPAP use were: (1) "Do you feel CPAP helped you sleep more soundly?" and (2) "If the doctor prescribes CPAP, do you think you will use it?". The association between CPAP compliance and the answer to the questions was analyzed. The sensitivity, specificity, positive and negative predictive values of the questions were calculated.

**Results:** There were 205 total patients who had obstructive sleep apnea and CPAP titration. CPAP was prescribed for all. Each patient was requested to return for follow-up or to notify the sleep center of their progress if they could not return. Of this group, there was follow-up for 99 patients (67 males, 32 females, age±SD = 55±14.3, mean AHI=7.6±12.3). Average follow-up was 159 days (range 7 to 714 days). There was no difference in sleep study results between those patients who had follow-up and those who did not. We have no follow-up information on the 106 patients who did not phone or return to the Mayo Clinic Sleep Disorder Center. Fifty-five of 99 patients stated that they used CPAP 4 or more hours per night. For question 1, the response "yes" has a sensitivity of 62% and a positive predictive value 68% in predicting CPAP use ≥4hrs while the response "no" has a specificity of 42% and a negative predictive value of 28% in predicting non-use (Table 1). For question 2, the response "yes" has a sensitivity of 80% and a positive predictive value of 65% in predicting CPAP use ≥4 hrs while the response "no" has a specificity of 17% and a negative predictive value of 38% in predicting non-use (Table 2).

**Table 1**

**Responses to "Do you feel CPAP helped you sleep more soundly?" and CPAP compliance\***

	Yes	Uncertain	No
CPAP use ≥4hrs/night	34	10	11
CPAP use < 4hrs/night	9	7	9
No use	7	4	8
Total	50	21	28

\*F exact p = 0.05

Table 2

Responses to "If the doctor prescribes CPAP, do you think you will use it?" and CPAP compliance*			
	Yes	Uncertain	No
CPAP use $\geq$ 4hrs/night	44	8	3
CPAP use < 4hrs/night	13	10	2
No use	11	5	3
Total	68	23	8

\*F exact  $p = 0.17$ 

**Conclusions:** We found that a subjective improvement in sleep quality with CPAP titration during split-night polysomnography and willingness to use it if prescribed predicted CPAP compliance. On the other hand, a lack of subjective improvement in sleep quality during CPAP titration and unwillingness to use it if prescribed did not predict failure in CPAP compliance. Our results would suggest that providers should continue to encourage CPAP use among patients with sleep-disordered breathing despite a lack of initial subjective improvement or willingness to fill the prescription. Compliance can still be achieved in many of these patients.

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## 648.J

### SLEEP RELATED BREATHING DISORDERS IN PATIENTS SEEN IN A PULMONARY HYPERTENSION CLINIC

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**Introduction:** Pulmonary hypertension can be divided into primary and secondary etiologies. Secondary causes can be further divided by pathophysiologic mechanisms: hypoxic vasoconstriction, obliteration of pulmonary vasculature, and volume and pressure overload. Optimal approach to therapy requires an accurate diagnosis of underlying disorders: the 5-year mortality of primary pulmonary hypertensive patients is 66%[1] whereas the outcomes may be much improved if a treatable cause or a contributing factor can be identified. Although obstructive sleep apnea is one cause of pulmonary hypertension[2], sleep disordered breathing may contribute to pulmonary hypertension due to other mechanisms. Focusing specifically on sleep related breathing disorders (SRBD), we sought to characterize SRBD in patients evaluated for pulmonary hypertension.

**Methods:** We performed a retrospective chart review of patients evaluated by one investigator in Pulmonary Hypertension Clinic in 2001. Of 79 patients, 26 underwent an overnight oximetry because of history and exam suggestive of SRBD. Of the 26 patients, only 3 patients were noted to have

a normal oximetry study and were excluded from further analysis. For the 23 remaining patients, information such as age, presumed etiology of pulmonary hypertension, and either right ventricular or pulmonary systolic pressures were recorded. Furthermore, as 6 of these patients had undergone a polysomnograph, their apnea-hypopnea index (AHI) was also gathered.

**Results:** 23 patients had an abnormal overnight oximetry based on lowest oxygen saturations and/or pattern of desaturations that is suggestive of SRBD. The mean age of this group was 57.8 with 30% males. Etiology of their pulmonary hypertension was considered to be primary in 6, collagen vascular disease related in 3, chronic thromboembolic disease related in 2, pulmonary fibrosis in 2, and miscellaneous causes such as portopulmonary hypertension, diet drug usage, systemic hypertension, obesity, metastatic breast cancer, restrictive pericarditis, and fibrosing mediastinitis. There are more than 23 causes as several patients had several etiologic considerations. Mean right ventricular or pulmonary systolic pressures were 71.3 mmHg. Six patients had undergone a polysomnograph which revealed sleep related breathing disorders in 5 patients based on AHI of  $\geq 20$ . The average AHI was 32.7 (one patient did not have AHI calculated due to severity of desaturations necessitating CPAP trial one hour into the study).

**Conclusions:** Abnormal overnight oximetry appears to be fairly common in patients with pulmonary hypertension. Although only 26% of these patients underwent polysomnographic evaluation, 83% had abnormal gas exchange during sleep, and may have specific and correctable SRBD. This further emphasizes the importance of carefully questioning all patients with pulmonary hypertension about sleep symptoms and completing an overnight polysomnographic evaluation in those with suggestive history or abnormal overnight oximetry. This becomes essential as treatment of their underlying sleep related breathing disorder might aid in better management of their pulmonary hypertension.

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## 649.J

### EFFECT OF OBSTRUCTIVE SLEEP APNEA ON QUALITY OF LIFE IN THE PATIENT AND THEIR BEDPARTNER

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**Introduction:** Obstructive sleep apnea (OSA) has been shown to affect the quality of life (QOL) in patients and to improve with nasal CPAP(1). Beninati, et al(2) has shown that OSA is associated with frequent arousals from sleep in the bedpartner. However, the effects on the QOL on the bedpartner of the patient with OSA has not been studied. We studied QOL in patients with OSA and their bedpartners and the effect of

CPAP therapy on QOL.

**Methods:** 88 patients seen for evaluation of OSA and their bedpartners were enrolled in the study. Following sleep disorders consultation, patients had polysomnography and subsequent treatment with CPAP based on in-laboratory titration. Both partners completed the SF-36, the Epworth Sleepiness Scale (ESS), and the Calgary Sleep Apnea Quality of Life Instrument (SAQLI)(3). Patients and bedpartners were followed-up at approximately 6 weeks of CPAP therapy and completed the same set of questionnaires. Complete data was obtained on 54 pairs.

**Results:** Of the 54 subjects who completed the study, 47 were males and 7 were females. The mean age was  $58.9 \pm 14.1$  years, mean BMI was  $34.3 \pm 9.5$ . The mean apnea-hypopnea index was  $48.4 \pm 33.3$ . For the subjects, the mean baseline ESS was  $12.9 \pm 4.4$  and following treatment with CPAP the ESS decreased to  $7.3 \pm 4.0$  ( $p < 0.001$ ). For the partner the mean baseline ESS was  $7.4 \pm 6.1$  and decreased to  $5.8 \pm 4.7$  following CPAP therapy for the subjects ( $p = 0.02$ ). The mean baseline overall score on the SAQLI was  $4.1 \pm 1.0$  for the subjects and  $4.5 \pm 1.2$  for the partners. Following treatment with CPAP the SAQLI increased in the subjects to  $4.9 \pm 1.2$  ( $p < 0.001$ ) and in the partners to  $5.1 \pm 0.9$  ( $p = 0.002$ ). The SF-36 showed positive changes in both subjects and partners. Significant improvements were observed in the subjects in the following domains (baseline versus post CPAP therapy): Role-physical ( $50.5 \pm 40.8$  versus  $72.7 \pm 37.7$ ,  $p < 0.001$ ), Vitality ( $36.2 \pm 25.5$  versus  $61.2 \pm 22.4$ ,  $p = 0.001$ ), Social Functioning ( $71.7 \pm 24.4$  versus  $85.6 \pm 23.9$ ,  $p = 0.001$ ), Role-Emotional ( $57.4 \pm 41.2$  versus  $81.5 \pm 19.2$ ,  $p = 0.004$ ). In the bedpartners, significant changes in SF-36 were observed in the following domains (baseline versus post-therapy): Role-physical ( $68.1 \pm 38.7$  versus  $79.2 \pm 32.8$ ,  $p = 0.03$ ), Vitality ( $51.0 \pm 25.4$  versus  $62.4 \pm 20.7$ ,  $p = 0.001$ ), Social Functioning ( $77.9 \pm 26.8$  versus  $89.4$ ,  $p = 0.001$ ), and Mental Health ( $72.6 \pm 21.2$  versus  $80.7 \pm 11.5$ ,  $p = 0.01$ ).

**Conclusions:** OSA results in impairment of QOL in both the patient and their bedpartner. Treatment with CPAP improves both general QOL. Both the subjects and their partners are affected by OSA and both benefit with effective treatment of OSA.

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## 650.J

### IS ZALEPLON EFFICIENT FOR ALLEVIATING SLEEP DISTURBANCES AT HIGH ALTITUDE?

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**Introduction:** Sleep disturbances such as increases in the number of arousals, increases in intrasleep wakefulness and duration of Stages 1 and 2, and decreases in slow-wave sleep (SWS) and rapid eye movement (REM) sleep are often reported by mountain climbers (1). Moreover, respiration during sleep at high altitude is also disturbed by periodic breathing (PB) with apneic periods and subsequent fluctuations in arterial saturation. It has been previously shown that zolpidem may be safely used by climbers since this drug improves sleep quality at high altitude without deleterious effects on respiration (2). However, the use of zolpidem by climbers can be limited by a too long duration (about 6 h) of its hypnotic effects. The aim of this study was to determine if a new hypnotic, zaleplon, which is characterized by an ultra-short half-life, has beneficial effects on sleep without detrimental effects on ventilation at simulated high altitude, compared with zolpidem.

**Methods:** 12 subjects spent four nights in an altitude chamber, the first one at sea level, the three others at a simulated altitude of 4,000 meters (PB = 616 hPa) with either 10-mg zolpidem (ZOL), 10-mg zaleplon (ZAL) or a placebo (PBO) in random order according to a double-blind, crossover, controlled design. Sleep and respiratory parameters were continuously recorded by respiratory polysomnography; O<sub>2</sub> arterial saturation was continuously measured by infrared oxymetry. Sleep and altitude-related breathing events were analyzed according to standard criteria (3).

**Results:** All subjects exhibited PB during sleep at simulated high altitude. Furthermore, altitude was associated with a poor quality of sleep. Compared to PBO, ZAL just tended to improve some characteristics of sleep at high altitude whereas under ZOL, we observed a significant increase in SWS duration, (ZOL: + 27 min,  $p = .017$ ; ZAL: + 11 min, NS), a significant increase in stage 4 sleep duration (ZOL: + 25.4 min,  $p = .004$ , ZAL: + 10.8 min, NS) and a significant decrease in stage 2 sleep percentage (ZOL: - 9.5 %,  $p = .003$ ; ZAL: - 4.6 %, NS). Nevertheless, stage 3 of sleep occurred significantly earlier under ZAL compared with PBO (+ 7 min,  $p = .027$ ). Furthermore, control of breathing was affected neither by ZAL nor ZOL.

**Conclusions:** Zaleplon seems to be less effective than zolpidem for alleviating sleep disturbances observed at simulated altitude of 4,000 meters. However, both hypnotic drugs do not show any deleterious effects on respiration, so that they could be safely used by climbers.

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### 651.J

#### AIRFLOW CONTOUR DURING CPAP TITRATION: AN UNDER-APPRECIATED ENDPOINT

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(1) The Cleveland Clinic Foundation

**Introduction:** The method(s) of determining the optimal CPAP pressure for a given patient can vary, but the conventional method is to determine the pressure which eliminates respiratory events (both obstructive apneas and hypopneas), oxygen desaturations, snoring and respiratory event-related arousals (RERAs) during a given CPAP titration study. These endpoints are those which contribute to symptomatology and the morbidity of Obstructive Sleep Apnea (OSA); therefore these are a critical element in determining a therapeutic CPAP pressure. When these endpoints are reached, intuitively it would imply unimpeded airflow through the upper airways. Despite reaching the conventional endpoints there are a number of patients who do not derive subjective improvement with prescribed CPAP pressures. We know from previous work that limited airflow correlates with residual upper airway resistance in both experimental and human models 1. We also know that optimizing airflow contour during CPAP titration has been validated as a noninvasive surrogate of lowering intrathoracic pressures, as determined by esophageal balloon manometry 1,2. In addition, the lowest esophageal pressures were obtained with titrating CPAP pressures above those which reached the other, more conventional endpoints 2. What is not known is the level of pressure required to normalize airflow, and its relation to the occurrence of conventional endpoints. This study is intended to identify the difference in pressure between achievement of traditional endpoints and normalization of airflow.

**Methods:** We retrospectively reviewed the data from CPAP titration studies performed over a 3 week period. All studies had already been diagnostically reviewed when the retrospective review was done. All data were recorded according to standard lab protocol. Airflow contour was recorded from a pneumotachograph attached to the CPAP mask. The records were reviewed by one reader, unaware of prescribed CPAP pressures, who determined the lowest pressure at which the airflow contour was normalized (if observed). To standardize the methodology, this pressure would normalize airflow for greater than 50% of each 30 second epoch, for greater than 50% of the epochs recorded for that pressure. The epochs during stages W, 3 and 4 sleep were eliminated from consideration. The previously prescribed CPAP pressure was compared to that which normalized airflow.

**Results:** Patient data are shown in Table 1. During the 3 week period there were 16 CPAP titration studies performed. In 10 of these studies airflow was optimized at a tested pressure. In the 6 remaining studies, however, airflow contour was not normalized with any tested pressure. In the normalized airflow group the mean prescribed CPAP pressure was 8 cm H<sub>2</sub>O

(range 5 to 13 cm H<sub>2</sub>O). In all cases the pressure which optimized airflow was at or above the level of pressure prescribed. The mean pressure which normalized airflow was 10.1 cm H<sub>2</sub>O (range 7 to 16 cm H<sub>2</sub>O). The mean difference between the pressure which achieved traditional endpoints and that which normalized airflow was 2.1 cm H<sub>2</sub>O (range 0 to 4 cm H<sub>2</sub>O). In the group in which airflow normalization was not observed the mean prescribed CPAP pressure was 9.3 cm H<sub>2</sub>O (range 6 to 14 cm H<sub>2</sub>O). The mean difference between prescribed pressures and highest tested pressures was 2 cm H<sub>2</sub>O (range 0 to 4 cm H<sub>2</sub>O).

**Table 1**

Patient Data	(N=16, 10 M, 6F)	
	Mean	Range
Age (yrs)	48.8	31 - 72
BMI (kg/m <sup>2</sup> )	33.9	23.3 - 49.4
Epworth score	10.3	0 - 24
AHI	31.8	5.2 - 77.4

**Conclusions:** This small series suggests that optimization of the inspiratory flow contour is an under-appreciated endpoint in both the titration and interpretation of CPAP titration studies. In only 1 of 16 studies was the airflow optimized when respiratory and respiratory-related events were eliminated. The mean pressure to achieve normal airflow was at least 2 cm H<sub>2</sub>O above that which satisfied traditional endpoints. The utilization of airflow as an endpoint has already been validated. Residual airflow resistance exists at the point when traditional endpoints are met, and may contribute to ongoing symptomatology and non-compliance 1,2. We believe that considering optimization of airflow contour in determining CPAP pressure will result in smooth airflow through the upper airway and may possibly increase patient confidence in CPAP therapy and, ultimately, compliance. Whether prescribing CPAP pressure at this typically higher level translates to a demonstrable improvement in compliance and outcome has yet to be studied.

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## 652.J

## EVENT-RELATED POTENTIALS DURING A TEST OF WORKING MEMORY DIFFERENTIATE SLEEP APNEA PATIENTS FROM HEALTHY SUBJECTS

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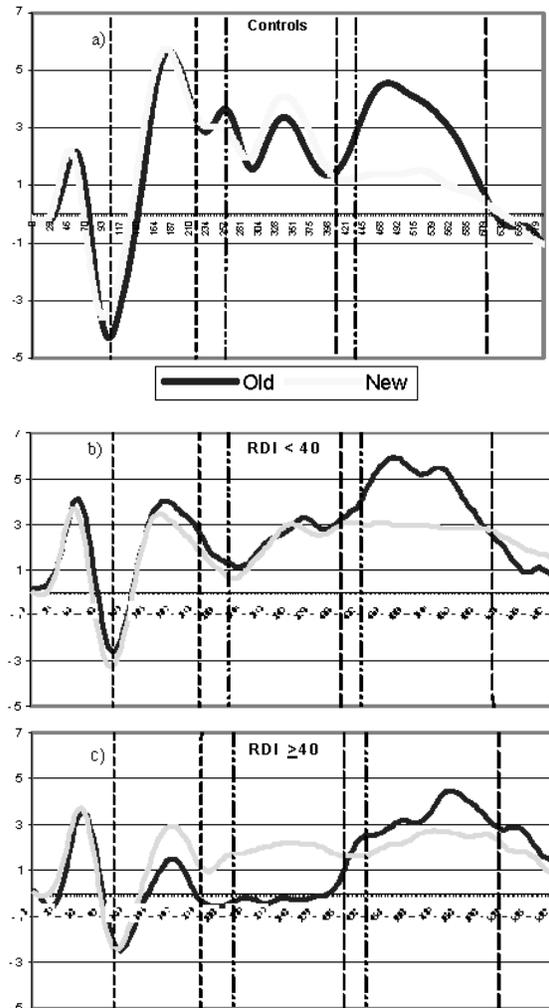
**Introduction:** Event-Related Potentials (ERPs) recorded during cognitive tasks track the neurophysiological correlates of information-processing. Because Sleep Apnea (SA) patients frequently suffer from impaired memory, ERPs were recorded during a test of working memory to determine whether there are differences between SA patients and healthy subjects. The memory task required the temporary maintenance of a group of 20 images in short-term memory storage, serving as a test of working memory. The paradigm offers a method for calculating an ERP-memory effect by sorting the ERPs in response to remembered images (Old) vs. New images.

**Methods:** Twenty-eight healthy subjects (15 males; 13 females; mean age=37, range 23-63) and twenty-seven patients (18 males; 9 females; mean age=43, range 22-65) diagnosed with SA (mean Respiratory Disturbance Index (RDI)=43, range 13-122) performed the working memory task three times between 8:00AM and 12:30PM. For each task, 20 images were presented sequentially twice during the training period ("Old" images) and then randomly interspersed with 80 "New" images presented for 100 ms. with a 2-second inter-stimulus-interval (ISI) between images. Subjects were required to identify each image as Old or New while EEG recordings were acquired from Fz and PO referenced to the left earlobe. Average stimulus-locked ERPs from the correct responses, screened for excessive artifact, smoothed with 20 Hz low-pass filter and detrended for DC/linear offsets, were computed separately for each subject to 1,500 ms post stimulus. The maximum amplitude (MA) and mean positive amplitude (PM) in the ranges 105-220, 260-440, and 410-610 ms were computed. Data were stratified into healthy, Low<40 RDI and High>40 RDI SA patients and the Old vs. New ERPs compared.

**Results:** One-way ANOVA revealed significant between-group differences in overall amplitudes in the P200 region at PO for both Old and New (Old: PM-F=3.702,p=0.031, MA-F=4.258,p=0.019, New: PM-F=4.276,p=0.044, MA-F=5.741,p=0.02) (Figures 1). As expected, the amplitude of the Late Positive (P300/P3b) component (peak at 500ms.) for the Old images was significant larger than the New images for healthy subjects (PM-F=9.112,p=0.004, MA-F=11.618,p=0.001) and SA-Low RDI patients (PM-F=5.211,p=0.03, MA-F=6.562,p=0.016). This memory effect was not significant in the SA-High RDI patients (Figure 2).

Figure 1a, b, c

ERP's from site PO resulting from Old and New stimuli during working memory task for: a) Healthy Controls (n=28), b) SA RDI<40 (n=16) and c) SA RDI>40 (n=11). Vertical lines identify ranges for 105-220, 260-440, and 410-610 ms, conventionally analyzed for P200, P300-a and P300-b components..



**Conclusions:** The late positivity (P300) or "memory effect" was clearly identified in the healthy subjects and Low-RDI patients but not in the High-RDI group. These data confirm previous results in healthy subjects reporting larger P300 for remembered items (1,2) and extend the application of ERPs to assess the neurophysiological correlates of impaired memory performance in SA patients. The functional significance of the group differences in the P-200 and the possibility of group differences in an early P300 (P3a) require further investigation. ERPs can be applied as probes to assess the neural correlates of memory and may have applications in the diagnostic assessment and treatment outcome evaluation of SA and other neurological disorders where memory is impaired.

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**653.J**

**MODAFINIL IMPROVES QUALITY OF LIFE IN OBSTRUCTIVE SLEEP APNEA**

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**Introduction:** Obstructive sleep apnea (OSA) is a common cause of excessive sleepiness, which is associated with decreased quality of life (QoL). Nasal continuous positive airway pressure (nCPAP) effectively treats nighttime respiratory abnormalities and improves QoL. However, some patients experience residual excessive sleepiness and reduced QoL despite regular use of nCPAP. Modafinil (PROVIGIL), a novel wake-promoting agent, improves health-related QoL in patients with narcolepsy.<sup>1</sup> Furthermore, in a 4-week, double-blind, placebo-controlled study, modafinil improved disease-specific QoL in nCPAP-treated patients with OSA experiencing residual sleepiness.<sup>2</sup> The present 12-week, double-blind, placebo-controlled study evaluated QoL when modafinil was used to augment nCPAP therapy in patients with OSA with residual sleepiness.

**Methods:** Patients with OSA and residual excessive sleepiness (Epworth Sleepiness Scale score ≥10 at screening) and who were using a regular nCPAP regimen with effectiveness during use entered a 12-week, randomized, double-blind, placebo-controlled, parallel-group study. Exclusion criteria included indicators of severe OSA, clinically significant uncontrolled illness, or use of sedating medications. During the 12-week treatment period, patients received placebo or modafinil 200 mg or 400 mg once daily. The dose of modafinil was titrated as follows: the 200 mg/d group received 100 mg/d on days 1 and 2 and 200 mg/d thereafter; the 400 mg/d group received 100 mg/d on days 1 and 2, 200 mg/d on days 3 and 4, 300 mg/d on days 5 and 6, and 400 mg/d thereafter. Functional status and QoL were assessed using the 30-item Functional Outcomes of Sleep Questionnaire (FOSQ) and the 36-item Short Form Health Survey (SF-36) at baseline and weeks 4, 8, and 12 of treatment. Adverse events were recorded.

**Results:** 327 patients (mean age 49 years; mean body-mass index 36.2) were randomized; 323 received treatment (n=109, modafinil 200 mg/d; n=106, modafinil 400 mg/d; n=108, placebo). Significant improvements in wakefulness with modafinil treatment are reported elsewhere. The mean change from baseline in FOSQ total score indicated significantly improved (p<0.001) QoL at week 12 of treatment with modafinil (Table 1). At week 12, significant improvements were demonstrated in the FOSQ domain scores for vigilance (p=0.0005 for mean change from baseline versus placebo),

general productivity (p=0.0008), activity level (p<0.03), and intimacy (p<0.03) in patients receiving modafinil. Analogous results were found for SF-36 domain scores for vitality (p<0.0001 for mean change from baseline versus placebo), general health (p<0.03), and physical composite index (p=0.005). Changes in the other domain scores of the FOSQ and SF-36 did not reach statistical significance. The most common adverse events were headache (modafinil 26%; placebo 12%), nausea (modafinil 11%; placebo 2%), and anxiety (modafinil 8%; placebo 2%).

**Table 1**

Mean FOSQ scores at baseline and week 12						
FOSQ	Placebo		Modafinil 200 mg		Modafinil 400 mg	
	Wk 0	Wk 12	Wk 0	Wk 12	Wk 0	Wk 12
Total score*	15.2	16.0	14.5	16.4	14.0	16.1
Vigilance*	2.7	2.9	2.7	3.1	2.6	3.1
Productivity*	3.3	3.4	3.1	3.4	3.0	3.4
Activity†	2.9	3.1	2.7	3.1	2.6	3.0
Social	3.2	3.4	3.0	3.4	3.0	3.3
Intimacy†	3.1	3.3	2.9	3.3	2.8	3.3

\* p≤0.001; † p<0.03 for mean change from baseline, modafinil versus placebo

**Conclusions:** Modafinil significantly improves QoL when used to augment nCPAP therapy in patients with OSA who experience residual sleepiness.

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**654.J**

**THE IMPLEMENTATION OF CPAP THERAPY: AN AREA IN NEED OF IMPROVED SERVICE DELIVERY**

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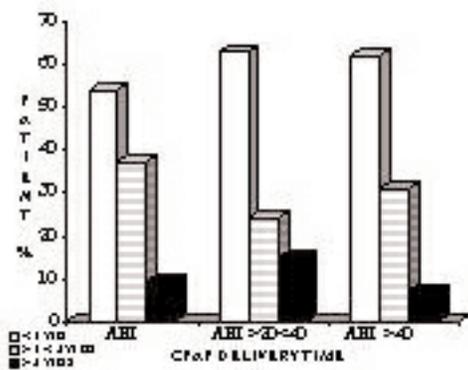
**Introduction:** CPAP has become one of the main treatments available to patients with Obstructive Sleep Apnea (OSA). While significant efforts have been made to educate patients concerning the importance of treatment adherence, little research has been done to assess the patient's awareness of the equipment they are prescribed, or to identify other variables, outside of the physician's influence, related to their satisfaction with the services they receive, that might directly impact the patient's will to comply with this lifelong treatment. In particular, the process involved in the implementation of CPAP therapy, following the point at which the physician writes the prescription, to the time at which the patient receives their equipment, has rarely been studied. The purpose of this study

was to characterize the process of CPAP implementation (and the patient's awareness of their equipment) among consecutive OSA patients.

**Methods:** Participants were asked to complete a survey questionnaire one month after their CPAP titration study. Patients were asked to identify their Durable Medical Equipment (DME) provider, the equipment's delivery timeframe, and whether the equipment was delivered to their home or if they were required to pick the equipment up from their provider. In addition, patients were asked to identify the brand of CPAP and airway interface they received. There were 173 consecutive patients who filled out the surveys. Of this, 138 (107 male, 31 female) were identifiable by name and were found to be representative of OSA populations with an average age of  $52 \pm 14$  and apnea/hypopnea index (AHI) of  $54 \pm 39$ . There were no significant differences in any of the variables studied between those who identified their names on the survey and those who chose to remain anonymous.

**Results:** Ninety five percent of patients were able to identify their DME provider. Six DME providers serviced 85% of the patients and 10% were serviced by a variety of other providers. While 43% received their equipment within 4 days, a significant proportion saw the delivery of the equipment delayed by more than one week (39%). Importantly, the severity of the patient's condition was not related to delivery time, as 38% of patients with severe AHI ( $> 40$ ) experienced a delay in the delivery of therapy by more than one week. Also relevant to a large metropolitan area, with limited public transportation, is the fact that the majority of patients reported picking up the equipment (54%) from the DME vendor instead of it being delivered to their home. More patients reported using a mask than nasal pillows (62% vs 38%). Regardless of the type of interface, only 16% knew the specific model they were using. Furthermore, only 34% were able to identify the CPAP model that was delivered to them.

Figure 1



**Conclusions:** The results of this study indicate that patients acquire only limited knowledge about CPAP equipment during the first month of treatment. From a clinical perspective, this study did not identify long-term consequences secondary to the delay in the implementation of treatment. However, this delay (in some cases by several weeks) resulted in the unnecessary exposure to the risks associated with untreated OSA. There seems to be an opportunity for physicians, DME

providers and medical insurance programs to improve the process of CPAP implementation, especially among those patients with severe OSA.

655.J

EVENT-RELATED POTENTIALS DURING A PSYCHOMOTOR VIGILANCE TASK IN SLEEP APNEA PATIENTS AND HEALTHY SUBJECTS

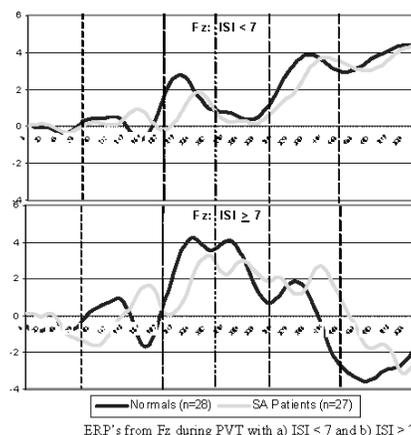
Levendowski DJ,<sup>1</sup> Westbrook P,<sup>1</sup> Berka C,<sup>1</sup> Popovic MV,<sup>1</sup> Ensign WY,<sup>2</sup> Pineda JA,<sup>3</sup> Zavora T,<sup>4</sup> Lumicao MN,<sup>1</sup> Zivkovic VT<sup>1</sup>

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**Introduction:** Event-Related Potentials (ERPs) recorded during cognitive tasks track the neurophysiological correlates of information-processing. Because Sleep Apnea (SA) patients exhibit excessive daytime drowsiness and impaired vigilance, ERPs were obtained during a Psychomotor Vigilance Task (PVT) to identify differences between SA patients and healthy subjects.

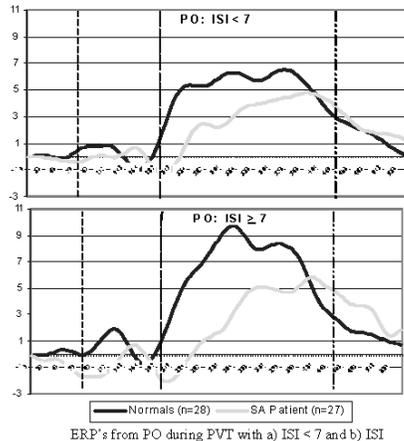
**Methods:** Twenty-eight healthy subjects (15 males; 13 females; mean age = 37, range 23-63) and twenty-seven patients (18 males; 9 females; mean age=43, range 22-65) diagnosed with SA (mean RDI=43, range 13-122) completed the ERP study between 8:00AM and 12:30PM. Visual ERPs were recorded from Fz and PO referenced to the left ear during a PVT. Subjects were required to respond to Primary and Secondary PVT stimuli presented for 200 ms at an 80:20 ratio with inter-stimulus-intervals (ISI) ranging from 1.5 to 10 seconds. Average, stimulus-locked ERPs from the correct responses, screened for excessive artifact, smoothed (20-Hz low-pass filter) and detrended for DC/linear offsets, were computed separately for each subject to 1,500 ms post-stimulus. To quantify the ERP components of interest, the maximum amplitude (MA), corresponding latency (LT), and mean positive amplitude (PM) in the ranges (identified in Figure 1 with vertical lines) 80-200(N1P2), 200-275(P3a), 200-475(Late Positivity), and 350-475(P3b) ms were computed for normals and SA patients and stratified by ISI into Fast-ISI (<7-secs) and Slow-ISI (>7-secs) groups.

Figure 1



**Results:** 2(group) X 2(ISI) ANOVAs were conducted for all of the variables at Fz and PO. As expected, when compared to healthy subjects, the SA patients evidenced much longer latencies for all components at Fz and PO for both Fast- and Slow- ISI ERPs(all  $p < 0.05$ )(Figures 1,2). As predicted, larger amplitude ERPs for stimuli preceded by longer ISIs were observed for N1P2 and the Late Positivity at Fz and PO(all  $p < 0.05$ )(Figures 1,2). Surprisingly, there were no significant interactions between group and ISI in any of the amplitude measures.

**Figure 2**



**Conclusions:** These data confirm previous reports of longer latency P300s for ERPs recorded from SA patients during an “oddball” paradigm (1,2). P300 amplitude reflects the degree or quality with which information is processed and P300 latency is a measure of stimulus classification speed—an index of the processing time required prior to response generation. Longer latencies were observed for all of the ERP components in the SA patients, suggesting an overall delay in speed of stimulus processing. As expected, stimuli preceded by longer ISIs elicited larger amplitude ERPs for all subjects, but no difference was observed between SA patients and controls. Delayed P300s have been related to the decline in cognitive abilities in dementing illnesses (3) and may be a result of chronic hypoxemia or excessive drowsiness in SA patients. Additional research is required to determine the functional significance of these results.

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**656.J**

**SEVERE SLEEP-DISORDERED BREATHING IS NOT ASSOCIATED WITH SCREENING FOR DEMENTIA IN ELDERLY JAPANESE-AMERICAN MEN**

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**Introduction:** Sleep disordered breathing (SDB) has been linked to neuropsychological deficits in epidemiological studies of primarily middle-aged adults<sup>1</sup>. However, its association with performance on screening instruments for dementia in elderly adults has not been studied<sup>2</sup>. The Cognitive Abilities Screening Instrument (CASI) was developed as a cross-cultural screening tool for dementia in elderly persons of Japanese ancestry. We studied the association between severe SDB and CASI performance among elderly Japanese-American men participating in the in the Honolulu-Asia Aging Study (HAAS) of dementia<sup>3</sup>.

**Methods:** The HAAS began in 1991-1993 as part of the 4th examination of 3,734 men participating in the Honolulu Heart Program, a study of cardiovascular disease that began in 1965. A total of 1,523 men aged 79 to 100 years of age participated in the 7th HHP examination in 1999-2000 (89% participation rate) and 718 (range 79 to 97 years of age) agreed to undergo in-home sleep monitoring (47% of the participants). Sleep monitoring was based on the Sleep Heart Health Study protocol and subsequent scoring was performed at its reading center. Measurements from nasal thermistry, chest wall impedance, and finger pulse oximetry were used to create an Apnea Hyponea Index (AHI) of events per hour. Persons with an AHI of 30 or higher were classified as having severe sleep disordered breathing versus those with mild to moderate (5<AHI<30) or no (AHI<5) SDB. The CASI score ranges from 0 to 100.0 (worst to best) and CASI<74 is considered a poor score and CASI<70 is used to refer participants for further neurological evaluation for presence of dementia.

**Results:** Severe SDB was present among 19% of the participants and only 28% of these very old men had no SDB. Among the persons undergoing sleep monitoring, 14% had poor performance on the CASI(<74), 4% were referred for neurological evaluation (CASI<70), and few (<1%) had been previously diagnosed with dementia. Those with severe SDB were not at increased risk of poor performance on the CASI (Odds ratio[OR]=1.48, 95% CI=0.89-2.45) compared to those with less severe or no SDB. Similarly, severe SDB did not significantly increase the risk for being referred for further neurological evaluation (OR=1.37, 95%CI=0.66-2.86). In contrast, among the 805 men who refused overnight sleep monitoring, significantly higher proportions had poor performance on the CASI (39%), were referred for neurological examination (31%), and had a history of a clinical diagnosis of dementia (20%).

**Conclusions:** SDB is common among elderly non-demented men. A high refusal rate (>50%) for sleep monitoring resulted in a bias toward higher cognitive functioning men who may have sufficient cognitive reserve to perform well on a screening test for dementia even in the presence of severe SDB.

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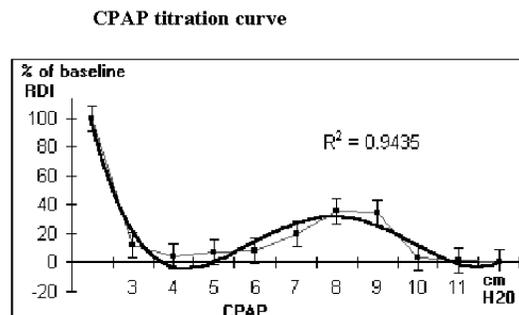
**657.J****BIPHASIC TREND IN RESPIRATORY DISTURBANCE INDEX DURING NASAL CPAP TITRATION: POSSIBLE MECHANISMS AND CLINICAL APPLICATION OF TITRATION CURVES**Peimer SI,<sup>1</sup> Kordana S,<sup>1</sup> Yefremov E,<sup>1</sup> Ringler JI

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**Introduction:** Nasal CPAP requires careful adjustment in order to determine therapeutic pressure Pt, a process known as titration. CPAP is thought to act as a pneumatic splint of the upper airway. Pt occurs when a critical increase in upper airway pressure prevents collapse and stabilizes breathing (1). The dynamics of CPAP titration are not understood. This study evaluates the relationship between increasing CPAP and reduction of RDI in patients with OSAS in whom Pt could be easily defined by absence of respiratory arousals.

**Methods:** A retrospective analysis of fourteen consecutive polysomnograms with CPAP titration in 1-cm increments. After standard scoring each value of CPAP was plotted against the percentage reduction of RDI from baseline. The CPAP Titration Curves (T-Curve) were averaged for entire group using polynomial trendlines

**Results:** Figure 1 represents the trend of T-Curves from 3 cm to 12 cm H<sub>2</sub>O and percentage reduction of RDI from the baseline (34.29±9.91/hour of sleep) to zero point. As shown, the RDI abruptly decreases at the beginning of titration (R<sup>2</sup> 0.89, P<0.01). The proportion of RDI remains low between 3 and 6 cm H<sub>2</sub>O. Further titration led to secondary increase in RDI percentage followed by secondary decline. The average Pt was between 10 cm and 11 cm. The biphasic response to CPAP remains incompletely explained. Possibly, reinitiating of sleep after CPAP application is associated with a transiently lower RDI. However for most patients, the RDI was lower at any given time after "lights out" for the CPAP titration as opposed to untreated sleep. REM rebound and increase in leaks might explain the second peak in RDI, but the more unexpected finding was the early drop. Another intriguing possibility is that a CPAP effect other than simple pneumatic splinting reduced respiratory events at low pressures. Upper airway flow receptors might increase upper airway tone in response to "subtherapeutic" pressures. Alternatively, increased expiratory load might stimulate upper airway dilators. Both mechanisms have been reported to reduce dyspnea in COPD patients (3). Clinically significant reduction of RDI may occur before critical airway opening pressure is achieved and the airway is fully splinted (2).

**Figure 1**

**Conclusions:** Our results demonstrate a biphasic trend in RDI during CPAP titration. Analysis of T-Curves may provide insight into upper airway pathophysiology in OSAS. The method may provide a practical way of facilitating determination of Pt, perhaps minimizing titration error.

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**658.J****NOCTURNAL HOME PULSE OXIMETRY TO DIAGNOSE PEDIATRIC OBSTRUCTIVE SLEEP APNEA (OSA)**Nixon GM,<sup>1</sup> McGregor CD,<sup>1</sup> Brouillette RT<sup>1</sup>

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**Introduction:** In our recent evaluation of pulse oximetry performed during polysomnography (PSG) we established oximetry criteria that have a high positive predictive value for OSA [1]. The current study evaluates these criteria in a consecutive series of nocturnal pulse oximetry performed in a home setting.

**Methods:** We reviewed sleep laboratory records of pulse oximetry performed at home from January 1st to November 18th, 2001 to evaluate children with suspected OSA. Sleep laboratory technicians selected suitable candidates for home oximetry on the basis of history. Parents picked up a pulse oximeter from the laboratory, placed it on their child before bedtime, and returned the oximeter the next day. A positive test result was evaluated from the Nellcor N-200 oximeter trend and event graphs, using the previously described criteria: >3 clusters of desaturations and >3 desaturations to <90%. Patients with negative or inconclusive oximetry were usually further evaluated with PSG.

**Results:** Nocturnal pulse oximetry was successful on the first

attempt in 77 of 83 (93%). Six children (7%) had unsuccessful studies due to early removal of the oximeter, leading to insufficient recording time. 20 of 83 (24%) patients had a positive pulse oximetry test and were referred directly for adenotonsillectomy. Oximetry was inconclusive due to movement artifact in 21/83 (25%), and failed to meet the criteria for a positive test in 13/83 (16%). Of these 63 negative/inconclusive tests, 46 (73%) were scheduled for PSG and 29 (46%) had had PSG at the time of abstract submission. 25 of these 29 PSGs (86%) were diagnostic of OSA, with a mean (SD) AHI of 4.5 (5.6) events/hour, a mean (SD) desaturation index of 7.3/hour (3.6) and an average (SD) saturation nadir of 90.1% (6.2). At the time of abstract presentation, symptomatic improvement based on parental assessment will be reported.

**Conclusions:** Non-attended home nocturnal pulse oximetry in children can be accomplished by parents with a high success rate. For 24% of children so evaluated, a positive pulse oximetry test eliminated the need for PSG with its attendant cost, waiting time and inconvenience. However, negative and inconclusive oximetries do not rule out OSA. A previous paper from our laboratory suggests that use of a short-averaging time/ motion resistant oximeter such as the Masimo Radical could further improve the reliability and usefulness of overnight pulse oximetry for evaluation of pediatric sleep disordered breathing [2].

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**659.J**

**IMPROVING DETECTION OF OXYGEN DESATURATION EVENTS WITH REFLECTANCE OXIMETRY**

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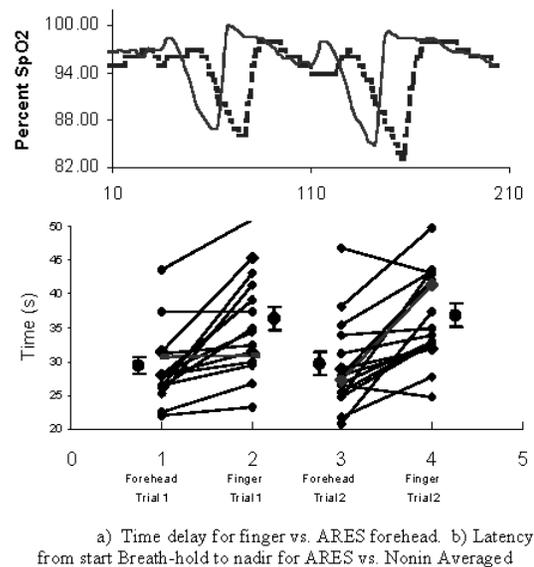
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**Introduction:** The identification of subtle upper airway obstructions can be improved with more accurate pulse oximetry. The lapse in time for detection of respiratory events using pulse oximetry can be reduced with the selection of the sensor site (1) and methods used to smooth the data (2). This investigation compared the Apnea Risk Evaluation System device (ARES), with forehead reflectance oximetry attached to the patient without wires, to the Nonin OEM oximeter (Nonin), to confirm the accuracy of ARES reflectance oximetry across individuals including a broad spectrum of skin-pigmentation (3).

**Methods:** Eighteen healthy adult volunteers (13 males, 5 females), with six darkly pigmented individuals, participated in multiple trials of 20-second breath-holds at residual volume while lying supine. Nonin-800R reflectance-sensors were placed on the foreheads over the super-orbital arteries. During

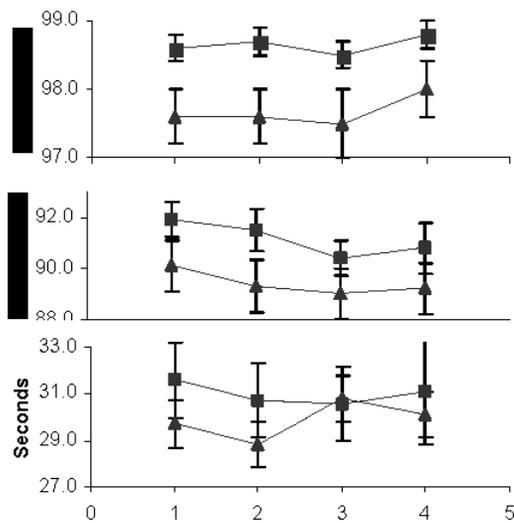
the first trial, two breath-holds were conducted with the reflectance-sensors inputted to the ARES and Nonin. The sensor inputs were reversed for the second trial. In the third trial, a transmittance sensor attached to the finger was inputted to the Nonin. Outputs were acquired simultaneously from both systems. A total of 32 finger-vs-forehead and 64 forehead-vs-forehead breath-holds were analyzed off-line to compute the SpO<sub>2</sub> at baseline (average 5-secs prior to breath-hold) and nadir, and the nadir latency. Nonin variables were derived using their proprietary averaging procedure. The ARES utilized median filtering of the red and Infra-red signals and a five-beat moving average.

**Figure 1**



a) Time delay for finger vs. ARES forehead. b) Latency from start Breath-hold to nadir for ARES vs. Nonin Averaged

**Figure 2**



SpO<sub>2</sub> from Ares ▲ vs. Nonin ■ during 4 breathholds at a) Baseline and b) Nadir, and c) latency to baseline (secs).

**Results:** For each breath hold SpO2 recording, we extracted baseline saturation (BS) defined as the 5 second average before the beginning of the breath hold, minimal desaturation (D) due to the breath hold and desaturation latency (TD). Comparison of the finger and forehead based measurements (RM ANOVA) showed that the forehead measurements produced significantly faster response to breath holding (29.1±1.3 s vs. 36.1±1.4 s, mean ± SE, p < 0.001, Figure 1). When both devices were applied to the forehead, the BS, D, and TD were significantly lower (RM ANOVA: p=0.001, p=0.001, p=0.012) in Ares compared to Nonin, but the effects of the breath holds were consistent for both devices (no significant interactions) (Figure 2).

**Conclusions:** Our results demonstrate that forehead reflectance oximetry permits faster identification of the desaturation events resulting from prolonged breath holds. The results obtained with the Ares oximeter and the Nonin OEM device showed comparable reliability and were not affected by the skin pigmentation. One of the limitations of the reflectance oximetry is sensitivity to sensor pressure, but our findings show that these effects are similar in darkly and lightly pigmented subjects.

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**660.J**

**OUTCOMES OF ESS-MEASURED SLEEPINESS IN TWO BMI PATIENT POPULATION TREATED WITH ORAL APPLIANCE**

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**Introduction:** The use of removable intraoral appliances is a treatment alternative for OSAHS. The authors report the evaluation of daytime sleepiness measure by Epworth Sleepiness Scale (ESS) in 330 OSAHS subjects treated with Mandibular-Lingual Repositioning Device - MLRD in two distinct BMI patient populations.

**Methods:** 330 patients (256M/74F), age: avg=46 (28-65/sd=8.18), RDI: avg=38.98 (10.2-103.1/sd=22.43), SatO2min.: avg=80.22% (49%-98%/sd=11.23). Two BMI groups were created. Group 1 (n=68): BMI=20.13 to 25.00 (avg=23.46), normal group. Group 2 (n=262): BMI=25.02 to 43.25 (avg=29.45). ESS was applied before and two months after treatment.

**Results:** See table.

**Table 1**

	Group 1 (20<BMI<25)		Group 2 (BMI>25)	
	ESS1	ESS2	ESS1	ESS2
<b>AVG</b>	12.53	5.69	13.60	5.90
<b>SD</b>	4.70	1.90	5.55	2.38
<b>Improvement:</b>		55%		57%

**Conclusions:** The mean ESS scores for all 330 patients from groups I and II before and 60 days after MLRD-treatment was statistically significant. The reduction of the ESS scores suggests a RDI-induced reduction in the number of arousals during sleep. However, both BMI patient populations displayed an equally significant ESS reduction despite different BMI. The reduction of the ESS scores induced by the MLRD arousal reduction. The subjective daytime sleepiness improvement induced by the oral appliance (MLRD) is generated by a probable reduction in the RDI independently of the BMI.

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**661.J**

**PROSPECTIVE TRIAL OF THE TAP ORAL APPLIANCE (FORMERLY KNOWN AS THE NELLCOR PURITAN BENNET, QUIETKNIGHT APPLIANCE) IN THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA AND SNORING**

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**Introduction:** Supporting evidence for the efficacy of oral appliances in the management of sleep disordered breathing is growing rapidly. There are few studies evaluating the characteristics of large population groups over extended periods. The TAP appliance has undergone multiple design changes and modifications since its development. This study aimed to assess the efficacy of a custom fitted modification of the TAP (the QuietKnight oral appliance) using a bilaminar material, in a large unselected cohort of patients over a two year period, evaluating sleep parameters, demographics, anatomical variations, and both objective results and subjective reports.

**Methods:** 134 consecutive, unselected patients, with varying degrees of obstructive sleep apnea and snoring referred by twelve respiratory sleep physicians, were evaluated over a two year period. Initial data included a PSG study, a cephalometric radiograph, BMI, and ESS Score. Efficacy was assessed by changes in AHI, SaO2, ESS changes, and subjective patient and partner reports. A custom made laboratory fabricated version of the QuietKnight appliance was fitted, with instructions to the patient for gradual advancement up to a maximum pro-

trusive position subject to patient comfort.

**Results:**

14 patients were lost to follow up  
20 had incomplete data  
100 patients had complete data  
Baseline data  
Age: 47±3 years (30-73 years)  
Sex: male 67 patients (67%)  
Female 33 patients (33%)  
BMI 31±8 Kg/m<sup>2</sup> (29-43), ESS mean 11±4  
AHI 39 ± 3/hr, minimum mean SaO<sub>2</sub> 86 ± 2%  
Assessment of efficacy  
Mean reduction of AHI - 30 ± 3/hr (39 ± 3/hr reduced to 9 ± 3/hr) (P < 0.001)  
Mean minimum SaO<sub>2</sub> increase - 8 ± 2% (86 ± 2% increased to 94 ± 2%) (P < 0.001)  
ESS reduction 4 ± 1 (11 ± 4 reduced to 7 ± 3)  
Snoring intensity - moderate to major reduction in 83% of patients.  
Snoring frequency - moderate to major reduction in 80% of patients.  
Fatigue/hypersomnolence - moderate to major improvement in 80%  
Patient satisfaction - 92% were satisfied or very satisfied and continued use of appliance  
Side effects - Common, but minor, mainly initial, tooth, jaw or muscle discomfort on waking, excess salivation, minor bite changes.

**Conclusions:** The modified custom fitted TAP appliance was highly effective in managing obstructive sleep apnea and snoring over a two year period in a varied group of unselected patients. Randomized placebo controlled trials in selected groups of patients are necessary to further define the utility of the TAP appliance.

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**662.J**

**EFFECT OF TONSILLECTOMY AND ADENOIDECTOMY ON THE SLEEP ARCHITECTURE OF CHILDREN WITH OSAS**

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**Introduction:** We had previously evaluated the sleep architecture of 83 children with OSAS and found that TST, SE% and REM% were decreased. We wanted to further assess whether the successful treatment of the OSAS with a tonsillectomy /adenoidectomy (T&A) would result in normalization of the sleep architecture in these children.

**Methods:** Our sample included 10 children that had been diagnosed with OSAS at our center between 1/97 and 11/00, and who underwent a T&A as treatment of their OSAS. Although these subjects came from a pool of 83 children with OSAS, only 10 patients returned for a repeat NPSG post-operatively to re-assess the status of their OSAS following surgical treatment. The ages of the children ranged from 2 to 17 years. Median age was 4. Average age was 6.6. There were 6 boys and 4 girls. OSAS criteria was defined as RDI=>1/hour. The RDI included both apneas and hypopneas that were associated with 4% or greater arterial oxygen desaturations and disturbed respiratory events which appeared to be apneas/hypopneas but were not associated with a 4% or greater arterial oxygen desaturation. All disturbed respiratory events were of at least two

respiratory cycles in duration. Disturbed respiratory events were counted even if they were not associated with an arousal. In these 10 cases, baseline diagnostic NPSG sleep architecture findings and respiratory data were compared to the post-T&A sleep study which was done at least 2 months post-operatively.

**Results:** Although they did not reach statistical significance, all of the respiratory parameters including the AHI, RDI, baseline arterial oxygen saturation, average minimum and minimum arterial oxygen saturation showed improvement on the post T&A sleep studies supporting the fact that the subjects' OSAS had been successfully treated. Although the sleep architecture parameters also improved, the TST, SE%, and REM% changes did not reach statistical significance. Baseline NPSG TST=379.8 (±82.1); SE%=85.2 (±8.6); REM%=14.6 (±9.8). Post T&A NPSG TST=385.2 (±47.4); SE%=89.0 (±8.9); REM%=13.2 (±8.6).

**Conclusions:** In our small sample of 10 children who underwent successful surgical treatment of their OSAS, their sleep architecture showed slight improvement (ie. SE% increased and TST increased), however, these findings did not reach statistical significance. Although a larger sample is required to confirm the current findings, this study suggests that underlying sleep architecture changes due to OSAS may not completely return to baseline despite the OSAS being successfully treated.

**663.J**

**SERIAL ASSESSMENT OF SYMPTOMS OF SLEEP-DISORDERED BREATHING IN PREGNANT WOMEN USING THE MULTIVARIABLE APNEA PREDICTION INDEX**

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**Introduction:** During pregnancy, physiologic and biochemical changes occur that can foster the development of sleep-disordered breathing (SDB). High estrogen levels promote hyperemia and edema of the pharyngeal mucosa, which may lead to airway narrowing. Uterine enlargement and fetal development elevate the diaphragm, changing the shape of the thorax and producing declines in expiratory reserve volume and residual volume. These changes can place pregnant women at increased risk for hypoxemia and SDB. In a cross-sectional study of SDB symptoms in women during the second or third trimesters, 14% of women reported frequent snoring, significantly more than non-pregnant controls. Another study in which subjects completed questionnaires retrospectively assessing their snoring history found that a significant proportion developed habitual snoring by the week of delivery. Most subjects reported that snoring began or markedly increased during the third trimester. We decided to perform a prospective study to determine whether incident symptoms of SDB are

likely to occur in pregnancy and to describe the time course of these symptoms.

**Methods:** We recruited 81 women presenting to our institution for prenatal care, whose pregnancy was less than 14 gestational weeks (i.e., first trimester), estimated by the last menstrual period. We used the Apnea Index (Index I) from the Multi-variable Apnea Prediction (MAP) Index, a previously validated risk index for assessing apnea symptom frequency. Subjects completed the questionnaire at study entry and at 28-29 and 34-35 weeks of pregnancy. The questionnaire was also administered within 48 hours after delivery; subjects were asked to recall SDB symptoms in the prior month. Index I scores from the time points in late pregnancy and post-delivery were compared to first trimester Index I scores using unpaired t-tests.

**Table 1**

	No. Subjects (%)	MAP Index I Score (SD)	p-value
First Trimester	80 (100)	0.402 (0.652)	
28-29 Wks Gestation	62 (77.5)	0.618 (0.896)	0.06
34-35 Wks Gestation	39 (48.8)	0.919 (0.957)	< 0.001
Post-Delivery	16 (20.0)	0.813 (1.00)	0.03

**Results:** Results are summarized in Table 1. The mean age of these subjects was 22.92±5.05 years. Mean BMI at study entry was 28.57±8.12. The first trimester mean MAP Index I score (SD) was 0.402 (0.652). Sixty-two subjects completed the MAP at 28-29 weeks of pregnancy, with a mean Index I score of 0.618 (0.896), higher than the first trimester Index I, but not reaching statistical significance (p=0.06). Thirty-nine subjects have completed the MAP Index at 34-35 gestational weeks. Their mean Index I score was 0.919 (0.957), significantly higher than the first trimester Index I score. Finally, 16 subjects have delivered and completed a final MAP questionnaire. These subjects had a mean Index I score of 0.813 (1.00), also significantly higher than the first trimester scores.

**Conclusions:** This study demonstrates that symptoms of sleep-disordered breathing are significantly more common with advancing pregnancy. MAP Index I score is increased early in the third trimester (28-29 gestational weeks) compared to first trimester values. Symptoms of SDB continue to develop during the third trimester, with a significant increase in MAP Index I score by 34-35 weeks which appears to be sustained through delivery. Further investigations may demonstrate whether clinical characteristics such as obesity, gestational weight gain or parity may influence the development of these symptoms, and whether the development of symptoms of SDB may impact negatively on maternal/fetal outcomes.

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**664.J**

**PLACEBO CONTROLLED HYPOTENSIVE EFFECT OF CPAP IN YOUNG MEN WITH ESSENTIAL HYPERTENSION**

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**Introduction:** This is continuation of our study which showed that young men with essential arterial HTN had statistically higher RDI compared with contr. To check hypothesis that subclinical and mild forms of OSA could be the trigger factor for development of essential arterial HTN trial of CPAP therapy compared with placebo (open mask) was done.

**Methods:** 24 young men with essential arterial HTN of first stage were divided equally into 2 groups for CPAP therapy and placebo. CPAP therapy after CPAP titration in main group and placebo CPAP therapy (open mask) in control group was done for one week. BP monitoring was done for 24 hours before and after treatment by wearing BP monitor BR-102 (Shiller, Swiss). Mean systolic, mean diastolic, maximal BP were calculated for wake and sleep. % of BP > 135/85mm Hg during wake and >120/75 during sleep were calculated.

**Table 1**

		CPAP		P	
		Before	After		
W	BPs	Mean	137.6± 7	129.7±10.4	0.017
		Max	164.4±16.3	157.3±9.9	0.18
		>135(%)	53.8± 23.8	34.2±24.0	0.004
k	BP	Mean	90.9± 6.3	84.9±7.2	0.027
		Max	116.3±9.1	105.4±7.5	0.009
		>85(%)	69.9 ± 22.1	48.5±25.0	0.006
S	BPs	Mean	120.9±10.3	113.9±8.2	0.024
		Max	138.7±12.7	135.6±12.6	0.609
		>120(%)	48.2 ± 39.2	25.2±16.9	0.001
e	BP	Mean	77.0 ± 8.8	72.1±7.2	0.095
		Max	138.7±12.7	135.6±12.6	0.609
		>75(%)	48.19±31.7	32.9±24.9	0.002

**Results:** Main and control groups consisted of 12 patients and were comparable by age (18.3±2.4, 18.5±1.9, p=0.775), BMI (26.3±3.4, 25.6±3.4, p=0.651), smoking (50±0.5, 50±0.5, p=0.731), RDI (6.4±5.6, 7.9±6.4, p=0.639), mean longevity of obstructive events (13.8±1.9, 15.2±1.5, p=0.893), maximal O2 desaturation % (2.7±2.2, 3±2.3, p=0.644), TI/TT (0.423±0.03, 0.417±0.03, p=0.707), mean oxygen level at night (96.5±0.8, 96.8±0.7, p=0.337) Results of BP monitoring before and after treatment presented on Table 1 and 2. No differences between groups before therapy and no changes in Placebo group after

therapy (table 2). CPAP pressure in main group was from 3-10mm H2O (4.9±1.5) and mean time of using CPAP therapy 6.2±1.7h. Statistically significant decreasing of BP was found in CPAP group after therapy comparing with this group before therapy (table 1). Individual analyses in main group showed that 8 young men had decreased most BP indexes, 3 patients had full normalization of BP indexes of HTN. These changes have been found not only during sleep but also during wake.

Table 2

			PLACEBO		P
			Before	After	
W a k e	BP s	Mean	138.9±9.4	138.9±9.1	1.0
		Max	163.0±9.6	163.1±10.4	0.983
		>135(%)	59.9±23.6	59.3±26.4	0.956
S l e e p	BP d	Mean	87.0±7.9	87.4±10.2	0.926
		Max	111.7±7.0	109.9±11.9	0.666
		>85(%)	58.1±33.8	56.1±31.4	0.885
S l e e p	BP s	Mean	124.6±8.5	123.18±8.8	0.697
		Max	147.2±17.3	144.5±17.4	0.716
		>120(%)	57.6±23.5	52.5±22.8	0.663
P e r i o d	BP d	Mean	78.8±7.5	75.9±9.5	0.435
		Max	147.2±17.3	144.5±17.4	0.716
		>75(%)	57.56±34	62.3±27.7	0.796

**Conclusions:** Short treatment with CPAP compared to placebo statistically significantly decreased BP in main group compared with placebo group. This confirmed the importance of mild obstructive sleep disorders in triggering arterial HTN. These changes were seen not only during sleep but also wake periods. Very important that in some patients, it was found practically full normalization of results of BP monitoring. We think that our positive results of CPAP therapy on BP monitoring is related to reversibility of early stage of arterial HTN in young men with essential HTN.

665.J

UPPER AIRWAY OBSTRUCTION DURING SLEEP IN YOUNG NON-OBESE MALES WITH ESSENTIAL ARTERIAL HYPERTENSION

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**Introduction:** Possible relationship of obstructive sleep apnea (OSA) and arterial hypertension (HTN) is actively discussing in literature(1). Interrelation OSA and HTN could be more clear and mostly important in the debut of HTN

**Methods:** 45 young men with BP >140/90 at least 3 times during the last year had been evaluated in the hospital after sequential referrals from military service medical commissions. Patients underwent physical exams, retinal evaluations,

ECG, stress tests, EchoCG, kidney ultrasound, quantitative UA, nuclear kidney scan, consulted by neurologist and endocrinologist. After exclusion of patients with kidney, endocrine and neurological disorders the main group consisted of 34 patients (mean age 18.7±3.1) with first stage of HTN. To exclude effect of obesity, 11 patients with BMI <23 kg/m<sup>2</sup> (mean 21±0.7 kg/m<sup>2</sup>) have been separated to a subgroup. In this subgroup, mean BMI was 21±0.7 kg/m<sup>2</sup>, age 18.7±0.7. 12 healthy young men of the same age (18±2.3) with normal BP made control group. Assessment of respiration during sleep was done by RIP with computation of RDI (respiratory disturbances index), times parameters of respiratory cycle, indexes of thoraco-abdominal coordination, flow volume loop parameters. BP and HR has been monitored for 24 hours. Analysis of BP and spectral analysis of HR was done for periods of sleep and wake.

Table 1

	MAIN GROUP	SUB-GROUP w/BMI<25	CONTROL LS	P1	P2
RDI	5.9±5	5.8±5.4	1.9±1.7	0.001	0.027
ADRE	14.5±2.4	15.5±2.3	10.1±6.8	0.02	0.022
ΔSO2 %	3.5±3.1	3.1±0.3	1.4±0.5	0.017	0.111

**Results:** No differences of Epworth scale in main 5.8±3 and control group 5.9±3 (p=0.96). Snoring was statistically higher in main group (47.1±0.5) than in control group 0 (p=0.004). Results of cardiorespiratory monitoring presented on Table 1 and 2. RDI and average duration of respiratory events (ADRE) were statistically higher in main group and sub-group with normal BMI comparing with the control group. Percent of maximal oxygen desaturation was statistically higher in main group but not in the sub-group with normal BMI. Fraction of inspiratory time (TI/TT), inspiratory asynchronous index (IAI), % peak inspiratory flow to inspiratory time (% PI/TI), changes of functional residual capacity (FRC) statistically higher in main group and normal weight subgroup compared to control group. 24 hours BP monitoring showed statistically high BP in main group than in control group. In 27 patients in main group (72.2%) BP during the night was higher than BP during the day. HR analysis showed circadian index (mean HR in wake/mean HR in sleep) was statistically less in main group than in control group. At the same time, no statistical difference between HR during wake and sleep in main and control group. No differences in spectral analyses including very low, low and high frequencies, standard deviation of RR intervals and root of sum square difference between RR intervals. P1 – differences between main and control group, P2 – differences between sub-group with BMI <25 kg/m<sup>2</sup> and controls

Table 2

	MAIN GROUP	SUB-GROUP w/BMI<25	CONTROL LS	P1	P2
TI/TT	0.424±0.03	0.423±0.03	0.39±0.02	0.005	0.009
ΔFRC	-216.1±111.1	-218.6±121.5	-139.1±52.8	0.021	0.041
%PIF/TI (%)	45.3±8.2	43.1±8.5	51.9±5	0.023	0.003
LAI	5±2.4	4.1±1.9	3±0.9	0.005	0.081

**Conclusions:** Results of the study revealed tendency of predominantly night-time increased BP in young men with first stage of essential HTN which associated with obstructive breathing disorders during sleep. One possible mechanism of development HTN may include activation of baroreflex by increased intrathoracic pressure. Absent of significant changes of oxygen saturation and sympathetic activity in our study confirmed this possibility.

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**666.J**

**ANATOMICAL AND FUNCTIONAL EVALUATION OF UPPER AIRWAYS IN YOUNG MEN WITH ESSENTIAL ARTERIAL HYPERTENSION**

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**Introduction:** Our previous data demonstrated that young men with essential HTN had statistically significant changes of respiration during sleep compared to control group. The purpose of this work was evaluation of structure and function of upper airway and genetic predisposition for development of obstructive sleep disorders in this group.

**Methods:** The main group consisted of 18 consecutive patients with a mean age of 18.7±3.1 with documented primary first stage arterial HTN and otherwise healthy. 11 healthy young men (mean age 18±2.3) with normal BP made control group. There was no significant differences in smoking in main and control groups (44.8% and 36.4%, p=0.639). Anatomical evaluation included cephalometric X-ray in lateral projection and for assessment of soft tissues MRI in lateral, axial and frontal projections. The assessment of linear distances was taken on the base of the literature data (1). Nasal

breathing during wake were analyzed quantitatively by parameters of flow volume loop taken in body-box (SensorMedics, USA). Geniologic analysis was done for 15 probands of main group and 9 of control group for history of arterial HTN and snoring for the age below 55 years. Of collected data, there were 148 relatives of main group and 118 of control group. We analyzed distribution of arterial HTN and snoring separately and in combination. Patients underwent night cardiorespiratory monitoring with using RIP. Results of cephalometric X-ray, MRI and nasal breathing were compared to results of cardiorespiratory monitoring for analyses of correlations.

**Results:** Relatives of patients of main group in 48.0% had HTN in 52.0% snoring and in 36.5% combination. Control group, 28.0% relatives had snoring, 20.3% had HTN and 11.0% combination. Differences between groups were statistically significant (p<0.05). Cephalometry showed that in the patients of main group, angles ANB, NAPg were increased and angles SNPg decreased (p<0.05) which indicated retrognathia. Mandibular size in both groups including subgroups with a low BMI were the same. Distance between angle of mandibular and hyoid was statistically longer in patients with HTN. The results of MRI demonstrated only statistically significantly increasing longevity of the tongue. For assessment results of MRI, main group was divided into 2 sub-groups with BMI <25 and >25 kg/m<sup>2</sup>. In normal weight patients, only longevity of the tongue were more than in control group (49.6±4.1 and 42.7±5, p=0.04). We did not find decreasing diameters of the pharynx in main group compared to the control group. Thickness of the neck soft tissues was increased only in patients with BMI >25. The study of nasal breathing did not show statistically significant differences between results in main and control group. Correlation analyses showed high negative correlation between force expiratory flow on 50% of FVC and RDI (-0.98), mean longevity of obstructive events (-0.88) and with maximal desaturation (-0.78). Correlation of distance between mandible angle and hyoid bone and RDI was 0.56 and longevity of obstructive events 0.57. ANB angle correlated with RDI and longevity events as 0.63 and 0.59. TI/TT index by RIP during the night correlated with ANB angle as 0.63 and with mandible hyoid distance as 0.58. Mandible hyoid distance correlated with inspiratory asynchronies index as 0.81.

**Conclusions:** Relatives of patients with essential arterial HTN have a high percentage of arterial HTN and snoring, which often present together and possibly inherit together. We did not find thickness of soft tissue of the neck in arterial HTN patients with BMI <25 but signs of mild retrognathia and macroglossia were statistically significant compared to the control group. There was no difference in nasal breathing in patients with HTN and controls, although there was good correlation of respiratory irregularities in sleep with flow-volume loop parameters of nasal breathing and cephalometry. Anatomical structures of upper airways and genetic predisposition for stabilization of arterial HTN can be important factors for development of essential arterial HTN in young men.

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## 667.J

## VESTIBULAR ABNORMALITY IN OBSTRUCTIVE SLEEP APNEA SYNDROME

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**Introduction:** The vestibular system is a phylogenetically very old, essential to successful adaptation of every animal operating in the earth's gravitational field. Our interest in the relationship between vestibular dysfunction and sleep disorders began with the evaluation of patients with the perilymph fistula syndrome (PLFS) and obstructive sleep apnea. PLFS is both an acute and chronic disorder arising from, at times, minimal physical trauma to the head and/or neck resulting in disruption of the round or oval windows. Individuals affected experience a wide range of otological as well as cognitive and emotional disturbances. It was discovered that virtually all experienced substantial sleep disruption<sup>1,2</sup>. Most recently, we reported on two cases illustrating the importance of obstructive sleep apnea in the management of perilymph fistula syndrome, one severe and the other mild mainly consistent with the upper airway resistance syndrome<sup>3</sup>. The emergence of their clinical sleep disorder following the development of PLFS raised the important question the possible role of vestibular dysfunction in the pathogenesis of obstructive sleep apnea syndrome. In light of this realization, and further supported by animal work completed elsewhere examining vestibular physiology and upper airway function, we have begun to explore this potentially enormously important relationship.

**Methods:** Subjects consisted of consecutive patients seen for the evaluation of obstructive sleep apnea syndrome in the Pacific Sleep Program. Comprehensive sleep/wake pattern surveys were completed by each subject. Patients were interviewed and underwent general physical and neurological examinations, the latter with special focus on balance assessment. All patients underwent diagnostic or split-night polysomnography meeting or exceeding AASM standards. Based upon the notable frequency of abnormality, the main clinical focus was the Romberg test. This was completed according to standard protocol. In particular, the tandem Romberg test was included. The latter was classified as mildly disturbed if abnormal levels of sway were found, moderate or severe when stumbling or falling were observed. Patients were grouped according to the level of vestibular dysfunction detected and then compared with the level of sleep related breathing disturbance identified.

**Results:** 36 patients, all adults, 7(18.9%) female 29(80.6%) male have been evaluated thus far. The age range was 26-70 years, mean 51±9.1. BMI mean was 32.7±6.8. OSAS was found in 30(81.8%), UARS was found in 6(16.2%), and there was 1 normal. Of those with OSAS; 23.3% were mild, 26.7% were moderate, 50% were severe. The mean RDI was 41.6±29.9. Tandem gait was marginally abnormal in 3 (8.3%). Romberg was abnormal in a single case. Tandem Romberg was abnormal in 29 (80.6%). The neurological examination was otherwise normal in all cases. Of those with abnormal Romberg findings 13 (44.8 %) were mild, 10 (34.5%) were moderate, and six (20.7%) were of severe degree. Those indi-

viduals with a mild degree of Romberg abnormality on average had mild sleep disordered breathing, while those with a severe degree of abnormality appeared to have a moderate to moderately severe level; however, this did not reach statistical significance.

**Conclusions:** Mild degrees of vestibular dysfunction, as evidenced by varying degrees of abnormality in the tandem Romberg clinical testing were extraordinarily common. This lends further support to the theory that the vestibular dysfunction may be important to the pathogenesis of obstructive sleep apnea syndrome. Further patients are undergoing evaluation and a more detailed analysis is in progress. Work has also begun on detailed neuro-otological testing of patient's vestibular function.

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## 668.J

## CPAP THERAPY ON BLOOD PRESSURE OF SLEEP APNEA-HYPOPNEA SYNDROME

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**Introduction:** Arterial blood pressure rises at the end of each apnea, and there is increasing evidence that the sleep apnea-hypopnea syndrome (SAHS) is associated with daytime hypertension.

**Methods:** We conducted a randomized study of the effects of four weeks nocturnal continuous positive airway pressure (CPAP) in 56 patients with OSAHS (42 males, 14 females; apnea-hypopnea index [AHI] range 31~73, median 44) with and without daytime hypertension. All subjects agree not to receive any medications related anti-hypertension during study period. Blood pressures in the morning (6:30AM) and night (while go to bed) were recorded everyday for 4 weeks. The diagnosis and CPAP titration were confirmed in the sleep lab with PSGs.

**Results:** 26 SAHS patients were daytime normotensive (as group A), 12 with morning hypertension (group B), 18 with both morning and night hypertension (group C). All patients receive four weeks CPAP therapy study. In group A, BP slightly dropped in the morning, but no significant different before and after CPAP both in the morning and night during four weeks study. In group B, BP decreased significantly in the morning during the first three days and maintain the level for the rest of study days. In group C, Daytime BP of 8 patients decreased remarkably to normal levels both in the morning and night, 9 with statistic dropped morning BP but no significant change in the night. 1 with sustained morning and night hypertension although 4weeks CPAP treatment.

**Conclusions:** There are close relationship between OSAHS and systemic hypertension. CPAP can improve hypertension

especially in the morning in the most of SAHS patients, along with effective reversed sleep apneas and nocturnal oxygen desaturation.

### 669.K

#### CSF DYNORPHIN A(1-8) LEVELS ARE NOT ALTERED IN HYPOCRETIN-DEFICIENT HUMAN NARCOLEPSY

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**Introduction:** Hypocretin (orexin) deficiency is the major pathophysiology in most of human narcolepsy cases. Cell bodies of Hypocretin containing neurons are exclusively located in the lateral hypothalamus (LH). It is still controversial whether the primary abnormality in hypocretin-deficient human narcolepsy is impaired hypocretin peptide production or a loss of hypocretin neurons. Dynorphin and prodynorphin mRNA colocalize within hypocretin neurons in the LH (1). Measurements of dynorphin signals differentiate between the loss of ligand production vs. ablation of hypocretin neurons in the two mouse narcolepsy models: prodynorphin mRNA is intact in the LH of hypocretin ligand knock-out mice, but absent in the LH of hypocretin/ataxin-3 transgenic mice, a hypocretin-neuron targeting cell death model of narcolepsy (2). Altered CNS dynorphin levels may also be reflected in the CSF, since a significant reduction in CSF dynorphin A levels were reported in patients with Alzheimer's disease (3). In this study, dynorphin A(1-8) levels were measured in the CSF of control subjects and narcoleptic subjects with and without hypocretin-deficiency.

**Methods:** CSF samples from 33 narcolepsy-cataplexy patients and 26 healthy controls were included in this study. CSF hypocretin-1 immunoreactivity (IR) levels of these narcoleptic subjects were previously measured using an 125I radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals, CA, USA). Twenty-five patients had undetectably low CSF hypocretin-1 levels (less than 100 pg/ml by a direct assay), while hypocretin-1 levels in 8 narcolepsy patients were in the range of normal controls, and thus defined as non hypocretin-deficient narcolepsy. Dynorphin A(1-8) IR was measured using an 125I RIA kit (Phoenix Pharmaceuticals). 200ul of CSF were used for duplicate crude measurements of each substance.

**Results:** Dynorphin A(1-8) IR was detectable in the CSF of all subjects (range; 24-69pg/ml). Dynorphin A levels did not differ between hypocretin-deficient (42±2pg/ml, mean±SEM), non hypocretin-deficient narcoleptics (42±4pg/ml), and controls (39±2pg/ml), (p=0.51, one-way ANOVA). Dynorphin A levels were not correlated with gender or age in patient and control groups.

**Conclusions:** Dynorphin A levels in the CSF of hypocretin-deficient narcoleptic patients were not significantly different from those of non-deficient narcoleptics and controls. Although our current findings do not support the loss of hypocretin/dynorphin containing cells in hypocretin-deficient human narcoleptic subjects, these results should be interpreted carefully. Dynorphin is produced in many brain regions other than the LH, including cerebral cortex, caudate putamen, amygdala and the spinal cord. Thus, in contrast with a global

CNS atrophy seen in Alzheimer's disease (3), selective loss of hypocretin/dynorphin neurons in the LH may not be reflected in the CSF dynorphin levels. Measurement of dynorphin peptide and/or prodynorphin mRNA in the LH of postmortem human narcoleptic brains will be required to finally answer this question.

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### 670.K

#### CORRELATION BETWEEN NOCTURNAL SLEEP EEG AND DAYTIME SLEEPINESS IN RESPONSE TO SODIUM OXYBATE

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**Introduction:** Analyses on the effects of sodium oxybate on nocturnal sleep parameters and daytime characteristics in narcoleptic patients have been presented previously 1,2. Positive effects were observed for both increases in delta power and the duration of Stage 3&4 sleep for the nocturnal parameters, and for increases in the Epworth Sleepiness Score and in the sleep latency for the Maintenance of Wakefulness Test, suggesting reduced daytime sleepiness. To ascertain the relationship between slow wave sleep and daytime sleepiness, a post-hoc correlation analysis was performed between nocturnal and daytime data.

**Methods:** A small open-label trial of 21 previously diagnosed narcoleptic patients were treated at 4 sleep centers. Stimulants for daytime sleepiness were held constant throughout the study. During an initial 4-week washout period, the patients were gradually withdrawn from all anti-cataplectic medications. PSGs were performed at the beginning and the end of this withdrawal-baseline period. Patients were then administered a 4.5g nightly oral dosage of sodium oxybate given in equal divided doses at bedtime and again 2.5-4 h later for a period of 4 weeks. The dose was subsequently increased at 2-week intervals to 6, 7.5 and 9g, in divided nightly doses. Overnight PSGs were again recorded on the first night of 4.5g treatment and at the end of 4 weeks. PSGs were again conducted on the final night of each 2-week dosing interval. Measures of daytime sleepiness included the Maintenance of Wakefulness Test (MWT) and the Epworth Sleepiness Scale (ESS). The MWT, which quantifies the ability to resist falling asleep (sleep latency), was conducted at the beginning and end of the washout period and again at the end of the 4.5g and 9g treatment periods. The ESS, showing higher values for greater

sleepiness, was completed at these same 4 time points and at the end of the 6g and 7.5g treatment periods. Spearman's correlation coefficients were generated using all paired comparisons between the four parameters for each patient with respect to the observed data and for change from baseline.

**Results:** A post-hoc analysis of the correlation between daytime sleepiness measures (MWT and Epworth) and selected nocturnal parameters (Stage 3&4 sleep and Delta Power) indicated trending correlations, some of which were statistically significant (Table 1). A statistically significant correlation between daytime and nocturnal parameters was observed between Epworth and Delta Sleep ( $p=0.0086$ ). The overall results were similar, but not as strong, for both an analysis based upon observed values and based upon a change from baseline. A strong correlation between the two nocturnal parameters ( $p<0.0001$ ) was observed. There was not a correlation between the two daytime parameters, as has been previously reported in different populations of patients.

**Table 1**

Spearman's Correlation Analysis, Observed Values			
Variable	Variable	Coefficient	P-Value
Epworth	Stage 3&4 Sleep	-0.17	0.0599
Epworth	Delta Power	-0.23	0.0086
Epworth	MWT	-0.11	0.2766
MWT	Stage 3&4 Sleep	0.21	0.0550
MWT	Delta Power	0.18	0.0914
Stage 3&4 Sleep	Delta Power	0.79	<0.0001

**Conclusions:** The post-hoc analysis in this small, open-label trial indicates a positive correlation between an enhancement of deep sleep (delta power) and subsequent reduced daytime sleepiness (ESS). Since the half-life of sodium oxybate is very short (90 minutes), this analysis leads to an interesting proposition of a mechanistic interrelation between a drug-supported improvement in the quality of nocturnal sleep which leads to better functioning in the daytime.

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**671.K**

**ANALYSIS OF DOSE EFFECTS OF SODIUM OXYBATE ON NOCTURNAL RESPIRATORY DISTURBANCES**

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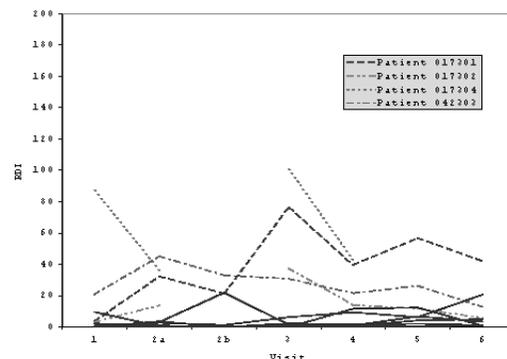
**Introduction:** Sodium oxybate has not been systematically evaluated with respect to its ability to influence respiratory

function during sleep when used for the treatment of the symptoms of narcolepsy. We present an analysis of the rate of occurrence and severity of respiratory disturbances during overnight PSG studies 1.

**Methods:** Objective nocturnal respiratory data collected during multiple overnight PSG recordings during an open-label clinical trial were used to assess the potential for sodium oxybate in increasing doses to produce respiratory disturbances in narcoleptic patients. The trial included 21 patients with narcolepsy who were treated with increasing dosages from 4.5 to 9.0 g/d sodium oxybate, including a first night dose of 4.5 g/d (Visit 2b), after 4 weeks of 4.5 g/d (Visit 3), and after 2 more weeks of treatment at each dose of 6.0g, 7.5g, and 9.0g/night in divided doses (Visits 4-6, respectively). Active treatment lasted 10 weeks. The trial included a valid baseline period of 2 weeks, prior to sodium oxybate treatment, at the end of which the same measurements were taken (Visit 2a). Respiratory response was characterized using standard, defined measures, including Apnea/hypopnea index (AHI), Respiratory disturbance index (RDI), and the total number of obstructive and mixed apneas (OMAs), central apneas, and hypopneas. These indices were calculated for the first and the second half of the night.

**Figure 1**

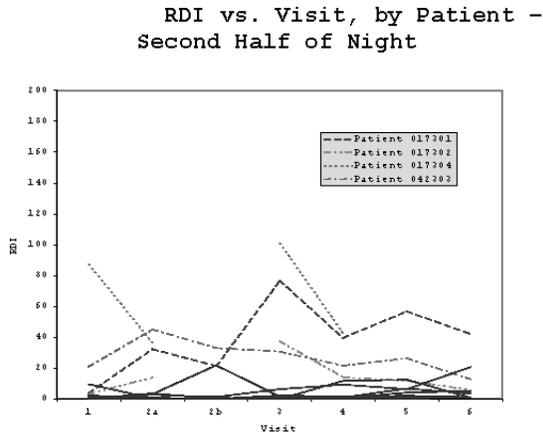
**RDI vs. Visit, by Patient - First Half of Night**



**Results:** There were no consistent clinically significant changes of nocturnal respiration for any dosage of sodium oxybate with respect to any respiratory parameter throughout the study. The only significant change from baseline was seen after 4 weeks of treatment with the lowest dose (4.5g/night) for RDI during the first half of the night (10.6,  $p<0.01$ ) and when averaged over the whole night (9.8,  $p<0.05$ ), corresponding to a minimal clinical significance. In general, there was high inter-patient variability for AHI and RDI throughout the entire trial (see Figure 1 and Figure 2). Throughout the trial, high inter- and intra-patient variability was observed for all respiratory indices. For OMAs, the only significant change from baseline for the whole night was seen after 4 weeks of 4.5 g/d (25.2,  $p<0.01$ ). No significant changes from baseline were seen for hypopneas or central apneas over the whole night. There did not appear to be any dose-response for any of the respiratory events and no overall difference in the respira-

tory events between the first and second half of the night. The two patients that had respiratory effects that could be considered clinically significant both had pre-existing sleep apnea.

Figure 2



**Conclusions:** In general, these data indicate that narcoleptic patients treated with sodium oxybate in dosages up to 9.0 g/d do not experience clinically significant increases in respiratory disturbance.

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Research supported by Orphan Medical, Inc.

**672.K  
STIMULANT MEDICATION USAGE IN A LARGE  
COHORT OF NARCOLEPTIC SUBJECTS**

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**Introduction:** The objective of this study was to assess stimulant medication usage in a large sample of narcoleptic patients. By determining the use of stimulant medications and the subjective efficacy from a patient perspective, a clearer understanding of what medications might be more appropriate and better tolerated can be provided to physicians.

**Methods:** A questionnaire designed by the authors was mailed to known narcoleptics across the United States. Four hundred and five people with narcolepsy identified through the Stanford Center for Narcolepsy Research and the Stanford Sleep Disorders Clinic were sent a questionnaire in the mail. Two hundred ninety-seven surveys were returned completed.

**Results:** Approximately 75% of our sample was currently taking a stimulant or wake-promoting medication. The majority of the sample was taking modafinil (41%). Approximately half

of the entire sample reported that the medication was very effective in treating the EDS. Around 25% of those using modafinil, methylphenidate, amphetamine or pemoline report that the medication was very effective in treating cataplexy. Oddly, over 80% of those taking modafinil report that they are taking it for the alleviation of their cataplexy. This contradicts the established literature, which states that modafinil has no direct ameliorative properties.

**Conclusions:** Many narcoleptic patients have tried, often unsuccessfully, several medications for the treatment of their narcolepsy. Successful medication treatment is contingent on a clear understanding between the physician and patient of the benefits as well as the side effects of a prescribed drug. By assessing medication usage and efficacy from a patient perspective, a clearer understanding of what medications should/could be prescribed is possible.

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**673.K  
EFFECT OF INCREASING DOSES OF SODIUM OXYBATE ON NOCTURNAL OXYGEN SATURATION: PRELIMINARY FINDINGS**

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**Introduction:** Sodium oxybate has not been systematically evaluated with respect to its effects on respiratory function during sleep when used for the treatment of the symptoms of narcolepsy. Arterial oxygen saturation (SaO2) determined by pulse oximetry during overnight PSG studies is an effective tool to characterize any effects across a range of doses.

**Methods:** Objective nocturnal saturated oxygen determinations were collected during multiple overnight PSG during an open-label clinical trial (designed to measure effects on sleep architecture1). This data was used to assess the potential for sodium oxybate to produce changes in SaO2 in narcoleptic patients. The trial included 21 patients with narcolepsy who were treated with increasing dosages from 4.5 to 9.0 g/d sodium oxybate. Active treatment lasted 10 weeks. Active treatment was preceded by a baseline period at the end of which the same measurements were taken. SaO2 measures included the following: Continuous SaO2 data (calculated as mean values of each 5 minute interval throughout the recording period) Intermittent SaO2 data (collected as mean values of 1 minute of data at 8 dispersed time points throughout the

recording period) to allow consideration of respiratory response to the variations in blood levels modeled on the kinetic profile of the drug. Since the blood levels of sodium oxybate differ from the first nighttime dose to the second dose 4 hours later, with a higher peak concentration (Cmax) with the second dose, the analysis included the individual effect of each of these 2 doses on the SaO2.

**Results:** There were no clinically significant differences for any dosage of sodium oxybate with respect to continuous SaO2 (5-minute mean data). The only statistically significant difference from baseline (95.5%) was a minimal decrease of 0.5% for continuous SaO2 (5-minute data) after 4 weeks at 4.5 g/d (Figures 1 and 2). Analysis of the intermittent SaO2 (1-minute data) indicate event-related intra-patient variability, and bear no relationship to increasing dosages of sodium oxybate, or to periods of peak plasma concentration or first vs. second nightly dose. Minimal changes in SaO2 occurred with increasing dosages of sodium oxybate. Two patients with a history of sleep apnea had respiratory effects that could be considered clinically significant. One of these patients discontinued due to a subjective increase in sleep apnea, although saturated oxygen values were no lower during active treatment than they were prior to treatment.

Figure 1

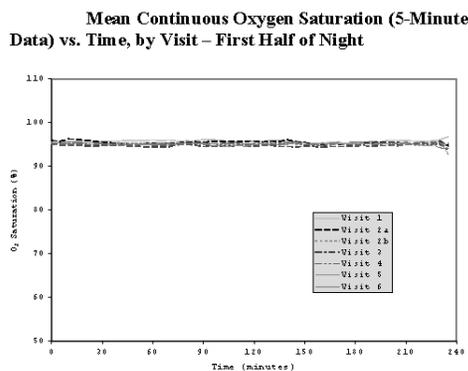
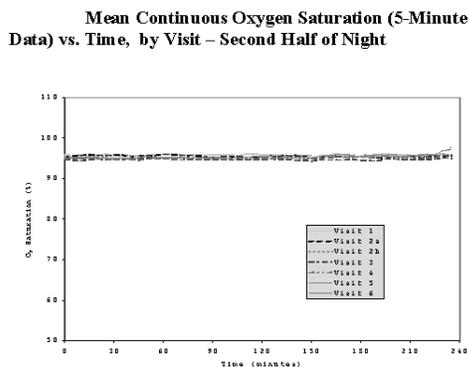


Figure 2



**Conclusions:** There were no clinically significant differences for any dosage of sodium oxybate, no evidence of a dose response, and no differences between the first and second half

of the night with respect to SaO2. The only statistically significant difference from baseline was a minimal (0.5%) decrease for continuous SaO2 (5-minute data) after 4 weeks at 4.5 g/d. These data indicate that narcoleptic patients treated with sodium oxybate in dosages up to 9.0 g/d do not experience clinically significant decreases in nocturnal oxygen saturation.

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Research supported by Orphan Medical, Inc.

**674.K**

**PATIENT WITH CATAPLEXY, SLEEP ONSET PARALYSIS WITHOUT SLEEPINESS OBSERVED BY SLEEP CENTER FOR SIX YEARS**

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**Introduction:** Cataplexy and excessive daytime sleepiness are cardinal manifestations of narcolepsy. We present the patient with witnessed cataplexy episode, sleep paralysis, hypnagogical hallucinations but without sleepiness.

**Methods:** 58 y/o man developed sleep problems 16 years ago. At this time, the patient developed recurrent sleep onset paralysis occurring several times per month, which in a few years increased in frequency up to several times per week. The patient was very frightened of these episodes. Occasionally he was able to terminate the development of paralysis by moving his leg. The patient had one witnessed episode of cataplexy when while playing cards with extreme laughter the patient fell from his chair to the floor. He experienced vivid dreaming upon falling asleep. The patient admitted difficulties falling asleep and had several awakenings during the night. He has never had any complaints of excessive daytime sleepiness. The patient went to bed at 1am and gets up at 8:15am on work days and 9:30am on weekends. He did not take any daytime naps. He also related symptoms of mild depression during first evaluation in sleep center 6 years ago. Past medical history: chronic sinus infection, history of exposure to different recreational drugs in the past, however during evaluation in sleep center he stated that he had not use any substances for several years. Habits: the patient quit smoking 12 years ago. He drank alcohol up to 1 ounce per month. Tonsillectomy in childhood. There is no evidence of sleep disorders in his family. Physical exam was normal, except for nasal septum deviation.

**Results:** Polysomnography showed prolong sleep latency to stage 1 at 54 minutes. Sleep efficiency was 52%. He had 9 episodes of awakenings. Stage 1- 6.4%, stage 2 - 38%, stage 3 - 1.7%, stage 4 - 0%, stage REM - 14%. REM latency was markedly shortened at 6 minutes. Periodic limb movements index = 5.9. No apparent arousals were recorded with PLMS. Total sleep time was 212 minutes. No snoring was recorded. 6 respiratory events were recorded with respiratory disturbance

index of 1.7. Nocturnal arterial oxygen saturation ranged from 97 to 84% with a mean level of 94%. Multiple sleep latency testing with 4 opportunities for naps showed a mean sleep latency of 10.4 minutes with 4 SOREM with mean latencies of 3.5 minutes. HLA testing was negative for DR 15. The patient was started on treatment with Doxepin 25mg qhs and then 50 mg qhs which patient continued for the last 6 years with no significant side effects. No difficulties with falling asleep, no more than one awakening at night. No repeated episodes of cataplexy and no sleep onset paralysis with the medication. The patient had no EDS. On several occasions the patient had attempted to stop the medication but each time within 2 days after discontinuing the medications, he developed episodes of sleep onset paralysis.

**Conclusions:** This patient has an unusual presentation. He has a history of cataplexy episode witnessed by his friends, sleep onset paralysis with 4 sleep onset SOREM on MSLT, questionable hypnagogical hallucinations. No excessive daytime sleepiness confirmed by MSLT after a night with 52% of sleep efficiency. DR15 was negative. The absence of daytime sleepiness distinguished isolated sleep paralyzes from narcolepsy. This case demonstrated possibility of cataplexy in patients with isolated sleep paralyzes.

### 675.K

#### CSF HISTAMINE CONTENT IS DECREASED IN HYPOCRETIN-DEFICIENT HUMAN NARCOLEPSY

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**Introduction:** hypocretin is dependent on the histaminergic neurotransmission, and it is abolished in the histamine receptor 1 knockout mice (2). Thus, impaired histaminergic neurotransmission may be an important pathophysiological mechanism in narcolepsy. In the current study, we have measured CSF histamine content in narcoleptic subjects with and without hypocretin-deficiency and in the controls to examine whether histaminergic neurotransmission is altered in human narcolepsy.

**Methods:** Forty-eight narcolepsy-cataplexy and age- and sex-matched 17 control (39±14 yrs [mean±SD] ) subjects were included. Thirty narcoleptic subjects (38±13 yrs) were shown to have undetectably low CSF hypocretin levels, while hypocretin levels in 18 narcolepsy-cataplexy (42±18 yrs) were in the range of normal controls (209-450 pg/ml), and thus defined as a non-deficient narcolepsy. CSF samples, collected between 9:00 am to 5:00 p.m., were frozen (-80C) immediately and kept until the measurements were done. Histamine measurements were done with a fluorometric HPLC system by injecting 50 micro litter of acidified CSF (from 0-4 ml fraction). All measurement was done blindly, and each CSF sample was measured twice, and the mean values of two measurements are reported.

**Results:** We found significantly lower histamine levels in hypocretin-deficient narcoleptic subjects (98±15 fmol/ml) vs.

controls (267±32 fmol/ml) (p< 0.0001, ANOVA with Scheffe Post-hoc). Decrease in histamine levels are mostly depended on hypocretin status; histamine levels (208±32 fmol/ml) in narcolepsy-cataplexy with detectable CSF hypocretin levels (non-deficient) were not significantly different from those in controls (p=0.29), and significantly higher than those in hypocretin-deficient narcoleptic subjects (p=0.0016). However, the ratio of subjects that showed low histamine levels (<150 fmol/ml) were significantly higher in hypocretin-deficient (25/30) and non-deficient (7/18) narcolepsy compared to controls (2/17), suggesting that a small subset of non-deficient narcoleptic patients may also have histamine abnormality. CSF histamine values were not significantly correlated with CSF hypocretin levels (in controls and non-deficient narcolepsy) and gender, age and status of the medication.

**Conclusions:** Similar to findings obtained in canine narcolepsy, histamine neurotransmission is decreased in hypocretin-deficient human narcoleptic subjects. Recent experiments using histamine receptor knockout mice have shown that CNS histamine is critically involved in vigilance and locomotor controls (2). Furthermore, leptin resistance and increased body weight are also observed in H1 knockout mice (3), strongly arguing that impaired histamine is involved in abnormal sleep and energy homeostasis in narcolepsy.

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### 676.L

#### PREDICTING SLEEP QUALITY WITH THE FLOYD-MEDLER SLEEP BELIEFS SCALE

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**Introduction:** The 25-item Floyd-Medler Sleep Beliefs Scale (FMSBS) has demonstrated sound factor structure and acceptable reliability. The instrument contains three sub-scales that tap beliefs in various consequences of poor sleep: (1) "Next-day Consequences", (2) "Health Consequences", and (3) "Psychological Consequences". In addition, there are six sub-scales that are quite distinct from one another: (1) "Sleep Need", (2) "Sleep Regularity", (3) "White Noise", (4) "Coping Strategies", (5) "Sleeping In", and (6) "Napping". The FMSBS was designed for use on healthy adults to reveal maladaptive thinking patterns that may lead to later insomnia. Therefore, to establish the validity of the scale we used multiple regression techniques where self-reported sleep quality was the criterion of interest and the FMSBS sub-scales were the predictors. Further, we intended to demonstrate that the sub-scales of the FMSBS are distinct from the main components of the published "Dysfunctional Beliefs About Sleep" scale (2).

**Methods:** Subjects responded to public announcements to participate in a survey of sleep beliefs, knowledge, and practices. This convenience sample from the general population consisted of 865 adults of which 68% were female. The average age

was 46.75 (S.D.=14.39) with a range of 16 to 90. Race composition was Caucasian 88%, African American 7%, and 5% "other". Through the use of multiple regression we used our nine FMSBS sub-scales as predictors of poor sleep quality as measured by the global score on the Pittsburgh Sleep Quality Index (PSQI).

**Results:** After controlling for age and sex, we found that "Health Consequences", "Sleep Need", and "White Noise" were all significant predictors. Belief that one has little need for sleep was a protective factor with the other two being positively related to early insomnia symptomology. The remaining five sleep beliefs were unrelated to the global PSQI, but sex was a significant predictor with females reporting more sleep problems than men. Age did not show a linear relationship with PSQI. As a second step to evaluating the instrument's validity we correlated each of the nine FMSBS sub-scales with three major components of the Dysfunctional Beliefs About Sleep scale (1). Correlational analyses showed a great deal of congruence between component 1, "Immediate negative consequences of insomnia" and the FMSBS sub-scale "Next-day consequences",  $r=.64$ . Component 2, "Negative long-term consequences of insomnia" was highly correlated with the FMSBS sub-scale "Health consequences",  $r=.38$ . The third component which pertained to control over insomnia did not appear to be related to any of the nine FMSBS sub-scales.

**Conclusions:** The Floyd-Medler Sleep Beliefs Scale (FMSBS) shows promise as a valid instrument for identifying maladaptive sleep beliefs in otherwise healthy adults.

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## 677.L

### NEUROPSYCHOLOGICAL FUNCTIONING OF PATIENTS WITH PRIMARY INSOMNIA

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**Introduction:** It stands to reason that chronic sleep loss should be associated with impaired cognitive performance. While it is true that patients with Primary Insomnia (PI) report problems with concentration and memory, it has been difficult to document these phenomena neuropsychologically. PIs have been found to be slower in comparison to normal controls on choice reaction time tasks (1) and do more poorly on tests of semantic memory (2). Their divided attention, however, has been found to be intact (3). In the present analysis (part of a

larger on going study), PIs were assessed using a brief neuropsychological assessment battery.

**Methods:** 18 subjects participated in this study, all were diagnosed with Primary Insomnia and were enrolled in a treatment outcome study. Neuropsychological tests were administered prior to treatment and on the first evening of in-lab study. The test battery consisted of the Hopkins Verbal Learning Test (HVLT), Trailmaking Test, Controlled Oral Word Association Test (COWAT: FAS), Digit Span (WAIS III), Brief Test of Attention (BTA: Numbers, Letters), Letter-Number Sequencing (LNS - WAIS III), Digit-Symbol (WAIS III) and the Stroop test (Golden version). Subject performance was assessed relative to normative data (matched for age, sex and education) using one-sample t-tests.

**Results:** PIs did significantly better than the established norms on the Digit Span test ( $p < .01$ ), on the LNS test ( $p < 0.05$ ) and on the BTA (Letters) ( $p < .01$ ). On tasks involving divided attention, such as the Digit Symbol test ( $p < .01$ ) and the Color/Word section of Stroop Test ( $p < .01$ ). PIs also did significantly better. In contrast to their performance on attention and divided attention tasks, PIs showed significant deficits on the COWAT, a verbal fluency task involving semantic memory ( $p < .05$ ). No significant differences between the PIs and the sample norms were found on the HVLT, Trailmaking Test, and the BTA (Numbers).

**Conclusions:** Our results are consistent with prior findings in two respects. First, patients with insomnia do not appear to exhibit deficits on attention or divided attention tasks (3). Second, patients with insomnia appear to perform more poorly than normals on semantic memory tasks (2). The implications of these findings are that PIs can process and respond to novel information (no effects on recent or working memory) but are less able to access and/or integrate information from long term memory and apply it to on-line problem solving. As put by Mendelson, although patients with insomnia "can easily learn new information, they are less able to use what they already know. Subjectively, this may be experienced as an inability to think in a clear, crisp fashion".

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## 678.L

### CROSS-VALIDATION OF THE CONTENT, RELIABILITY, FACTOR STRUCTURE, AND PREDICTIVE VALIDITY OF THE SELF-STATEMENT TEST (SST) WITH YOUNG ADULTS

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**Introduction:** Clinical work with insomniacs has highlighted cognitive activity at nighttime, as an important factor exacerbating

bating insomnia among distressed poor sleepers(1). A questionnaire evaluating mental activity was devised by Fichten and validated with elderly insomniacs(2). This study assessed the utility of the SST for measuring the cognitive processes among healthy young adults, evaluating content validity, reliability, factor structure, and relationship to two measures of poor sleep outcome: the Pittsburgh Sleep Quality Index (PSQI), and total days meeting criteria for Level I and II insomnia assessed from a one week sleep log.

**Methods:** 242 College students in their twenties participated in four phases of study: 1) a review of the content of the measure, to determine the adequacy of content areas sampled for the younger cohort, 2) a three week test-retest reliability study, during final exams and again after, 3) an exploratory and confirmatory study of the factor structure with a principal components analysis using a Varimax rotation, and 4) a study of the predictive validity of the measure, correlating the SST subscales with PSQI and days of Level I and II insomnia.

**Results:** Content review demonstrated that the young adults had only minor suggestions for content revision. Four questions about relationships, and school related tasks, were added to the questionnaire, and minor wording changes made on some items. The test-retest reliability study yielded excellent results for the revised test: Positive Subscale  $\alpha = 0.903$  and Negative Subscale  $\alpha = 0.894$ . The factor analysis of the SST for young adults replicated the essential features of the original instrument, again with minor variances. The factor analysis yielded a six-factor solution. The items in the Positive Thoughts Factor (elderly cohort) clustered as three unique components for the young, and included sixteen questions accounting for 27% of variance. The Negative Thoughts Factor included fifteen items clustered as two components (23% variance). Predictive validity of the instrument was also good: components of the SST significantly correlated to both the PSQI and Levels of insomnia, some anticipated, some not.

**Conclusions:** This study demonstrated that the SST, a questionnaire recently available to evaluate positive and negative mental activity among insomniacs, has excellent reliability and validity with young adults. Results validated the psychometric properties, established norms for a young adult population, cross-validated the factor structure reported by Fichten confirming that the Negative, Positive, and State of Mind factors are all very robust, consistent across stressful and non-stressful conditions, and predictive of sleep outcomes. However interpretation of the thought structure of younger adults appears more complex, with three main factors, two of which have subcomponents. This study demonstrated that evaluating mental processes of young adults is important for understanding the potential for disturbed sleep among them. Ongoing studies with adult insomniacs will allow assessment of clinical cutoffs to further improve the utility of the SST for assessment of insomnia.

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**679.L**

**INTENSIVE SLEEP ONSET TRAINING FOR SLEEP ONSET INSOMNIA**

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**Introduction:** Stimulus control therapy is considered the most effective long term behavioral treatment for sleep onset insomnia. By following its instructions a patient would obtain a single rapid sleep onset each night. This rapid sleep onset usually follows several unsuccessful sleep onset attempts each night, particularly in the early weeks of therapy. In practice, compliance to instructions can be a problem since it can involve increased daytime sleepiness. The question is, could the goals of stimulus control therapy be achieved in a more intensive, short duration therapy? Such a therapy may be administered by facilitating a large number of rapid sleep onsets during acute sleep deprivation.

**Methods:** In a pilot study four healthy sleep onset insomniacs (mean age of 28.5 years) were obtained by advertisement in local newspapers. All had subjective (two weeks sleep diary) and objective (PSG) sleep onset latencies > 30 minutes with a mean TST of 6.4 hours and sleep efficiency of 75%. Following a night of PSG subjects continued with a 40 hours of wakeful bedrest but including half-hourly multiple sleep latency tests (MSLTs). The MSLTs allowed a possible 25 minutes in which to initiate sleep which was defined as the first of three consecutive 30 second epochs of sleep. At each sleep onset the subject was aroused to ensure the continuation of acute sleep deprivation. Over the 40 hour period this provided at least 70 sleep onsets in all subjects. Two weeks of sleep diary were collected at home after a night of recovery sleep and again at eight weeks follow-up.

**Results:** Mean subjective sleep latency decreased significantly from 51.5 min pre-treatment to 27.5 min at short term ( $t(3) = 3.61, p < 0.025$ ) and 29.9 min longer term follow up ( $p < 0.05$ ). Subjective TST increased from 385 min to 445 min ( $p < 0.025$ ) and 441 min ( $p < 0.05$ ) at follow ups. Mean sleep efficiency increased 10% to 85% ( $t = 2.05$ ) but this did not reach significance. Fourteen good sleepers followed the same methodology (as part of another study) and, apart from the first six hours of the routine, showed the same mean sleep latencies at each time point of the laboratory session. Only over the first 10-12 MSLTs were sleep latencies longer indicating initial hyperarousal in the sleep onset insomniacs. After that their sleep latencies normalized. From the first night of sleep deprivation and for the next 20 hours of the session the insomniacs experienced sleep onset latencies usually less than five minutes in duration. They were pleased at how well they tolerated the method and with the experience of so many short sleep latencies.

**Conclusions:** One can tentatively say that this procedure promises to be an effective treatment for sleep onset insomnia. It provides rapid improvement in sleep that would normally take 4-6 weeks of stimulus control therapy to yield comparable improvements. Issues of expense, generality to the home environment, and combination with cognitive therapy need to be explored as well as confirmation in a larger sample of sleep onset insomniacs.

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**680.L**

**SLEEP VARIABLES, SLEEP QUALITY, AND DAY-TIME FUNCTIONING DEFICITS**

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**Introduction:** Sleep latency (LAT), wake time after sleep onset (WASO) and sleep efficiency (SE=Time in Bed/Total Sleep Time) are three sleep variables that are important in evaluating sleep performance. It is not clear, however, which variable among the three is most correlated with subjectively related poor sleep and associated daytime complaints. In this study we obtained information on the self-reported mental and physical health of a randomly selected population in the metropolitan Memphis (TN) area. The subjects completed two weeks of sleep diaries, which affords us a thorough assessment of their sleep patterns. This investigation will focus on the relationship between the three sleep variables and sleep quality as well as daytime sleepiness, and daytime fatigue.

**Methods:** We used random-digit dialing to recruit at least 50 men and 50 women in each decade from 20 to 80+. Volunteers were paid between \$15 and \$200 (older adults were paid more) for completing 14 days of sleep diaries and questionnaires regarding daily functioning. Sleep quality was measured from 1 (poor sleep) to 5 (excellent sleep). Measures of daily functioning included the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), and the Fatigue Severity Scale (FSS).

**Results:** We have data on 771 participants, and these individuals had a quality rating of 3.4. Of the three sleep variables SE was the better predictor of sleep quality and daytime functioning deficits. The correlations between SE, WASO and LAT with sleep quality were .49, -.43, and -.32 respectively. As expected, higher SE and lower WASO and LAT were associated with higher quality of sleep. Stepwise multiple regression was conducted using the three sleep measures as independent variables. SE was included in the first model and explained 24% of the variance in sleep quality. WASO added an additional .05% in explained variance, and LAT was excluded from the analysis. Correlations between the sleep variables and daytime sleepiness and fatigue are reported in table 1. SE had slightly higher correlations with FSS scores as compared with LAT and WASO, and WASO had the highest correlation with ESS.

Table 1

Correlations	FSS	ESS	SSS
SE	-.235*	-.082*	.204*
LAT	.225*	.011	.181*
WASO	.212*	.113*	.181*

\*= correlation is significant at the .05 level.

**Conclusions:** As expected, all three variables were significantly associated with sleep quality, and SE had the highest association. LAT and WASO only added an additional 5% in explained variance after accounting for SE. Correlations between daytime sleepiness and fatigue scores were slightly higher for SE as compared with LAT and WASO. Although the correlation differences were somewhat minimal it appears that SE is the better predictor of sleep quality, daytime fatigue and sleepiness. SE is an aggregate measure of sleep performance and does not inform the clinician of specific sleep concerns. However, it might be more informative when evaluating overall perceived sleep quality and certain daytime complaints.

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**681.L**

**SLEEP DISRUPTION AND PSYCHOLOGICAL CHARACTERISTICS IN CHRONIC FATIGUE SYNDROME**

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**Introduction:** Chronic fatigue syndrome (CFS) has been a contentious diagnosis for many years. Without definitive laboratory tests, no specific etiology, and no effective treatment, it has long been characterized a functional disorder with a very substantial psychological component<sup>1</sup>. An alternative to treating CFS itself is to treat its symptoms. Pilot data from our laboratory as well as indications in the literature<sup>2</sup> suggested that treatable medically based sleep disorders might characterize an important subgroup of people with CFS. If this is confirmed, then a subgroup of CFS patients may benefit from treatment. To shed light on this issue the goal of this preliminary study was to compare CFS patients and normal controls on sleep and daytime functioning as well as psychological adjustment.

**Methods:** Ten persons with CFS (mean age 47) were recruited primarily through CFS support groups. 10 controls (mean age 41) were recruited from the community. They were compared on nighttime sleep quality and daytime functioning (polysomnography and questionnaires) as well as measures of psychological adjustment.

**Results:** On polysomnographic measures, individuals with CFS had significantly greater sleep disruption (based on respiratory disturbance and periodic limb movements) than controls. On self-report measures, significantly more CFS participants report insomnia than controls. This includes longer sleep onset latency and nocturnal wake times as well as more daytime sleepiness, fatigue and difficulty concentrating. On psychological adjustment measures, individuals with CFS do not differ from controls on Anxiety (Spielberger State-Trait Anxiety Inventory: STAI), Depression (Beck Depression Inventory: BDI), or Neuroticism (Eysenck Personality Questionnaire:

EPQ).

Table 1

Sleep Variables

PSG	CFS	Control	t-test
Sleep onset latency (min.)	31.10	15.70	1.42
Nocturnal wake time (min.)	27.38	14.33	1.40
PLM arousals	2.04	0.31	2.73**
RDI	11.00	9.33	2.98**
<b>Questionnaire (Sleep)</b>			<b>X<sup>2</sup></b>
Insomnia: Yes	90%	20%	9.90**
Sleep onset insomnia	80%	30%	5.05*
Middle of the night insomnia	80%	20%	7.20**
Terminal insomnia	50%	0%	6.67**
Nonrestorative sleep	100%	20%	13.33***
<b>Questionnaire (Daytime)</b>			<b>t-test</b>
Refreshed in morning (1-10)	1.3	7	5.06**
Sleep quality (1-10)	2.2	8.1	0.14
Sleep satisfaction (1-10)	1.5	8.4	0.00
Fatigue (1-10)	9.2	2.4	3.95**
Sleepiness (1-10)	6.5	2.3	1.74
Concentration difficulties	8.1	2.7	0.89

\* p<.05 \*\*p<.01 \*\*\* p<.001 Note. (1-10): 1 = lo, 10 = hi

Table 2

Mean Scores On Psychological Variables

Measure	CFS	Control	t-test
Anxiety (STAI)	40.89	31.10	0.99
Depression (BDI)	15.00	6.50	0.60
Neuroticism (EPQ)	5.40	2.80	0.36

Note. All tests non significant.

**Conclusions:** Our findings do not support the widespread belief that there is a high concordance between CFS and psychological disorder<sup>3</sup>. Instead, they highlight the significant amount of sleep disruption based on physiologically based sleep disorder and the very high rate of insomnia complaints. The findings raise intriguing questions about cause and effect for CFS patients: To what extent does primary sleep disorder have an etiological significance? Is CFS primarily an overlooked sleep disorder<sup>3?</sup> Even if not implicated in etiology, will treatment of sleep apnea and periodic limb movement disorder (RLS/PLMD) have beneficial effects? What role does reported insomnia play in either etiology or maintenance of CFS? What are the implications of insomnia treatment for relief of the symptoms? An investigation is currently ongoing in our laboratory to investigate these questions.

**References:**

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682.L

IS HYPOTHYROIDISM A POTENTIAL RISK FACTOR FOR DEVELOPMENT OF INSOMNIA?

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**Introduction:** As part of an ongoing series of studies on primary insomnia, we have noted that an unexpected number of subjects have reported being diagnosed with hypothyroidism. While hyperthyroidism has long been thought to be a predisposing and/or maintaining factor for insomnia, there is no literature to suggest that this is also the case for hypothyroidism. In the present report, we provide descriptive data on the prevalence of hypothyroidism in a sample of 90 individuals.

**Methods:** Subjects for this analysis were evaluated as part of a recruitment procedure for two ongoing studies of insomnia. Potential participants were directed to call an information number (4-SLEEPY) where they were provided with instructions regarding study eligibility. Those who believed that they were eligible completed a comprehensive screening questionnaire. This instrument was either administered by phone or was completed online at our website (www.sleeplessin-rochester.com). Over the last six months, we obtained self-report information from 90 subjects on a wide range of topics including quantitative and qualitative measures of sleep disturbance, medical and psychiatric illness and history, medication and substance use. Approximately 70 of the 90 screenings were performed by phone; the remaining were submitted electronically.

**Results:** Of the 90 subjects screened to date, 7 (8%) presented with a history of overt hypothyroidism. None reported being hyperthyroid. This 8% rate appears substantially higher than the epidemiologically assessed 0.4% estimated population prevalence (1). Moreover, this rate of occurrence more than doubled the second most common medical condition reported in our sample - fibromyalgia. This disorder was reported by 3 subjects (3.3%).

**Conclusions:** Give these descriptive data, it appears that hypothyroidism may represent a risk factor for development of insomnia. That is, acute hypothyroidism may precipitate sleep initiation and/or maintenance problems. It is unlikely, however, that hypothyroidism is responsible for chronic insomnia as all of the subjects in the present report were euthyroid. One way that insomnia may occur in association with acute hypothyroidism is as a systemic response. This possibility follows from evidence derived from several sleep deprivation studies which show that thyroid stimulating hormone (TSH) levels rise in response to both partial and full-night sleep loss (2). A second possibility is that over the course of the thyroid disease, the initial decrease in thyroid function results in transient increases T3/T4 which in turn are associated with the first-onset episode of insomnia. In either case, the persistence of insomnia beyond the initial phase of thyroid illness may occur (as with primary insomnia) for reasons more related to the engagement of maladaptive coping strategies and/or thru conditioned arousal. In order to assess if hypothyroidism is a

common feature of primary insomnia, we are currently gathering a broad panel of endocrine measures on all our subjects.

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**683.L**

**LATENCY AND RATE OF DISCHARGE OF SLOW WAVE SLEEP IN PATIENTS WITH PRIMARY INSOMNIA AND GOOD SLEEPER CONTROLS**

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**Introduction:** Given that patients with Primary Insomnia (PI) reliably get less sleep than is desired, it follows that this form of chronic sleep loss would affect the latency to, amount of, and/or rate of discharge of Slow Wave Sleep (SWS). Accordingly, we hypothesized that patients with insomnia, as compared to good sleepers, would exhibit SWS profiles that are akin to those found in sleep deprived subjects. Specifically, PIs would enter into SWS more quickly, exhibit greater percentages of SWS, and/or discharge SWS at a slower rate over successive cycles. In order to evaluate these possibilities, PSG data from 40 subjects (20 Primary Insomniacs, 20 good sleepers) were evaluated.

**Methods:** Two groups were evaluated: Primary Insomnia (n=20) and Good Sleeper Controls (n=20: no history of medical/psychiatric/ sleep disorders). Groups were matched for age, sex, and body mass. The sample was 66% female and the mean age was 37.5 (± 10.7). Subjects spent at least two nights in the sleep laboratory. PSGs included 2 EOGs, 6 EEGs and a sub mental EMG. Digital acquisition was governed by Stellate Harmonie™ software and accomplished by a BSMI 519 AD board. All records were scored in 30 second epochs according to Rechtschaffen and Kales criteria. In addition to the normal sleep continuity and architectural variables, we calculated 3 latency values for SWS and total sleep times and SWS percents for each of the first 4 NREM sleep cycles. The two groups were compared on the latency variables using ttests. The two groups were compared on the NREM cycle data using two Two-Way (2\*4) ANOVAs.

**Results:** As can be seen in the table, patients with insomnia did not enter into SWS more quickly, nor did they differ for the percent of slow wave sleep per cycle. Total sleep time also did not vary significantly within the limited 4 cycle window, except for during the 4th NREM cycle.

**Table 1**

Good Sleepers VS Primary Insomniacs SWS distribution			
	GS (n=21)	PI (n=20)	P
LATENCY TO SWS	min. (SD)	min. (SD)	
1 <sup>ST</sup> EPOCH SLEEP TO 1 <sup>ST</sup> EPOCH SWS	30.2 (36.3)	34.4 (39.6)	ns
1 <sup>ST</sup> EPOCH SLEEP TO 1 <sup>ST</sup> EPOCH SWS (3 MIN)	52.6 (63.6)	79.0 (81.1)	ns
1 <sup>ST</sup> EPOCH 8 OF 10 SLEEP TO 1 <sup>ST</sup> EPOCH SWS	24.4 (24.6)	31.4 (39.9)	ns
1 <sup>ST</sup> EPOCH 8 OF 10 SLEEP TO 1 <sup>ST</sup> EPOCH SWS (3 MIN)	56.3 (66.8)	71.1 (82.4)	ns
<b>TIME ASLEEP PER CYCLE (1<sup>ST</sup> 4 cycles)</b>	<b>min. (SD)</b>	<b>min. (SD)</b>	
TST (Total 1 <sup>ST</sup> 4 cycles)	347.7 (40.9)	327.7 (53.7)	0.18
TST CYCLE 1 (minutes)	105.3 (42.2)	103.4 (41.3)	ns
TST CYCLE 2 (minutes)	96.4 (18.5)	105.1 (30.6)	ns
TST CYCLE 3 (minutes)	89.9 (17.6)	86.5 (38.3)	ns
TST CYCLE 4 (minutes)	56.2 (38.8)	32.8 (30.7)	0.04
<b>PERCENT SWS PER CYCLE (1<sup>ST</sup> 4 cycles)</b>	<b>% (SD)</b>	<b>% (SD)</b>	
AVG %SWS	14.6% (11.4)	15.4% (11.2)	
%SWS CYCLE 1	27.1% (20.7)	27.7% (21.1)	ns
%SWS CYCLE 2	16.8% (14.8)	18.9% (16.0)	ns
%SWS CYCLE 3	8.3% (10.2)	9.4% (12.9)	ns
%SWS CYCLE 4	3.6% (4.6)	4.6% (7.2)	ns

**Conclusions:** We observed no evidence of altered SWS in our sample of patients with Primary Insomnia. This does not, however, suggest that SWS is normal in PIs. Given that chronic sleep loss is a feature of PI, it would be expected that they would exhibit evidence of increased homeostatic pressure for sleep. Instead, it appears that the homeostatic drive for sleep in PI's may be weaker than in normal good sleeping subjects. That is, although PIs have less TST, they did not show the kind of homeostatic adaptation one would expect to occur in chronically sleep deprived individuals. The present data are consistent with the recent work of Stepanski et al., who found that when PI subjects are subjected to substantial sleep deprivation (< 10 minutes of sleep allowed over the course of one night) they do not show the increases in SWS during recovery that occur in healthy good sleepers.

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**684.L**

**EXTENDING SLEEP OR DECREASING TIME IN BED FOR INSOMNIA: A COMPARATIVE TRIAL**

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**Introduction:** Behavioral therapy has been shown to be an effective insomnia treatment. The two main types address one of two issues: 1) extending sleep time, or 2) reducing time spent in bed. Sleep restriction (SR) therapy employs the latter approach. Two meta-analytic reviews concluded that SR is a highly effective intervention (Morin, Culbert, & Schwartz, 1994; Murtagh & Greenwood, 1995). SR is, however, used primarily in older adults. The absence of SR in non older-adult samples is perplexing given that the reason for using it in older adults, the absence of sleep deprivation (i.e., there is little need in extending sleep), is present in all age groups. An estimated 70% of PWI exhibit no daytime impairment, suggesting that a large percentage would benefit from SR. Therefore the factors that make SR effective in older adults are clearly present in

young and middle-aged adults.

**Methods:** These preliminary data include six randomly assigned adults with primary insomnia recruited from the community. Treatment consisted of six weekly individual sessions, each lasting approximately 45 minutes. Active treatments included Sleep Compression (a variant of SR that gradually reduces time in bed; SC) and Progressive Muscle Relaxation (PMR). A placebo biofeedback (PB) condition was also used to control for nonspecific effects. There are two participants in each of these three groups (there will be 20 in each group by June). Sleep and daytime functioning data were gathered at baseline, posttreatment, and at 3-month follow-up. The sleep measures were: sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), and sleep quality rating (SQR, from 1 = very poor to 5 = excellent).

**Results:** Baseline analyses on basic demographic information revealed no significant between treatment conditions. Mean ages were as follows: SC=35.4, PMR=37.1, PB=36.3. Table 1 documents the sleep data from baseline, posttreatment, and follow-up. We performed a 2 x 3 repeated measures MANOVA comparing the three treatment groups and three time-points on the set of sleep variables. Both MANOVAs were nonsignificant for the gender x race interaction. There was a significant main effect for ethnicity on the sleep MANOVA. AA had more WASO, less TST, and lower SQR. There was not a main effect for ethnicity on the daytime functioning MANOVA.

Table 1

Variable	SLEEP MEASURES								
	Placebo			Sleep Compression			PMR		
	Base	Post	Follow	Base	Post	Follow	Base	Post	Follow
WASO	36.7	30.2	30.0	40.3	10.2	15.2	37.1	20.5	17.0
TST	338.2	343.5	350.6	347.8	403.7	418.3	329.5	417.6	412.8
SQR	2.2	2.4	2.5	1.9	3.6	3.9	2.0	3.4	3.5
SOL	45.3	42.4	40.5	46.5	18.3	17.5	48.3	22.4	20.8

Note. Values indicate means across 2-week period

**Conclusions:** These preliminary data suggest that Sleep Compression therapy is a viable treatment option for young and middle-aged adults. Treatment gains were not statistically different than the treatment of choice for these age groups (Progressive Muscle Relaxation), and were significantly better than placebo biofeedback. These modest gains were also well-maintained at 3 month follow-up.

685.L

**DETERMINING SLEEP ONSET: IS THERE A DEFINITION THAT WILL MINIMIZE SUBJECTIVE VS OBJECTIVE DISCREPANCIES?**

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**Introduction:** When self-report measures of sleep onset are compared to polysomnography, discrepancies between the measurement strategies are apparent. These discrepancies are

most marked in patients with insomnia, but are also evident across diagnostic categories. The goal of the present study was to assess whether subjective-objective discrepancies could be minimized or eliminated by using more conservative PSG definitions (1).

**Methods:** Three groups (n=20 per group) were evaluated: Primary Insomnia, Major Depression, Good Sleeper Controls (no history of psychiatric/sleep disorders). Groups were matched for age, sex and body mass. The sample was 66% female and the mean age was 37.5 (± 10.7). Subjects spent at least two nights in the sleep laboratory and completed sleep diaries each morning. PSGs included 2 EOGs, 6 EEGs and a sub mental EMG. All records were scored in 30-second epochs according to Rechtschaffen and Kales criteria. Digital acquisition was governed by Stellate Harmonie™ software. Subjective estimates of sleep latency were evaluated for their relationship to formal PSG definitions. To accomplish this, several PSG definitions for sleep latency were calculated for each subject. PSG definitions for sleep latency used the following cutoffs: 30 seconds any stage sleep; 30 seconds stage 2; 90 seconds any stage sleep; 8 of 10 minutes any stage; 10 minutes any stage; 15 minutes stage 2 or deeper. The differences between the subjective and objective latencies were expressed as difference scores and these were evaluated using a Two Way ANOVA (3x6) followed by serial One Way ANOVAs.

**Results:** The Two Way ANOVA yielded significant differences for both the group factor and the within subjects factor for the difference scores. Serial one-way ANOVAs revealed significant differences between groups for each objective definition except the 15 minutes of stage 2 or deeper. Differences across objective definitions were also significant for each group.

Table 1

GRP	DEF1 STG1 30 S	DEF2 STG2 30 S	DEF3 STG1 90 S	DEF4 STG1 8/10 MIN	DEF5 STG1 10 MIN	DEF6 STG2 15+ MIN	p
PI	48.45	43.11	46.65	44.63	41.81	18.28	.03
MDD	14.95	12.23	14.58	14.40	9.78	3.68	.01
GS	12.68	7.50	9.63	5.93	-85	-8.08	.02
p	.05	.05	.05	.05	.05	.28	

**Conclusions:** Our results are consistent with prior findings that suggest that only the most conservative definitions of sleep latency serve to attenuate subjective-objective discrepancies between primary insomniacs and other groups (1). These findings suggest that the subjective-objective discrepancies that occur in patients with Primary Insomnia are in part related to the tendency of PIs to perceive fragmented sleep (i.e., the non-consolidated sleep which can occur following the use of less conservative definitions for sleep onset) as wakefulness. The occurrence of subjective-objective discrepancies for 5th definition (and possibly the 6th definition) where sleep is continuous suggests that sleep misperception occurring relative to these intervals must be related to other factors. One possibility is the persistence of high frequency EEG activity into the initial 15-30 minute segments following sleep onset in patients with Primary Insomnia (2,3).

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**686.L**

**CAN STIMULANTS BE USED IN COMBINATION WITH BEHAVIORAL THERAPY FOR INSOMNIA? THE EFFECTS OF MODAFINIL ON SLEEP CONTINUITY IN SUBJECTS WITH PRIMARY INSOMNIA**

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**Introduction:** While effective, the Cognitive Behavioral Treatment (CBT) of insomnia tends to produce transient worsening in the daytime symptoms of disorder, during the acute phase of therapy. While it is unclear whether this influences subjects' willingness to comply with, or stay in, treatment, it stands to reason that a diminution of such effects would be desirable. The present study was undertaken to assess whether modafinil may be combined with traditional CBT treatment without diminishing its therapeutic effects. It was hypothesized that modafinil would not negatively affect treatment outcome and might, in fact, potentiate treatment gains. Augmentation effects might occur in association with appropriately timed withdraw effects, increased daytime activity, increased daytime adrenergic tone, and/or reciprocal interaction effects on sleep promoting neuronal substances. The data below are garnered from the first third of an ongoing clinical trial.

**Methods:** 12 subjects who met ICSD criteria for Primary Insomnia have participated in this study to date. Subjects were recruited from several sources and were screened via a multi-tier process which included: completion of preliminary questionnaire by phone or via the Internet ([www.sleeplessin-rochester.com](http://www.sleeplessin-rochester.com)), an in-house clinical interview, a physical with a comprehensive blood & urine chemistries panel, a one to two week sleep diary monitoring period, and an in lab sleep study to rule out intrinsic sleep disorders. Following recruitment, physically and mentally healthy subjects were randomized to one of three treatment conditions: 1) Placebo + 8 week CBT Tx for Insomnia (P+CBT), 2) 10 mg Modafinil + CBT (M+CBT) and 3) 10 mg Modafinil + a monitor only condition. In the present analysis, we provide interim data for the two CBT conditions on prospective measures of sleep continuity (daily sleep diaries).

**Results:** The mean age of the group was 41.1 yrs. (15.3) and 83% of subjects were female. The mean pre-treatment sleep continuity profiles for the two groups did not significantly differ (except on total sleep time TST: M+CBT = 272.2 (51.6) P+CBT = 391.9 (23.0),  $p < 0.09$ ). Both groups exhibited mean sleep latency and wake after sleep onset times that were > 40 minutes in duration. Baseline data were compared to end-of-

treatment data for the subjects in both treatment conditions. Outcome measures were rendered as percent change for sleep latency, number awakenings, wake after sleep onset time, and total sleep time. All pre-post comparisons, regardless of group membership, were significant at  $p < .05$ . Between group contrasts revealed two trends. First, subjects in the P+CBT group tended ( $p < 0.25$ ) show more improvement on sleep latency measures. Second, subjects in the M+CBT group tended show more improvement on sleep maintenance measures (See Table 1).

**Table 1**

PERCENT CHANGE FROM PRE TO POST TX

	P+CBT	M+CBT	P
Sleep Latency $\Delta$	75.8% (9.7)	53.6% (33.4)	0.25
Number of awakenings $\Delta$	56.3% (26.2)	57.4% (32.0)	0.95
Wake after sleep onset $\Delta$	50.5% (37.7)	78.9% (18.8)	0.18
Total Sleep Time $\Delta$	0.69% (12.6)	31.9% (24.1)	0.05
Sleep Efficiency $\Delta$	16.3% (10.0)	39.8% (28.2)	0.15

**Conclusions:** These data suggest that modafinil, when administered qam at a 10 mg dose, does not interfere with the successful conduct of cognitive behavioral therapy for insomnia. Moreover, it appears that modafinil may interact with CBT to acutely increase sleep maintenance effects. Whether modafinil positively effects treatment tolerability, day time function, or mood remains the subject of ongoing investigation.

**Research supported by a Grant From Cephalon Co**

**687.L**

**CAN VALERIAN HELP INSOMNIA PATIENTS AFTER BZD WITHDRAWAL?**

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**Introduction:** Valerian root, a natural product, used in many countries by patients with sleep complaints, could be an interesting alternative in the withdrawal of BZDs. In rats, valerian prevents the development of the withdrawal syndrome resulting from the removal of diazepam following prolonged periods of treatment (1). The overall results in the literature are usually positive when poor sleepers are the targeted group compared to healthy volunteers. Valerian is considered a mild sedative and hypnotic substance (2) that does not induce daytime somnolence or toxicity nor alterations of sleep architecture in rats and in humans (3). Thus, we studied the sleep of patients with insomnia who complained of poor sleep despite chronic use of benzodiazepines (BZDs). After withdrawing BZDs we treated them with 300 mg/day of valerian (concoction of valepotriates)

**Methods:** The sample consisted of 19 patients (mean age 43.3 ± 10.6 years) with primary insomnia (DSM-IV), who had taken BZDs nightly, for 7.1 ± 5.4 years. The control group was composed of 18 healthy individuals (mean age 37 ± 8 years). Sleep EEG of the patients was analyzed with Period Amplitude Analysis (PAA) and associated algorithms, during chronic BZD use (Night 1), and after 15 days of a valerian /placebo trial (initiated after washout of BZD, Night 2). Sleep of control subjects was monitored in parallel.

**Results:** Valerian subjects reported significantly better subjective sleep quality than placebo ones, after BZD withdrawal, despite the presence of a few side effects (sleep quality analogical-visual scale average was 7.4 ± 0.9 for valerian subjects, and 5.4 ± 0.8 for placebo subjects, p=0.000). However, some of the differences found in sleep structure between Night 1 and Night 2 in both the valerian and placebo groups may be due to the sleep recovery process after BZD washout. Example of this are: the decrease in sleep stage 2 and in sigma count; the increase in slow wave sleep (SWS), and delta count, which were found to be previously altered by BZD ingestion. There was a significant decrease in wake time after sleep onset (WASO) in valerian subjects when compared to placebo subjects; WASO values were similar to normal controls. Nonetheless, valerian-treated patients also presented longer sleep latency and increased alpha count in SWS than control subjects. They also presented a non-significant trend towards increase in SWS % and delta power during SWS. Statistical analysis were performed using MANOVA and Student-Newman-Keuls test. Some of these results can be seen in tables 1, 2, and 3. table 1: Student-Newman-Keuls test \* differ from control group, p<0.05. table 2: \* - differs from Night 1; p < 0.05, MANOVA. # - differs from placebo.

**Table 1**

Sleep parameters	Night 1 Control (N=18)	Night 2 Placebo (N=9)	Night 2 Valerian (N=10)	T and p values
Total sleep time (min)	418.0 ± 36.5	361.2 ± 59.7*	356.2 ± 67.7*	6.04; p=.006
Alpha count stage 3	1.5 ± 1.2	3.3 ± 1.6*	4.5 ± 1.8*	13.77; p<.0001
Alpha count stage 4	0.8 ± 1.0	3.0 ± 1.7*	3.8 ± 1.7*	17.39; p<.0001

**Table 2**

Sleep Parameter	Placebo (N = 9)		Valerian (N = 10)	
	Night 1 baseline	Night 2 after treatment	Night 1 baseline	Night 2 after treatment
WASO (%)	14.6 (±10.4)	19.3 (±6.9)	16.2 (±7.8)	12.5 (±6.4)#
Stage 3 (%)	6.8 (±6.0)	10.2 (±5.5)*	8.4 (±5.2)	14.3 (±7.0)*
Stage 4 (%)	5.5 (±5.6)	8.0 (±7.2)*	3.3 (±4.8)	9.5 (±7.2)*

**Conclusions:** The decrease in WASO may be associated with the mild sedative effect of valerian, and appeared to be the major contributor to subjective sleep quality improvement found after 2-week of treatment in insomniacs who had withdrawn from BDZs. Despite subjective improvement, sleep data showed that valerian did not produce faster sleep onset; the increase in alpha count compared with normal controls may point to residual hyperarousability, which is known to play a role in insomnia. Nonetheless, we lack data on the extent to which a sedative drug can improve alpha sleep EEG. Thus, the authors suggest that valerian had a positive effect on withdrawal from BDZ use.

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**688.M**

**COMPLEX NOCTURNAL VISUAL HALLUCINATIONS**

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**Introduction:** Hypnopompic hallucinations are brief episodes of dream-like imagery occurring just after waking. Although long associated with narcolepsy, they also occur commonly in normal individuals and are generally short-lived and benign. A far less common variant, not described in the International Classification of Sleep Disorders, is that of prolonged episodes of complex, vivid, visual hallucinations after waking during the night. [1] The aim of the study was to delineate the clinical features and causes of this syndrome. We hypothesized that we would identify a common clinical picture with diverse etiologies.

**Methods:** Ten patients seen at the Mayo Sleep Disorders Center between 1997 and 2001 with complex visual hallucinations on waking during the night were identified. Demographic, clinical and etiologic factors were analyzed.

**Results:** Nine of ten patients were female. Ages of onset of symptoms ranged from 5-80 years. Hallucinations had been present 6 months to 19 years at presentation. All patients saw vivid, detailed, relatively immobile images of people or animals on waking at various times during the night. The images were silent, although two patients experienced unrelated non-verbal auditory hallucinations on waking. In only two patients did the hallucinations appear to have arisen from preceding dreams. Episodes lasted between a minute and an hour and occurred between twice a week and several times a night. Hallucinations disappeared if the lights were switched on. At least initially, patients had reduced insight into their unreality and the events were associated with considerable anxiety. One patient experienced several injuries jumping out of bed in response to the images. Other phenomena noted included sleep walking (2 patients), somniloquy (2), REM sleep behavior disorder (1), sleep paralysis (1) and lucid dreaming (1). Five patients underwent polysomnograms but events were recorded

in only one, arising out of alpha rhythm from stages 2 and 3 NREM sleep. EEG recordings in seven patients showed no epileptiform activity. Diverse associated conditions were identified: idiopathic hypersomnia (one patient), beta blocker use (3), Lewy body dementia (1), brainstem ischemic changes and visual loss from macular degeneration (1), and anxiety disorder (3). In one patient the hallucinations appeared to be a lifelong idiopathic parasomnia. No other symptoms to suggest psychoses were present.

**Conclusions:** The clinical features were very similar, despite different etiologies, suggesting a shared pathogenic mechanism. The syndrome appears to be far commoner in women. The hallucinations are vivid and detailed images of people and animals, typically lasting many minutes, and disappearing with increased room illumination. Other parasomnias may coexist. They are similar to hallucinations described during wakefulness in patients with visual loss (Charles Bonnet hallucinations) or with diencephalic-mesencephalic pathology (peduncular hallucinations). [2] A common factor may be reduced afferent input into the visual association areas at night. In older patients, Lewy body disease should be considered and at all ages the effects of medications.

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## 689.M

### CLINICAL CHARACTERISTICS OF THE NOCTURNAL SLEEP-RELATED EATING SYNDROME

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**Introduction:** Nocturnal sleep-related eating syndrome (NES) is a relatively uncommon, poorly defined entity. There are few reports in literature, with a limited number of patients (1,2). Clinical features include: onset in early adulthood, nocturnal eating, including binges, occurring during partial arousals or full awakenings from sleep, variable morning recall, daytime symptoms of morning anorexia, abdominal distention and weight gain (1,2). The characteristics overlap with another similar entity, the night eating syndrome that consists of nocturnal hyperphagia, insomnia and daytime anorexia. We report our experience with NES, and compare the clinical profiles of our patients with those reported in previous series.

**Methods:** We reviewed the records for a 5 year period from '96 to '01 of patients diagnosed to have NES at Winthrop University Hospital Sleep Disorders Center. Of these patients, 7/9 (78%) patients had overnight polysomnography with seizure montages. We analyzed the demographic data, clinical presentation and sleep indices for these patients.

**Results:** There were 9 patients diagnosed to have NES in the study period, with 66% females and 33% males. The age distribution was 25-54 years (mean: 41.4 yrs) with BMI 21.6-35.5 kg/m<sup>2</sup> (mean: 27.7). The duration of complaints prior to presentation had been from 1 year to 29 years (mean 13.3 yrs); the number of episodes of eating at night ranged from 2-

5 (mean 3.5; associated weight gain ranged from 0-40 lbs (mean: 20 lbs). The most common presentations were nocturnal awakenings with eating (78%) and sleep initiation or maintenance insomnia associated with eating episodes (22%). None of the patients described daytime anorexia/bulimia. The type of food ingested at night, similar to previous reports (2) was variously described as "things I would not eat in the daytime", "high calorie" and "junk and bizarre food". Interestingly, 1 patient reported episodes of nighttime binge eating, 2 reported smoking at night with burn marks on the clothes and 1 described eating dishwashing fluid, detergent, bleach and frozen food. Recall for the episodes was present in 22%, absent in 33% and mixed in 44% patients. History of sleep disorders in the past included enuresis in 22%, past on ongoing sleep walking (unassociated with eating) in 66%, sleep talking in 22%, bruxism in 22% and narcolepsy in 11% patients. In addition, 70% patients had associated mild OSA on polysomnography. 2 patients reported a perception (unjustified) of being fat, while 1 reported the onset of symptoms in pregnancy. 33% patients said that they would not indulge in these episodes in unfamiliar surroundings. 1 patient had several members of the family (mother/siblings/son) with NES. 33% of patients had a diagnosis of depression and 22% gave a history of childhood physical or sexual abuse. Salient polysomnographic features included: sleep latency of 1.5 to 40 minutes (mean: 16.3), sleep efficiency of 65-94% (mean: 78.5), % REM sleep 13-22% (mean: 18.6), RDI 0.6-19.7 (mean: 9.1), with Epworth Sleepiness Scores ranging from 0-18 (mean: 10). There were no seizures documented in any of the patients and only one patient had 2 episodes of snacking when awake during the study.

**Conclusions:** The study revealed several interesting aspects of the NED. The demographic characteristics, including sex and age distribution were similar to previously described reports (1,2). Clinical features consistent with past reports included poor recall, unusual food combinations and significant incidence of somnambulism (1,2). Distinctive features in this group of patients included a history of enuresis in 22%, history of childhood sexual abuse in 22%, and coexistent nocturnal smoking behavior in 22% patients. The lack of witnessed eating episodes during polysomnography, and absence of this behavior in unfamiliar environments in a significant number of patients is noteworthy, and suggests a degree of volitional control over the abnormal behavior. The incidence of mild OSA (70%) in our patients is striking and suggests the need for further studies to explore both the nature of the relationship between sleep-disordered breathing and the NED and the possible therapeutic implications of this relationship.

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## 690.M

## VALIDATION OF A QUESTIONNAIRE FOR THE DIAGNOSIS OF REM SLEEP BEHAVIOR DISORDER

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**Introduction:** Rapid eye movement sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during rapid eye movement (REM) sleep with prominent motor activity and dreaming. Recent data indicates that when associated with parkinsonism and/or cognitive impairment, RBD may reflect an underlying synucleinopathy (1), suggesting that RBD associated with neurodegenerative disease has significant clinical diagnostic and pathophysiologic implications. RBD can precede parkinsonism or cognitive impairment by years or decades, suggesting that RBD may be the earliest manifestation of an evolving neurodegenerative disorder. Confirmation of RBD requires polysomnographic (PSG) evidence of REM sleep without atonia. Due to the expense and technical/staffing issues related to performing PSGs, a screening measure for the diagnosis of RBD would be desirable for clinical and research purposes.

**Methods:** We had previously developed the Mayo Sleep Questionnaire (MSQ) to screen for the presence of RBD and other sleep disorders. We assessed the validity of the MSQ by comparing responses of patients and their bedpartners with findings on PSG; REM sleep without atonia on PSG was considered the gold standard for the diagnosis of RBD.

**Results:** Among consecutive patients referred to the Sleep Disorders Center at Mayo Clinic Rochester and evaluated by one of two neurologists over a one month period, 48 had symptomatology warranting PSG. All patients and 24 of their bedpartners completed the MSQ prior to PSG. The patients' responses to two questions yielded a sensitivity (SN) of 100% and specificity (SP) of 86% for the diagnosis of RBD. The bedpartners' responses to two questions yielded a SN of 100% and SP of 83%. A combination of responses by patients and bedpartners yielded a SN of 100% and SP of 77%. False positive responses tended to occur in patients with obstructive sleep apnea and/or narcolepsy.

**Conclusions:** These pilot data suggest that among patients referred to a sleep disorders center, responses by patients or their bedpartners on the MSQ have high sensitivity and adequate specificity for the diagnosis of RBD, particularly in patients without obstructive sleep apnea or narcolepsy.

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## 691.M

## THE USE OF IMAGERY REHEARSAL FOR NIGHTMARES IN CHILDREN

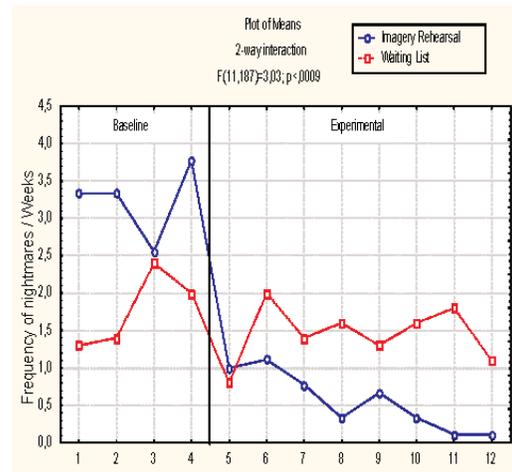
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**Introduction:** The treatment of chronic nightmares requiring the person to modify the nightmare and mentally rehearse the modified version has proven to be quite effective with PTSD victims (Krakow & al., 1993). A similar approach has been proposed for children with nightmares. Specifically it requires following a "Four R" process: reassure, rescript, rehearse, resolution (Siegel, 1998). While it seems that this method would work with children, no controlled study with children has been carried out so far. We have started a study to assess its efficacy in reducing nightmares by comparing it to a waiting list group.

**Methods:** Nineteen children with moderate to severe nightmares (1 or more/week) but without PTSD and aged between 9 to 11 (M=10.26) have so far participated. They attended a first individual meeting to fill in questionnaires. They then kept a daily journal for 4 weeks noting the quantity of dreams and nightmares and their level of distress. From then on, they were divided randomly into two groups: imagery rehearsal treatment, or waiting list. The treated group (N=9) were asked to record on tape their nightmares each morning and rate their level of distress in a journal for a period of 8 weeks. Whenever they recorded a nightmare in the morning, they were trained for and asked to apply the following treatment: "1) Before going to sleep, lie down on the bed, relax and decide a way to change, in any way you want, the nightmare of the morning so that it is not a nightmare anymore; 2) Then, with your eyes close, imagine and tell yourself for about 10 minutes a story which is the modified version of the nightmare. Make sure you see the images in your head." The waiting list group (N=10) were asked to note in a journal the number of nightmares and dreams they had during this period. Following this 8 week period they all filled in the above questionnaires again. Finally, the waiting list groups received the treatment (follow-up currently ongoing).

Figure 1



**Results:** A repeated measure ANOVA was performed on the mean frequency of nightmares per month. There was a main effect of passage of time ( $F(11,187)=4.19$ ,  $p<0.00002$ ) and, as Figure 1 illustrates, a significant interaction ( $F(11,187)=3.03$ ,  $p<0.001$ ). Unidimensional analyses revealed that the waiting list group did not change significantly over time, while the treated group showed a significant decrease between week 1 and 12, 2 and 12 and 4 and 12.

**Conclusions:** These preliminary results suggest that the imagery rehearsal treatment is effective with children as young as this age group to reduce the frequency of nightmares. We are currently conducting a follow-up of these children to study the long-term efficacy of the treatment.

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## 692.N

### AUGMENTATION OF THE RESTLESS LEGS SYNDROME IN RELATION TO LONG-TERM TREATMENT WITH PRAMIPEXOLE AND CABERGOLINE

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**Introduction:** Dopaminergic agents are currently considered the most successful drugs for the treatment of Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD). Augmentation has been reported as major adverse effect of treatment with l-dopa. Pergolide (a D1/D2 receptor agonist, half life 7-16 hours) has been proposed for patients who experienced an augmentation of symptoms with l-dopa; however the same phenomenon has been observed in more than 25% of RLS patients treated with pergolide (1). In sixty RLS patients treated by pramipexole (D3 agonist, half life 6 hours) for at least 6 months we observed an augmentation in only 5 (8.3%) subjects (2). In the present study we evaluated a larger group of RLS patients treated with pramipexole, as well as a group of patients treated with cabergoline (D2 agonist, half-life > 65 hours), in order to: a) eventually confirm our previous data on pramipexole; b) evaluate the relationship among augmentation, elimination half-life and specific receptor activity of different dopaminergic agents.

**Methods:** In our open-label clinical series we examined the occurrence of RLS augmentation in RLS patients treated with pramipexole or cabergoline for at least 6 months. RLS diagnosis was made according to ICSD criteria and nocturnal PSG showed PLMS in all the patients.

**Results:** Pramipexole group: One hundred-two patients were included in the study (mean age= 56 yrs, range 29-90 yrs; mean RLS duration= 26 yrs, range 0.5-60 yrs; primary form= 78; secondary form= 24). Seventy-two patients have been pre-

viously treated with other medications (clonazepam in 39, gabapentin in 23, l-dopa in 18, pergolide in 17, others compounds in 33). Pramipexole dose was variable: 0.25 mg in 68 patients, 0.5 mg in 18 patients, 1.0 mg in 16 patients (single dose 1h before bedtime for all patients). RLS augmentation has been observed in 9 patients (mean age= 59, range 49-75 yrs; mean RLS duration= 23 yrs, range 11-30; primary form= 4; secondary form= 5; pramipexole dose= 0.25 mg in 6 patients, 0.5 mg in 2 cases and 1.0 mg in 1 case). Augmentation has been observed after 4 weeks in 2 case, after 8 weeks in 4 cases, after 12 weeks in 2 cases and after 15 weeks in 1 case. Cabergoline group: Sixteen patients were included in the study (mean age= 58 yrs, range 38-73; mean RLS duration= 18 yrs, range 2-53 yrs; primary form= 16). Cabergoline dose was variable: 0.5 mg in 3 patients, 1 mg in 12 cases and 2 mg in 1 case (single dose 2 h prior to bedtime for all patients). Four patients have been previously treated with clonazepam, 2 with pergolide, 1 with pramipexole, 1 with opioids. None of the patients presented augmentation.

**Conclusions:** Our study confirms that RLS augmentation occur in a very low percentage of patients treated with pramipexole (8%). This complication seems to be unrelated to the dose of medication and occurs within the first 4 months after initiation of treatment. Augmentation with pramipexole seems to be more frequent in secondary forms of RLS respect to idiopathic ones ( $p=.03$ , Fisher test), confirming our previous results (2). We did not observe augmentation in our patients treated by cabergoline and this suggests the use of this compound in patients who develop augmentation under other dopaminergic therapies, as recently indicated by Stiasny et al (3). Globally, our results suggest that the half-life elimination of the dopaminergic compound does not represent the crucial aspect for developing the augmentation phenomenon in RLS.

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## 693.N

### INFLUENCE OF THE TIME OF DAY IN THE CLINICAL RESPONSE TO L-DOPA IN PATIENTS WITH RESTLESS LEGS SYNDROME: PRELIMINARY RESULTS

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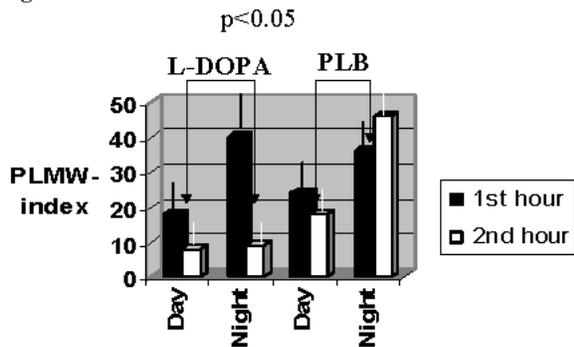
**Introduction:** A central dopaminergic dysfunction is believed to play a keyrole in the pathogenesis of Idiopathic Restless Legs Syndrome (RLS) 1. The severity of RLS displays a circadian pattern, with an increase of both motor and sensory symptoms in the evening and at night 2. A circadian fluctuation in dopaminergic activity has been postulated to play a role

in modulating the severity of symptoms, as a recent study has found circadian variations in neuroendocrine response to L-DOPA3. Objective: The objective of this study was to investigate circadian changes in clinical response to L-DOPA in patients with RLS.

**Methods:** 6 consecutive patients diagnosed with Restless legs Syndrome according to the criteria of the IRLSSG were included in the study. Diagnostic procedures included medical history, physical and neurological exam, blood count, biochemistry, iron plasma levels and polysomnography. All patients had been diagnosed recently and had never received dopaminergic treatment. Following randomization for the order of treatment (night first versus morning first), patients underwent on two occasions the suggested immobilization test (SIT). During each SIT, patients were asked to remain quietly in bed, and only move their limbs if they needed to alleviate their symptoms. The procedure was performed for 2 hours starting at 22:00 and was repeated again the next morning at 10:00 hr. One hour after the beginning of each SIT, 100 mg of L-DOPA/25 mg carbidopa (or placebo) were administered under double blind conditions. During the morning SIT, the alternative medication was administered. The same procedure was repeated a week later with a reversed order of treatments.

**Results:** Preliminary results on 6 patients are shown on the attached Figure:

Figure 1



**Conclusions:** Our results show an increased therapeutic efficacy when L-DOPA is administered at night (compared to the morning use). The circadian variations in therapeutic efficacy could be related to an increased sensitivity of dopaminergic receptors at night, in line with the previously reported changes across the day in neuroendocrine response to L-DOPA3. These results are preliminary as a higher number of patients is needed to perform a correlation analysis with the severity of symptoms at baseline.

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L-dopa in patients with restless legs syndrome: a pilot study. *Sleep* 2001;24:A2(Abtract)

**694.N**

**POLYSOMNOGRAPHIC AND HEALTH OUTCOMES IN AN EPIDEMIOLOGICAL SAMPLE OF INDIVIDUALS WITH RESTLESS LEG SYMPTOMS**

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**Introduction:** The few population-based studies on restless legs syndrome (RLS) have estimated the prevalence of this disorder to be between 6-10% of the general population (1,2). There are currently no polysomnographic data available in epidemiological RLS samples. As part of a larger investigation of daytime sleepiness in the general population, the present study assessed sleep disturbance and its relationship to health-related morbidity in individuals complaining of restless legs.

**Methods:** Thus far, 1648 individuals have been assessed for "restless" or "twitching" feelings in the legs and for Epworth sleepiness scores (ESS) as part of a larger random-digit dialing phone survey in Metropolitan Detroit. Data were collected on nocturnal sleep (PSG), daytime sleepiness (Multiple Sleep Latency Test), and physical/mental health status (SF-36, Beck Depression Inventory) for N=256 of the larger sample. ANOVA and follow up t-tests were used to compare daytime sleepiness in individuals who reported never having RLS symptoms to those reporting "rarely", "sometimes", or "often". The prevalence of periodic limb movements (>10/hr sleep, PLMs) and disturbed sleep (Sleep efficiency [SE] <85%) was compared in the "often" and "never" RLS laboratory samples using Chi-Square and two-factor ANOVA.

Table 1

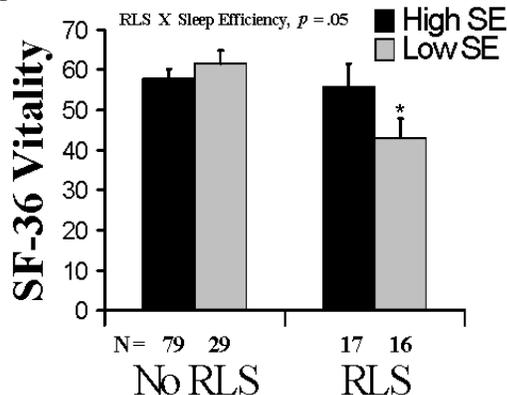
Outcome Variables	RLS- (n=112)	RLS+ (n = 32)
Sleep Efficiency	87.47 ± 9.12	82.35 ± 14.23*
Stage 1%	12.69 ± 10.33	12.02 ± 7.38
Latency to Pers. Sleep	21.35 ± 28.38	23.98 ± 22.07
PLM index	2.86 ± 9.20	6.99 ± 10.53*
MSLT	11.35 ± 4.54	10.74 ± 5.74
BDI-II	5.91 ± 6.25	12.50 ± 7.65*
SF-36 Vitality	58.7 ± 20.53	49.7 ± 22.01*
SF-36 General Health	75.89 ± 19.33	60.36 ± 26.24*
SF-36 Mental Health	65.28 ± 14.60	55.56 ± 14.59*
Age	38.14 ± 13.04	42.69 ± 11.71
Gender	49F, 63M	15F, 17M
Epworth (n = 841, 189)	7.02 ± 4.1	9.3 ± 5.1*

Values are means ± standard deviation, \* p < .05

**Results:** One-hundred and ninety (11.5%) individuals were RLS+. Individuals who were RLS+ had significantly greater ESS daytime sleepiness [F (1,1644) = 41.48, p < .001]. However, MSLTs were similar F (3,247) = .95, p = .42. On nocturnal PSGs, RLS+ participants had lower sleep efficiency (82 vs 88%), t(142) = 2.5, p = .02, and a greater PLM index (7.0 vs 2.9), [t(142) = -2.9, p = .02]. In addition, depression scores and health outcome measures were significantly worse in RLS+ individuals (Table). The prevalence of PLMs (10/hr sleep) (27.3% vs 6.3%) and disturbed sleep (48.5% vs 25.9%) was

greater in the RLS+ compared to RLS- groups, respectively ( $p < .05$ ). Further analyses were performed on the health-related impact of sleep disturbance in RLS. ANOVA revealed a significant interaction, RLS X Sleep Efficiency, for the SF-36  $F(1, 137) = 3.77, p = .05$ , and BDI  $F(1, 139) = 4.62, p = .03$ , indicating that RLS+ individuals with disturbed sleep had significantly higher depression scores and lower SF36 Vitality scores than RLS+ individuals without disturbed sleep. Thus, RLS+ individuals with sleep efficiencies  $> 85\%$  were similar to RLS- individuals (Figure 1). In contrast, + and - PLMs were not related to morbidity in RLS.

Figure 1



**Conclusions:** RLS prevalence (11.5%) was similar to previous population-based samples. While individuals with RLS symptoms reported greater daytime sleepiness, they had a similar physiological sleep tendency compared to individuals without RLS symptoms. RLS+ individuals with poor sleep had significantly poorer health-related outcomes (SF-36) and greater depression than the RLS+ individuals with “good sleep”, suggesting that poor sleep is a primary mediator of morbidity in this population.

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### 695.N

#### CABERGOLINE IN RLS - A DOUBLE-BLIND PLACEBO-CONTROLLED MULTICENTER DOSE-FINDING TRIAL

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**Introduction:** The short duration of action and the development of augmentation or time-shifting of symptoms after starting therapy may limit the clinical use of levodopa in RLS. Dopamine agonists (DAs) proved also to be effective but even under DAs augmentation occurs. Different trials suggest an

inverse correlation between elimination half-life and incidence of augmentation. Objective: To assess the efficacy and the minimum effective dose of cabergoline (CAB) (plasma half-life  $> 65$  hours) in RLS patients on the basis of a double-blind randomized placebo-controlled multicenter study of parallel group design.

**Methods:** 86 patients with moderate to severe RLS were stratified into four treatment groups receiving a target dose of 0mg (placebo), 0.5mg, 1mg and 2mg CAB once in the evening. Primary endpoint was the reduction of RLS severity at night between baseline and week 5 (scale 0 to 10).

**Results:** Demographic characteristics were comparable in all groups: mean age:  $56 \pm 9.8$  yrs., m:f-ratio: 25:59, duration of RLS:  $220.4 \pm 158.2$  months, previous LD/DA use: 60.7/44%, RLS severity at night:  $6.5 \pm 1.9$ . All three CAB treatment groups showed a clinical improvement of 1) the RLS severity at night compared with baseline (0.5mg:  $6.7 \pm 1.8$  (BL) vs.  $2.3 \pm 2.8$  (week 5); 1mg:  $6.0 \pm 1.3$  vs.  $1.9 \pm 2.5$ ; 2mg:  $7.0 \pm 2.3$  vs.  $2.2 \pm 3.2$ ), in contrast to placebo ( $6.2 \pm 2.0$  vs.  $4.8 \pm 3.2$ ) and statistical comparison showed highly significant differences for all 3 CAB doses vs. placebo (0.5mg:  $p = 0.0046$ ; 1mg:  $p = 0.0085$ ; 2mg:  $p = 0.0016$ ). Similar results have been found for 2) the RLS severity before bedtime (0.5mg:  $p = 0.0426$ ; 1mg:  $p = 0.0041$ ; 2mg: 0.0137), 3) RLS severity at day (0.5mg:  $p = 0.3512$ ; 1mg:  $p = 0.0126$ ; 2mg: 0.0021), 4) overall RLS severity in the IRLSSG rating scale (0.5mg:  $p = 0.0013$ ; 1mg:  $p = 0.0017$ ; 2mg:  $p = 0.0032$ ) and 5) satisfaction with sleep (0.5mg:  $p = 0.0449$ ; 1mg:  $p = 0.0561$ ; 2mg:  $p = 0.0038$ ). The number of AEs with possible relationship to the study drug were 0mg: 54.5%, 0.5mg: 66.7%, 1mg: 55% and 2mg: 59.1%. No serious AE occurred.

**Conclusions:** Cabergoline is a highly efficacious and well tolerated option for the treatment of RLS patients. While even low doses of 0.5mg CAB given once daily in the evening led to a significant improvement of RLS symptoms at night, a single evening dose of 2mg covers RLS symptoms over the whole 24h period.

### 696.N

#### LACK OF DOSE-RELATED EFFECTS OF SODIUM OXYBATE ON PERIODIC LEG MOVEMENTS

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**Introduction:** In patients diagnosed with Periodic Leg Movements Disorder (PLMD), sodium oxybate had been reported to induce progressive increase of periodic leg movements across the night so that the PLM index met the diagnostic criteria for pathology. In contrast, sodium oxybate did not increase the PLM index at any time during the night for those patients previously diagnosed with PLMD 1. In an effort to further develop an understanding of the effect of sodium oxybate on periodic leg movements, an analysis was performed on PSG data generated over 10 weeks of sodium oxybate exposure at increasing doses.

**Methods:** Multiple overnight PSGs were performed during an

open-label clinical trial of the sodium oxybate and the potential for induction of leg movements in narcoleptic patients was assessed. Patients with severe sleep disruption due to restless leg syndrome were excluded from the trial. The trial included 21 evaluable patients with narcolepsy who were treated with increasing dosages from 4.5 to 9.0 g/d sodium oxybate. PSG assessments included the first night dose of 4.5 g/d, after 4 weeks of 4.5 g/d, after 2 weeks of 6 g/d, after 2 weeks of 7.5 g/d, and after 2 weeks of 9.0 g/d. The trial included a 2-week baseline period, prior to sodium oxybate treatment, during which the same measurements were taken. The dosing was split equally between bedtime and 4 hours later. Leg movements were recorded as anterior tibialis EMG recordings, and the following indices were calculated for each half of the night: (1) the total number of periodic leg movements (PLMs), (2) the total number of PLMs accompanied by arousals, and (3) a periodic leg movement index. PSG data, collected from four investigative sites, were centrally scored.

**Results:** Sodium oxybate administration at the doses used 4.5-9g/night) did not cause an increase of PLMs. There was no evidence of a dose response, and no differences between the first and second half of the night. Of interest is a trend for decreased number of PLMs accompanied by arousals as a function of increasing doses. After 4 weeks of treatment with 4.5 g/night (Visit 3), two patients exhibited an elevated number of PLMs. At baseline, as throughout the study, there was a sizeable portion of patients (ca. 40%) who exhibited elevated levels of PLMs that would be diagnostic for RLS (>5 events per hour).

**Conclusions:** In contrast to previously reported increased PLMs in response to sodium oxybate, these data indicate that narcoleptic patients treated with sodium oxybate in dosages up to 9.0 g/d do not exhibit increased PLMs whether or not they had a baseline PLMs that could be considered pathological. A decrease in arousals following PLMs is suggested.

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### 697.N

#### PROFILE OF PATIENTS PRESENTING WITH PERIODIC LIMB MOVEMENTS SYMPTOMS

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(1) Cleveland Clinic Foundation

**Introduction:** Periodic limb movement disorder (PLMD), periodic limb movement in sleep (PLMS) and restless legs syndrome (RLS) represent an array of disorders that disrupt sleep architecture perhaps leading to symptoms of daytime somnolence, resulting in an adverse impact on quality of life. The prevalence of these underdiagnosed disorders ranges from 1-15% with the true value likely approximately 5%. A PLM is scored when there is a sequence of at least 4 muscle contractions recorded, each lasting .5 to 5 seconds and recurring at

intervals of 5 to 90 seconds based upon Coleman's definition as revised by the American Sleep Disorders Association (ASDA). We have previously reported the similarity in daytime hypersomnolence, sleep fragmentation and insomnia in those patients with a solely elevated PLM-index (PLM-I) without a concomitant elevated PLM-arousal index (PLM-AI) suggesting comparable treatment for the solely elevated PLM-I group. The incidence of PLMS per polysomnogram (PSG) as well as the relationship of Epworth Sleepiness Scale (ESS) scores and sleep-disordered breathing (SDB) in those patients that present with nocturnal leg symptoms has not yet been established.

**Methods:** A retrospective review was conducted of the PSG and questionnaires for those patients from 4/98-11/01 who presented with a primary complaint of nocturnal leg symptoms including leg jerks, thrashing of the legs and irresistible urge to move legs. Special attention was directed to the PLM-I, PLM-AI, ESS and presence of SDB.

**Results:** Only 27% (12 of 44) patients had an elevated PLM-AI. Of these patients, the means and ranges for the PLM-AI, PLM-I and ESS score were 16 (range: 8-26), 61 (range: 16-167), and 13.0 (range: 0-15) respectively with a 33% (4 of 12) incidence of SDB. 34% (15 of 44) had a solely elevated PLM-I with a mean of 25.8 (range: 5-101) and mean ESS score of 10.8 as well as a 67% (10 of 15) incidence of SDB. 38% of these patients had normal PLM indices with a mean ESS score of 8.6 (range 3-15) and 35% (6 of 17) incidence of SDB.

**Conclusions:** It is interesting to note that 38% of patients presenting with primary nocturnal leg complaints have no PSG evidence supporting PLMS. Perhaps the presence is obscured due to sampling error secondary to night-to-night symptom variability. In addition, the normal, solely elevated PLM-I and elevated PLM-AI groups respectively demonstrate progressively increasing relationship with respect to mean ESS scores (8.6, 10.8, 13.0) and mean PLM-I in the latter two groups (25.8, 61.0). Contrary to the results of our previous review, this suggests that the elevated PLM-AI group has more symptoms of subjective EDS (despite less incidence of SDB as a contributor to EDS) as well as higher incidence of PLM overall in comparison to the solely elevated PLM-I group.

### 698.N

#### PERIODIC LEG MOVEMENTS DURING SLEEP IN NORMAL TEENAGERS AND YOUNG ADULTS

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**Introduction:** Several studies have shown that periodic leg movements in sleep (PLMS) increase with advancing age both in non-complaining subjects and in patients with various sleep disorders. In non-complaining subjects most studies have focused on middle-aged and elderly individuals and no study has ever looked at the prevalence of PLMS in subjects before the age of 20. In patients with sleep disorders, PLMS are best documented with the criteria for the restless legs syndrome (RLS). RLS is considered a disease of middle-aged individu-

als but recent studies reveal that in several patients, RLS starts before the age of 20. Therefore, it is important to study RLS and PLMS in teenagers. The aim of the present study is to assess the prevalence of PLMS in teenagers and to compare this prevalence to those obtained in young adults (e.g. between 20 and 30 years of age).

**Methods:** Thirty-four adolescents with the mean age of 14.9 + 0.9 years and 21 young adults (19 men and 2 women) underwent one-night polysomnographic recording. Sleep was recorded and scored according to Rechtschaffen and Kales. In addition, EMG's were recorded from right and left anterior tibialis muscles and leg movements were scored according to the method developed by Coleman. Micro-arousals were scored according to the criteria developed by the ASDA Task Force.

**Results:** Results are presented in Table 1. Compared to young adults, adolescents showed more periodic leg movements while awake (PLMW) during the night (index=73.3 + 36.5 vs 44.9 + 31.9; p=0.0006). However, there was no between-group differences for the duration of leg movements or mean duration of intervals between successive leg movements. There was no between-group difference for the mean PLMS index (4.7 vs 3.8; p=ns). However, a large number of subjects in each group had elevated PLMS index (>5) e.g. 11/34 teenagers (32%) and 6/21 in young adults (21%). On the other hand, leg movement duration and mean inter-movement intervals were similar in the two groups. Only a small proportion of leg movements in each group (11.5% for teenagers and 11.7% for young adults) were associated with EEG-defined micro-arousals.

**Table 1**  
Sleep and PLM characteristics in healthy teenagers and young adults.

	Adolescents	Young adults	p
Sleep efficiency	90.4 ± 8.5	89.7 ± 11.9	NS
Wakefulness duration	40.6 ± 37.3	51.3 ± 63.0	NS
<b>PLMW</b>			
index	73.3 ± 36.5	44.9 ± 31.9	0.006
duration	4.2 ± 0.6	4.1 ± 0.6	NS
mean interval	25.1 ± 6.2	26.3 ± 8.5	NS
<b>PLMS</b>			
index	4.7 ± 5.3	3.8 ± 5.2	NS
duration	2.5 ± 0.5	2.2 ± 0.4	NS
mean interval	33.6 ± 8.6	40.1 ± 12.1	NS
% of PLMS with MA	11.5 ± 17.1	11.7 ± 12.2	NS
PLMS index > 5	11	6	NS*

Data expressed as mean ± standard deviation  
Student-t-tests except for \* (Khi-square) (significance was set at 0.01)

**Conclusions:** These results show that the teenagers and young adults have similar prevalence and characteristics of PLMS. Data obtained in teenagers may be used as normative data for the study of teenagers affected with various sleep or behavioral disturbances. The increase in PLMW was unexpected. It may reflect a general trend towards increased motor activity in teenagers.

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**699.N**

**RESTLESS LEGS SYNDROME IN PRIMARY CARE: A VALIDATION STUDY**

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**Introduction:** The Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness of sleep disorders and to determine their prevalence within a primary care practice in Moscow, Idaho. Preliminary data gathered by our group indicate that 24.0% (504/2099) of the patients within the Moscow Clinic population responded positively for Restless Legs Syndrome (RLS) symptoms on the RLS Questionnaire (RLSQ), a standardized diagnostic questionnaire. To determine if this indication for a high prevalence of RLS was isolated to this specific population, a second primary care population was surveyed at the Stanford Family Practice in Stanford, California. The Stanford sample represents a more urban and ethnically diverse population than the Moscow population.

**Methods:** The Stanford Family Practice, an office with 11 family physicians and 3 internists, was surveyed for a four-week period beginning July 30, 2001. Each day the research assistants asked approximately 70 adult patients with scheduled appointments to enter the study. Participants completed a general sleep questionnaire, a daytime sleepiness questionnaire, and the RLSQ, all of which were utilized in the Moscow Clinic survey. Once the questionnaires were completed, the RLSQ was scored based on the four diagnostic criteria previously established by RLS experts. Each patient was assigned either an RLSQ positive or an RLSQ negative diagnosis. This report includes preliminary data on the 539 patients surveyed on-site.

**Results:** A total of 17.3% (93/539) of the patients questioned at the Stanford practice met the criteria for RLS symptoms. The mean age for the RLSQ positive patients was 42.0 ± 12.5 compared to 38.6 ± 13.0 for the RLSQ negative patients. The ancestry of the Moscow Clinic population is compared to the Stanford Family Practice population in Table 1. The prevalence of RLSQ positive patients at the Stanford Family Practice is broken down by ancestry in Table 2.

**Table 1**

	No Northern European Ancestry	Possible Northern European Ancestry	Northern European and Other Ancestry	Only Northern European Ancestry
<b>Moscow Clinic</b>	7.4%	8.8%	16.2%	67.6%
<b>Stanford Family Practice</b>	42.5%	6.6%	19.5%	31.4%

Table 2

Stanford Family Practice Ancestry	Number of RLSQ Negative Patients	Number of RLSQ Positive Patients	Percent of RLSQ Positive Patients
Northern European Ancestry Only	115	32	21.8%
Northern European and Other Ancestry	72	19	20.9%
Possible Northern European Ancestry	25	6	19.4%
No Northern European Ancestry	176	23	11.6%
No data on Ancestry	58	13	18.3%
TOTAL	446	93	17.3%

**Conclusions:** Our preliminary results reveal that 17.3% of the Stanford primary care population was positive for RLS symptoms based on the RLSQ. This is slightly less than the prevalence we found in Moscow (24.0%), yet still higher than the 5-15% prevalence reported in the literature using similar or even less specific questionnaires. This increased prevalence could be isolated to primary care or could be due in part to the fact that the frequency of symptoms was not factored into the RLSQ diagnoses. Prior research found that RLS is more prevalent in individuals of Northern European ancestry; therefore, the increased proportion of patients with Northern European ancestry in Moscow could explain the difference between our two populations. Additionally, we found that RLSQ positive patients were significantly older than the RLSQ negative patients ( $t = -3.05, p < .001$ ). This finding is consistent with our data in Moscow. We are currently mailing the questionnaires to all patients who were not already approached during the four-week Stanford study.

Research supported by the Pharmacia Corporation.

700.N

TREATMENT OF RLS IN PRIMARY CARE: QUESTIONNAIRE-BASED MEASURES

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**Introduction:** The Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness of sleep disorders and to determine their prevalence within a primary care practice in Moscow, Idaho. Data gathered by our group documented that 29.3% (368/1,254) of the patients within the Moscow Clinic population had symptoms of Restless Legs Syndrome (RLS) (1). These preliminary RLS diagnoses were based on only a few RLS-specific questions. To solidify the diagnoses for this group of identified patients, the RLS Project was implemented in 1999. Detailed RLS questionnaires from this study preliminarily revealed that 24.0% (504/2099) of patients were positive for RLS symptoms.

**Methods:** The three participating primary care physicians

were trained by an expert to diagnose and treat RLS. Each patient seen at the clinic in a one-year period was asked to complete the ten-question Restless Legs Syndrome Questionnaire (RLSQ), a validated diagnostic questionnaire. After scoring the questionnaire as either positive or negative for RLS symptoms, all positive patients and a randomly selected number of negative patients were asked to complete additional patient questionnaires. These patients were also subjected to a structured diagnostic interview (SDI) performed by their primary care physician. If the physician diagnosed the patient with RLS, treatment was considered. If the physician felt the symptoms were subclinical, if treatment was not addressed, or if the patient refused treatment, the patient was placed in the no treatment group. Patients who were prescribed a pharmacologic agent or treated with iron were placed in the treatment group. An RLS expert independently reviewed the medical charts and assigned either an RLS negative or RLS positive diagnosis to each patient with a SDI.

**Results:** The SDI was performed on 278 patients and 176 of these patients completed additional questionnaires. Three groups were formed: 1) RLSQ negative patients with no treatment, 2) RLSQ positive patients with no treatment, and 3) RLSQ positive patients with treatment. The mean scores on questionnaire-based measures are described for each group in Table 1. Preliminary follow-up data after one year has been compiled on 71 of the 176 patients who completed all components. The follow-up data reveals that 45% (9/20) of the patients who were originally treated for RLS are still being treated after one year.

Table 1

	Mean (SD) Epworth Score	Mean (SD) BDI- II Score	Mean (SD) Quality of Sleep Score	Mean (SD) Ferritin level (ng/ml)
RLSQ Negative, No Treatment	6.3 (±3.7) [72]	7.3 (±7.3) [68]	1.9 (±0.8) [70]	112.7 (±91.4) [79]
RLSQ Positive, No Treatment	7.3 (±5.0) [46]	8.7 (±7.4) [46]	2.3 (±0.7) [43]	148.7 (±139.6) [93]
RLSQ Positive, Treatment	8.7 (±4.7) [49]	11.9 (±8.9) [50]	2.6 (±0.8) [48]	83.7 (±89.9) [63]

Numbers in brackets indicate number of subjects

**Conclusions:** Our results indicate that patients who were treated for RLS scored differently on the questionnaire-based measures than the patients who were not treated. Treated RLS patients scored significantly higher ( $p < .05$ ) on the Epworth, the Beck Depression Inventory-II, and rated their sleep more poorly than untreated RLS patients as well as patients who did not have RLS. The ferritin levels for treated patients were significantly lower ( $p < .05$ ) than untreated patients and the patients without RLS. These findings suggest that the patients who are clinically prescribed pharmacotherapy for RLS have adverse symptoms from the RLS including daytime fatigue and an increase in the symptoms of depression. Our prelimi-

nary follow-up data reveals that almost half of the patients who were treated for RLS are still continuing their treatment after one year. We are continuing to collect follow-up data on this population.

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## 701.O

### DAYTIME SLEEPINESS AND SLEEP ATTACKS IN PARKINSON DISEASE: A CLINICAL AND POLYSOMNOGRAPHIC STUDY

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**Introduction:** Excessive Daytime Sleepiness is reported to be common in Parkinson Disease(1).Some reports support the occurrence of irresistible, sudden sleep onset during daytime (so called "sleep attack")in PD patients,particularly in those who are assuming dopamine agonists. However the real incidence and ultimate significance of sleep attacks in PD remain controversial.This study is aimed at evaluating the pattern of daytime sleepiness by means of continuous 24 hours Ambulatory Polysomnography (A-PSG) in PD patients unselected for sleep disorders.

**Methods:** Thirty-one subjects (18 males; mean age 69 years, range:61-82; Mean Body Mass Index 24.7 Kg/mq, range: 16.8-34.8) with a definite diagnosis of PD were recruited at the PD Unit of the institute of Neurology "C. Mondino". Sleep studies were done at the Sleep Centre of the Institute.Daytime Sleepiness was assessed by clinical structured interview and Epworth Sleepiness scale (ESS).Subsequently each patient was prepared for a 24 hours A-PSG which took place at home.

**Results:** Twenty-five out of thirty-one patients reported daytime sleepiness.Twelve patients (group A) reported mild to moderate daytime sleepiness without falling asleep except for voluntary naps during relax times.Thirteen patients (group B) reported daytime sleepiness and urge to sleep.In eight of these patients some episodes of daytime falling asleep appear to share the features of the so called "sleep attacks" as they occurred suddenly against a background of wakefulness,without prior feeling of sleepiness nor any other heralding symptoms.ESS scores were significantly higher in group B than in group A of patients ( 12.0 sd 5.2 versus 7.5 sd 4.5; p< 0.05 at Kruskal Wallis Test).At A-PSG transient drowsiness and voluntary naps were recorded during daytime hours in more than 60% of the patients of the group B and in less than 50% of the others.In two patients belonging to group B, episodes of sudden falling asleep with fast transition to slow waves sleep, but not REM sleep, were recorded.The episodes were of short duration and they clearly occurred against a background of normal EEG activity of wakefulness.In no case the patients signaled the episodes in the sleep-log or by means of the

event-marker.Total Nocturnal Sleep Time is higher in patients of group A than in those of group B(366 minutes sd 54 versus 284 minutes sd 104 ) even though the difference is not statistically significant.As far as the demographic and illness parameters were compared between the two groups of patients, the patients of group B resulted to be characterized by prevalence of male sex (77% versus 50%), higher prevalence of snoring (92% versus 53%), longer illness duration (11 years sd 3.2 versus 6.6 years sd 1.9; p< 0.05 at Kruskal Wallis test) , higher daily dose of L-Dopa and Dopaminergic agonists (700 mg sd 221 versus 690 mg sd 318 and 510 mg sd 350 versus 362 mg sd 215 , respectively).

**Conclusions:** Our data confirm that daytime sleepiness is very common in PD patients.Urge to sleep in daytime hours is not infrequently reported but true sleep attacks are a rare condition which can be better defined at A-PSG recordings.Male sex, snoring, long illness duration and higher doses of L-Dopa or dopaminergic agonists, appear to be the main risk factors for developing severe daytime sleepiness in PD patients.

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## 702.O

### POLYSOMNOGRAPHIC PATTERNS IN ANGELMAN SYNDROME

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**Introduction:** Angelman syndrome (AS) is characterized by developmental and severe language delay, movements disorders, epilepsy, hyperactivity and attention disorders, happy mood and typical awake EEG patterns (4-6 Hz rhythms, prolonged 2-3 Hz bouffees, high amplitude 3-4 Hz spike-waves). AS is linked to a deletion of chromosome 15q11-13 of maternal origin in 75% of cases (1,2). Although AS patients showed a high prevalence of sleep disorders (42%)(3), no systematic evaluation of sleep architecture and of modification of EEG patterns during sleep have been carried out. The aim of this study was to investigate the sleep organization and to characterize the evolution of EEG patterns during sleep in patients with AS.

**Methods:** Ten patients (4 M, 6 F, mean age 7,8 yrs, range 3-12 yrs) with AS confirmed by DNA molecular analysis in 8 subjects and clinically suspected and negative to methylation test in 2, underwent a nocturnal polysomnography after one adaptation night. Sleep staging was based on R&K criteria. Data were compared with polysomnographic data of an healthy age-matched control group.

**Results:** Sleep architecture was preserved, with regular alternation of NREM and REM stages. We found a persistence of slow-waves rhythms specific to AS in all sleep stages; REM and SWS sleep were significantly reduced; spindles and rapid eye movements were poorly represented. The typical EEG patterns of AS observable in awake EEG were also represented during sleep:- 5-6 Hz rhythms generalized or prevalent in pos-

terior regions, present in all sleep stages- 2-3 Hz rhythms poorly represented in Wake stage, but present all over the sleep stage, especially in brief sequences (<10 sec)- 3-4 Hz rhythms were less recognizable during sleep; they were evident only in the younger child, all over the sleep stages.- epileptiform spikes, polyspykes and sharp waves were prevalent on temporal regions, always associated with slow rhythms. As reported in awake EEG studies, we found a decrease with age of the 5-6 Hz rhythms while 2-3 Hz rhythms were present in all patients. The 2-3 Hz and 3-4 Hz rhythms were characterized by a pseudoperiodism less evident in SWS stages.

**Conclusions:** The deletion of chromosome 15q11-13 determines the alteration of GABA<sub>A</sub> receptor beta3 subunit (2). This alteration could lead to a dysregulation of thalamic gabaergic reticular neurons that could explain the alterations of sleep architecture and the over-representation of EEG slow rhythmic activities typical of AS.

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### 703.O

#### REM SLEEP BEHAVIOR DISORDER AND PARKINSON'S DISEASE (PD): RELATIONSHIP TO PD ONSET AND TREATMENT.

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**Introduction:** Rem sleep behavior disorder (RBD) has been found to occur in PD. Fifteen percent of PD patients and their caregivers report the clinical symptoms of RBD (1). A considerable number of RBD patients eventually developed PD (38%) (2). The objective of this study was to assess the relationship among disease onset, dopaminergic treatment, and RBD in a large series of PD patients.

**Methods:** We have conducted a survey in 200 consecutive non-demented non-depressed PD patients referred to our Parkinson Center over a period of 3 months. All patients have been previously evaluated in our institution and have been on stable dopaminergic treatment for at least 3 months (mean age 67±8 years; mean Hoehn & Yahr 2.3±0.7; mean PD duration 6.8±5 years; Mini Mental score >24). Medications included: levodopa (n= 200), entacapone (n= 46), pergolide (n= 20), ropinirole (n= 38) and pramipexole (n= 66). Patients and their spouses were interviewed by a sleep medicine specialist for the reported presence of RBD. RBD was diagnosed clinically if the minimal criteria according to ICDS were fulfilled. The minimal criteria include limbs or body movements associated

with dream contents and one of the following features: potentially harmful behavior during sleep or dreams that seem to be acted out, or discontinuation of the nocturnal sleep episode because of sleep-associated behavior.

**Results:** RBD was reported by 46% (n= 92) of PD patients. A mild form was observed in 24 cases, moderate in 59 and severe in 9, according to ICSD. In 52 patients the onset of RBD preceded the first symptoms of PD; in these patients the dopaminergic medications did not modify the severity of RBD. In the other patients with the onset of RBD after the appearance of PD (n= 40), the dopaminergic treatment was not significantly different (in terms of type of medication and equivalent doses) from the one of patients without RBD (n= 108).

**Conclusions:** Our study confirms that RBD may precede the onset of PD symptoms in a considerable percentage of PD patients (26%). Anecdotal reports suggest that dopaminergic medication may reduce the severity of RBD in PD patients (3). Dopaminergic treatment in our non-demented PD population appeared to have no influence on the development as well as on the severity of RBD.

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### 704.O

#### INCREASED SYMPTOMS OF EXCESSIVE DAYTIME SLEEPINESS IN CHILDREN WITH EPILEPSY

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**Introduction:** The interactions between epilepsy and sleep remain an area of active study. Understanding these interactions may lead to better treatment of epilepsy and sleep disorders in these children. The objective of our study was to quantify symptoms of sleep disorders in children with epilepsy as compared to age matched controls.

**Methods:** As part of larger study examining sleep disorders in children with neurological problems. 39 children with epilepsy and 39 children matched for age, sex and zip code were administered a 111 item IRB approved questionnaire assessing: bedtime behavior, nighttime behavior, arousals, parasomnias, seizures, morning behavior and daytime functioning. From these questions, symptom scores were developed for sleep-disordered breathing, excessive daytime sleepiness (EDS), insomnia, restless sleep, parasomnias and narcolepsy

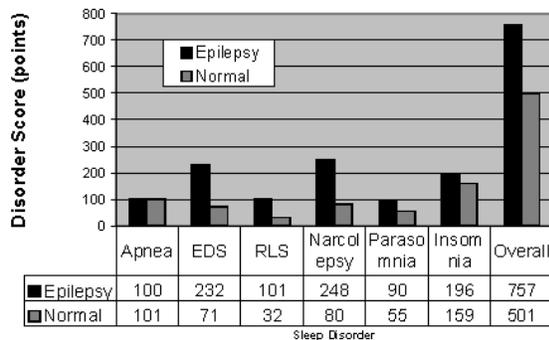
**Results:** 39 were epilepsy patients (26 male: 13 female) with a median age of eight years. The closest obtainable matched control group consisted of 39 patients (25 male: 14 female) with a median age of eight years. The epilepsy group obtained scores of 100, 232, 101, 248, 90, and 196 for sleep apnea, excessive daytime sleepiness, restlessness, narcolepsy, parasomnias, and insomnia respectively. The control group

obtained scores of 101, 71, 32, 80, and 55 for sleep apnea, excessive daytime sleepiness, restlessness, narcolepsy, parasomnias, and insomnia respectively. Use of t- statistics observing relationships showed p values for the following disorders: sleep apnea p= 0.487757, EDS p= 0.0000773, restless sleep p= 0.005206, narcolepsy p= 0.000103, parasomnias p= 0.072913, and insomnia p= 0.145796. . The overall added score of all sleep disorders gave the epilepsy group a total disorder score of 757 compared to the control group's 501(p= 0.003224).

**Table 1**

Problem	Epilepsy Score	Normal Score	p Value
Apnea	100	101	0.49
EDS	232	71	0.0000773
Restlessness	101	32	0.005206
Narcolepsy	248	80	0.000103
Parasomnias	90	55	0.074
Insomnia	196	159	0.15
Overall	757	468	0.003224

**Figure 1**



**Conclusions:** Children with epilepsy have higher incidence of EDS and restlessness during sleep than normal controls. There is no difference in the incidence of parasomnias, apnea or insomnia in the two groups. The difference in the narcolepsy score is related to symptoms of excessive daytime sleepiness only. Further characterization of these sleep symptoms is in progress to assess seizure type and therapy in a larger group.

**705.O**

**EFFECTS OF DONEPEZIL HCL ON SLEEP AND COGNITIVE FUNCTIONING IN ALZHEIMER'S DISEASE PATIENTS: A PILOT STUDY**

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**Introduction:** Sleep disturbances are common in patients with Alzheimer's Disease (AD). Documented architectural changes include diminished slow wave sleep, decreased REM density, and increased REM latency. The relationship between sleep stage changes and the cognitive symptoms in AD is unclear. Furthermore, the effects of cognitive medications for AD on

sleep are unknown. Cholinergic agonists used to treat the memory symptoms of AD are likely to increase REM sleep, which could be related to their effect on memory in this population. To date, only two studies have addressed this possible relationship. The first showed an increase in the amount of REM sleep with the administration of donepezil HCL in AD patients.<sup>1</sup> The second study showed a positive relationship between changes in REM sleep and memory in healthy elderly on donepezil HCL.<sup>2</sup> We examined the relationship between sleep and memory in newly diagnosed patients with AD who were treated with donepezil HCL.

**Methods:** Seven participants (mean age = 74.7; 2 women) were recruited from local memory clinics. Participants met the NINCDS criteria for AD and were free of vascular dementia, current antidepressant treatment, and other serious medical conditions. Participants underwent baseline polysomnography (PSG) and completed neuropsychological testing before beginning six weeks of treatment with 5 mg of Donepezil HCL (Aricept). After six weeks, participants underwent a second PSG and neuropsychological assessment. Multiple cognitive domains were assessed, including verbal memory and processing speed.

**Results:** Administration of donepezil HCL had a moderate effect on percent of REM sleep (t= -.570, d=0.47), and a large effect on REM density (t= -.938, d=0.84). There were no other changes in sleep stages in this small pilot study (see Table 1). Change in percent of REM sleep was modestly related to change in delayed recall, and change in REM density was related to change in processing speed (see Table 2). Each REM variable, however, was not related to changes in the other cognitive variable.

**Table 1**

	Time 1	Time 2	t	p	d
% REM	14.1 (9.0)	16.7(8.1)	-0.57	0.30	0.47
REM Dens.	3.0(1.9)	4.0(4.6)	-0.94	0.20	0.84

**Table 2**

	Change Delayed Recall	Change Processing Speed
Change %REM	0.49	0.09
Change REM Dens.	-0.01	-0.80

**Conclusions:** Donepezil HCL appears to increase REM variables in patients with AD. Increases in these variables may be related to changes in cognitive functioning, but this relationship is unclear as yet and requires further investigation in this population. The lack of robust findings may be related to the

fact that many of the participants had significant apnea.

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## 706.O

### NOVEL WAKE PROMOTING AND CORTICAL ACTIVATING AGENTS LACKING DOPAMINERGIC ACTIVITY

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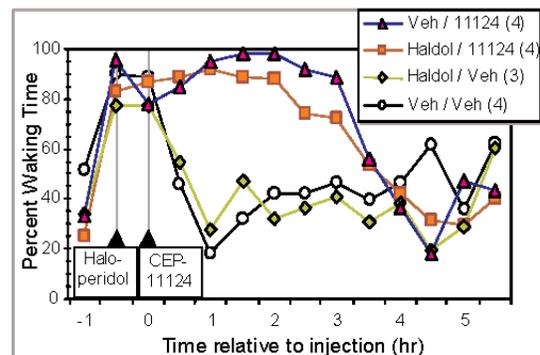
**Introduction:** Excessive daytime sleepiness (EDS) contributes to poor quality of life associated with several sleep (narcolepsy, sleep apnea), neurologic (head injury, multiple sclerosis), or psychiatric disorders (depression). Stimulants such as amphetamines or Ritalin which may be used to treat EDS are often associated with undesired effects such as peripheral sympathomimetic activation, abuse, and addiction resulting from increased dopaminergic activity. Here we describe effects of CEP-11124, a prototype for a series of novel, non-dopaminergic wake-promoting agents unrelated to traditional CNS stimulants such as amphetamine.

**Methods:** Sleep and wake states in rats were evaluated using standard electroencephalographic (EEG) and electromyographic (EMG) techniques. All animal experimentation was approved by the Cephalon Animal Care and Use Committee, and conforms to NIH guidelines. Adult, male Sprague Dawley rats were anesthetized and fitted with chronic EEG and EMG recording electrodes (1). Animals were placed in individual containers and connected to the recording apparatus 1 day prior to testing. A 7 am on – 7 pm off light cycle was used and white noise was used to mask background noise. Time spent awake was determined using EEG and EMG data scored with ICELUS software (M. Opp, U. Mich.) using standard criteria for wake, REM, and non-REM sleep (2). CEP-11124 was suspended in sterile 0.25% methylcellulose and administered at noon via intraperitoneal injection. CFos activation was evaluated in rats dosed via chronic intraperitoneal catheters at noon, anesthetized 2 hrs. later and fixed with paraformaldehyde. The brain was removed and processed for cFos immunohistochemistry using AB-5 (Oncogene).

**Results:** CEP-11124 enhanced wakefulness in rats for over 3 hrs ( $p < 0.0001$  vs. vehicle), but did not increase motor activity beyond that normally associated with wakefulness. Broad profiling of over 60 known molecular targets revealed no consistent interactions with these compounds. In particular, CEP-11124 produced no displacement of 3H-WIN-35428 (dopamine-transporter) or 3H-spiperone (D2-dopamine recep-

tors). The waking produced by CEP-11124 was approximately equivalent to that produced by 0.5 mg/kg sc. amphetamine. However, haloperidol (1 mg/kg ip.) antagonized amphetamine-induced waking but had no effect on waking produced by CEP-11124 [Figure 1; Haloperidol or vehicle (DMSO) was administered at 11:30 am followed by either CEP-11124 (100 mg/kg ip.) or vehicle (methylcellulose) at noon]. cFos in frontal association and anterior cingulate cortex and the hypothalamus was significantly increased by CEP-11124, while it was unchanged in dopamine-responsive areas, including striatum.

Figure 1



**Conclusions:** These results demonstrate that wake-promoting activity and cortical activation, as well as potentiation of motivation (see accompanying abstract), can be obtained with agents, typified by CEP-11124, which do not directly or indirectly activate dopaminergic systems. These compounds may have clinical utility in treating EDS and conditions of insufficient cortical activity without the undesired effects typically associated with dopaminergic agents.

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## 707.O

### EXCESSIVE DAYTIME SLEEPINESS AND SLEEP-DISORDERED BREATHING IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY

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**Introduction:** REM sleep dysfunction leading to REM sleep behavior disorders, hypnagogic hallucinations and narcolepsy-like excessive daytime sleepiness have been reported in patients with Parkinson's disease (1). The dysfunction may be caused by lesions in brainstem structures controlling REM sleep. In patients with progressive supranuclear palsy (PSP),

parkinsonism and ophthalmoplegia are associated with a progressive decrease in the duration of REM sleep (2). The objective of the study was to examine the occurrence of excessive daytime sleepiness and rapid eye movement (REM) sleep abnormalities in patients with PSP.

**Methods:** Fifteen severely disabled patients, aged 55-81 years and suffering from PSP for a mean  $5 \pm 3$  years underwent night polysomnography and multiple sleep latency tests. Mean mini-mental score was  $22 \pm 6$ , one patient had hallucinations and one patient was obese. Nine patients were being treated with levodopa ( $494 \pm 204$  mg/d), 6 with benzodiazepines (BZD) and 5 with serotonergic antidepressant drugs.

**Results:** Mean daytime sleep latency was abnormally low ( $< 2$  minutes) in 5 patients and normal ( $> 8$  minutes) in 10 patients. A REM period during daytime sleep was observed only once during the study. As expected, the percentage of REM sleep was reduced in all patients during the night (mean  $\pm$  SD:  $6.3 \pm 6\%$ ) and REM sleep without atonia was present in 5 patients (range: 61-98%). Sleep fragmentation was severe (mean  $\pm$  SD:  $52 \pm 25$  arousals per hour; range: 22-127 arousals per hour). It was caused by obstructive sleep apnea syndrome in 13 (87%) patients, 6 of whom were receiving BZD (apnea-hypopnea index  $> 15$  for 6 patients; apnea-hypopnea index  $> 30$  for 7 patients,) and periodic leg movement syndrome in 5 (33%) patients (range: 32-99 leg movements per hour).

**Conclusions:** One-third of PSP patients suffered from non-rapid eye movement severe daytime sleepiness caused by sleep-disordered breathing and/or periodic leg movements. Sleep-disordered breathing is usual in PSP patients. The prognostic importance of this finding remains to be evaluated.

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## 708.O

### CSF HYPOCRETIN CONCENTRATION IN VARIOUS NEUROLOGICAL DISORDERS AND SLEEP APNEA SYNDROME.

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**Introduction:** Recent CSF and postmortem brain hypocretin measurements in human narcolepsy suggest that hypocretin deficiency is involved in the pathophysiology of the disease (1,2). Thus, it is important to study whether neurological dis-

orders may also have abnormal CSF hypocretin levels (3). We therefore measured hypocretins in the CSF of various neurological disorders and sleep apnea syndrome to identify altered hypocretin levels. The results will also be useful in further evaluating the specificity of low hypocretin levels in narcolepsy-cataplexy.

**Methods:** CSF was collected from patients with (1) idiopathic narcolepsy-cataplexy (n=11), (2) sleep apnea syndrome (SAS, n=16), (3) neurodegenerative disorders, such as Alzheimer's disease and Alzheimer type dementia (AD, n=9) and Parkinson's disease (PD, n=19), (4) intracranial neoplasms (n=5), (5) multiple sclerosis (n=10), (6) infections (i.e. meningitis and encephalitis) (n=23), (7) inflammatory neuropathy, such as Guillain-Barre syndrome (GBS) (n=16), (8) poliomyelitis (n=35), (9) epileptic seizures (n=22), (10) motor neuron diseases (n=8), (11) hematological disorders (ALL and AML n=11, malignant lymphoma n=5), (12) congenital abnormalities (n=12) and (13) cerebrovascular disorders (CVD, n=20). Either patients or families gave informed consent for the lumbar puncture. CSF hypocretin-1 was measured in crude CSF samples (0.1ml duplicate) using a commercially available radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals). Intra-assay variability was 4.3% and the detection limit was 40 pg/ml. Statistical analysis was made using one way ANOVA and Fisher's PLSD.

**Table 1**

diseases	n	mean $\pm$ -SD	under 200pg
Narcolepsy-cataplexy	11	88 $\pm$ -87	9/11
SAS	16	289 $\pm$ -90	2/16
AD	9	282 $\pm$ -63	1/9
PD	19	289 $\pm$ -66	3/19
intracranial neoplasms	5	232 $\pm$ -20	1/5
multiple sclerosis	10	273 $\pm$ -54	0/10
infections	23	273 $\pm$ -62	2/23
GBS	16	206 $\pm$ - 72	5/16
poliomyelitis	35	292 $\pm$ -27	0/35
epileptic seizures	22	305 $\pm$ -55	1/22
motor neuron diseases	8	308 $\pm$ -31	0/8
hematological disorders	11	304 $\pm$ -44	0/11
congenital abnormalities	12	289 $\pm$ -87	2/12
CVD	20	320 $\pm$ -99	2/20

**Results:** Hypocretin levels were undetectable or very low from the majority of narcoleptics tested (9 out of 11). Hypocretin levels in patients with SAS (289 $\pm$ 90 pg/ml) and neurodegenerative disorders (AD: 282 $\pm$ 63 pg/ml, PD 289 $\pm$ 66 pg/ml) were within the control range. Levels in patients with multiple sclerosis (273 $\pm$ 54 pg/ml), infections (i.e. meningitis and encephalitis, 273 $\pm$ 62 pg/ml), poliomyelitis (292 $\pm$ 27 pg/ml), epileptic seizures (305 $\pm$ 55 pg/ml), motor neuron diseases (308 $\pm$ 31 pg/ml), hematological disorders (304 $\pm$ 44 pg/ml), congenital abnormalities (289 $\pm$ 87 pg/ml) and cerebrovascular disorders (320 $\pm$ 99 pg/ml) were in the control range. However two SAS, one AD, three PD, two infection, one epileptic seizure, two congenital abnormalities and two

CVD patients were lower than 200 pg/ml. Patients with intracranial neoplasms were also in the control range ( $232 \pm 20$  pg/ml), except for a patient with hypothalamic tumor (102 pg/ml). GBS patients had significantly lower hypocretin-1 levels ( $206 \pm 72$  pg/ml). CSF hypocretin-1 levels in 5 out of 16 patients were lower than 200 pg/ml (64, 103, 123, 155, 181 pg/ml).

**Conclusions:** The majority of narcoleptic subjects had extremely low hypocretin levels (less than 100 pg/ml). Although a significant decrease in CSF hypocretin levels was observed in GBS patients, levels in patients with SAS and neurological diseases such as AD, PD, MS, CNS infections and other disorders were within the control range. SAS is a disabling condition characterized by secondary excessive daytime sleepiness, severe snoring, repeated episodes of upper airway obstruction during sleep, and nocturnal hypoxemia. Among sleep disorders, idiopathic hypersomnia (Kanbayashi T et al in this issue) and SAS had normal hypocretin levels, suggesting that extremely low hypocretin levels are highly specific for narcolepsy-cataplexy.

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### 709.P

#### EFFECT OF THE MENSTRUAL CYCLE ON SLEEP DISTURBANCES & PAIN IN WOMEN WITH RHEUMATOID ARTHRITIS

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**Introduction:** Sleep disturbances and pain are common symptoms in people with rheumatoid arthritis (RA). The majority of people with RA are women, with the female to male prevalence of approximately 3.5:1, however the ratio is exaggerated during reproductive years at about 5:1. These symptoms change with large shifts in ovarian hormone levels, abating during pregnancy and returning in the postpartum period. However, no study has investigated the effects of smaller shifts in ovarian hormone levels that occur over the menstrual cycle on sleep disturbances and few exist on pain differences. Thus, the purpose of this study was to investigate the effect of the menstrual cycle on sleep disturbances and pain in women with RA.

**Methods:** Serum progesterone levels verified menstrual cycle phase. Sleep disturbances were measured by wrist actigraphy for 48 hours in the follicular and mid-luteal phases of one menstrual cycle. Daily pain ratings (NRS 0-10) were averaged over 3 nights in each phase.

**Results:** The sample consisted of 15 women with RA, ranging

in age from 21-45 years (mean =  $33.2 \pm 8.2$ ). Progesterone levels in 3 women failed to rise sufficiently in the mid-luteal phase. Since the purpose was to study the effect of changing hormone levels over the menstrual cycle, only women with progesterone increases in the mid-luteal phase were included in the analyses. Sleep disturbances and pain were worse in the mid-luteal phase compared to the follicular. Women had decreases in total sleep time (TST) ( $p=.04$ ), sleep efficiency ( $p=.01$ ), and the mean number of minutes in a sleep episode ( $p<.001$ ); while they experienced increases in WASO ( $p=.02$ ), longest wake episode ( $p=.03$ ), and pain ( $p=.05$ ) in the mid-luteal phase compared to the follicular. No significant difference was found in sleep latency between phases. While higher (91.5%) in the follicular, sleep efficiencies decreased to a low level (83.1%) in the mid-luteal phase. Also in the mid-luteal phase, increased pain was associated with decreased sleep efficiency ( $r= -.47$ ), decreased mean number of minutes in a sleep episode ( $r= -.54$ ), and increased sleep latency ( $r= .62$ ). However in the follicular phase, pain had little relationship to any sleep parameter (correlations ranged from .11 to .29).

**Conclusions:** Women with RA experienced greater sleep disturbances and higher pain intensity in the mid-luteal phase when progesterone levels are high. Sleep disturbances had higher correlations with pain in the mid-luteal phase than in the follicular phase. Thus, shifting hormone levels seem to affect the symptoms of sleep disturbance and pain in premenopausal women with RA.

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### 710.P

#### RELATIONSHIP BETWEEN SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISORDER AND PARAMETERS OF SLEEP CONTINUITY

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**Introduction:** Sleep researchers have recognized the effect of gastroesophageal reflux disorder (GERD) on sleep quality. Although arousals associated with GERD have been demonstrated by polysomnogram with simultaneous esophageal pH monitoring, the correlation of the clinical symptoms of GERD with sleep quality has not been fully investigated. In this study, we examine the relationship between symptoms of GERD and

sleep quality.

**Methods:** Patients who had a full clinical evaluation at the Sleep Disorders Center by a sleep disorders specialist and underwent baseline polysomnography were selected. All patients had been referred for evaluation of suspected obstructive sleep apnea (OSA). Patients with additional causes of sleep disruption (such as those with narcolepsy and periodic limb movement disorder) were excluded. For each patient a structured 15 item questionnaire assessing presence and severity of GERD symptoms and the effect of these symptoms on the patient's quality of life was completed. Full inpatient standard polysomnography was performed with a 16 channel paperless system. We analyzed the following polysomnographic parameters: arousal index (AI), wake after sleep onset (WASO), sleep efficiency (SE), and apnea hypopnea index (AHI).

**Results:** Questionnaire data were available for 26 patients selected based on the above criteria. All but 7 patients had used various medications for GERD as-needed in the past, but not at the time of the polysomnogram. Analysis of the results indicates that there is no difference between the subjects who had GERD symptoms (as identified by questionnaire) compared to those patients who did not: AI (mean  $11.1 \pm 1.67\%$  versus  $14.3 \pm 4.2\%$ ;  $p=0.51$ ), WASO ( $72.6 \pm 9.37$  versus  $77.4 \pm 21.8$  minutes;  $p=0.86$ ), SE ( $83.4 \pm 2$  versus  $79.8 \pm 7.27\%$ ;  $p=0.54$ ), respectively. Because of the non-normal distribution of data, log-10 of the GERD symptom severity scores were used to test correlations. There was no significant correlation between the log-10 of the GERD symptom score and AI ( $R=0.02$ ;  $p=0.91$ ), SE ( $R=0.44$ ;  $p=0.54$ ), WASO ( $R=-0.37$ ;  $p=0.112$ ), AHI ( $R=0.65$ ;  $p=0.78$ ), or the age ( $R=0.145$ ;  $p=0.54$ ).

**Conclusions:** We did not find any significant difference in the AI, WASO, or SE between patients who had symptoms of GERD compared to those who did not. Also, we did not find any relationship between these parameters and the severity of GERD symptoms. Symptoms of GERD alone may not be reliable in assessing the relationship between this disorder and sleep continuity. Further prospective study of this relationship would require 1) exclusion of all sleep disorders that typically cause sleep disruption (since the presence of OSA and associated sleep disturbance may have interfered with meaningful analysis of arousals in our study) and 2) a clear medication-free period prior to study.

**711.P**

**THE EFFECTS OF OBESITY ON SLEEP AND DAY-TIME SLEEPINESS IN THE ABSENCE OF SLEEP-RELATED BREATHING DISORDERS**

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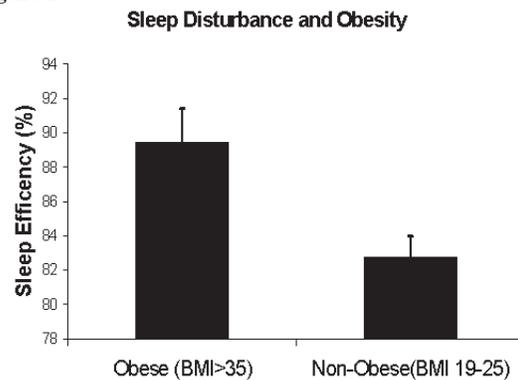
**Introduction:** Previous clinic-based studies have demonstrated that obese patients in the absence of sleep related breathing disorders have decreased sleep efficiency, increased wake during sleep, and increased daytime sleepiness compared with non-obese healthy controls (1). However, the relationship between obesity and sleep disturbance has yet to be demon-

strated in a representative asymptomatic population. The objective of the present study was to assess sleep and daytime sleepiness in an epidemiological sample using standard laboratory based measures of sleep and daytime sleepiness.

**Methods:** Given that previous studies have looked at obese patients (Body Mass Index [BMI] >35) compared with non-obese samples, we assessed polysomnographic and daytime sleepiness variables in obese individuals (BMI >35, N=32) and non-obese (BMI <30, N=32) age and sex matched controls from a representative sample. Individuals were excluded for having REI >5, narcolepsy or a BMI <19. Group differences were assessed using independent sample t-tests set at  $\alpha=0.05$ .

**Results:** Obese patients had decreased sleep efficiency  $t(62)=2.86$ ,  $p=0.006$  (Figure) and increased latency to persistent sleep  $t(60)=-2.36$ ,  $p=0.02$ . No other group differences were found for polysomnograph and daytime sleepiness measures (Table).

**Figure 1**



**Table 1**

	Obese (N=32)	Non-obese (N=32)
SLPEFF	*82.73 ± 11.25	89.42 ± 6.99
LATPS	≥ 26.52 ± 24.57	14.66 ± 13.44
STG1%	13.51 ± 9.35	9.93 ± 6.22
STG2%	57.78 ± 9.39	59.71 ± 7.32
SWS%	11.31 ± 6.67	11.96 ± 7.57
STGREM%	17.40 ± 6.89	18.39 ± 7.15
STG1LAT	16.63 ± 17.24	11.41 ± 11.18
MSLT	10.08 ± 5.44	10.03 ± 4.44
ESS	9.05 ± 4.96	10.14 ± 4.65
TST2-wk diary	7.44 ± .82	7.23 ± 1.14
AGE	41.34 ± 11.65	41.38 ± 11.41
BMI	*41.43 ± 1.07	22.34 ± .31

≥  $p<0.05$  \* $p<0.01$

**Conclusions:** Obesity is associated with decreased sleep efficiency and increased latency to persistent sleep in population-based sample of asymptomatic individuals. The present study replicates and extends previous findings. In contrast, obesity was not related to daytime sleepiness. Thus, obese individuals appear to be at risk for disturbed sleep with minimal impact on daytime alertness. The behavioral and health-related morbidity of sleep disruption in this population should continue to be explored in future studies.

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**712.P**

**PATIENTS ON CARDIOVASCULAR MEDICATIONS HAVE LOWER SLEEP EFFICIENCY WHEN COMPARED TO THOSE NOT ON CARDIOVASCULAR MEDICATION**

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**Introduction:** Various cardiac medications can affect sleep in many different ways. Although there are some reports of insomnia, sedation, and nightmares with the use of some cardiac medications, the role of these medications on sleep efficiency is not well described. We evaluated the impact of various cardiac medications on sleep efficiency.

**Methods:** The records of 206 patients who underwent a polysomnogram for excessive daytime somnolence (EDS) in our accredited Center for Sleep Disorders were reviewed. The sleep efficiency and list of cardiac medications were recorded. Cardiac medications were limited to ACE inhibitors, B-blockers, Ca-channel blockers, digoxin, diuretics, and nitrates. Data analysis was performed using SAS statistical software in which mean values were compared using the two sample T-test methodology. Statistical significance was calculated at  $&\#61537;=0.05$ .

**Results:** 206 patients were studied, 153 males and 53 females. 134 (65%) were not on any cardiac medications, 43 (21%) patients were on one cardiac medication, 29 (14%) were on 2 or more cardiac medications. No one was on any more than 3 cardiac medications. In total 72 (35%) were on at least one cardiac medication. 33 patients were on ACE inhibitors, 23 were on B-blockers, 30 on Ca-channel blockers, 5 on digoxin, 14 on diuretics, and 3 on nitrates. No other cardiac medications were noted. There was a statistically significant difference in sleep efficiency when patients on cardiac medications were compared to patients not on cardiac medications (61.4 and 71.2, respectively,  $p=0.0005$ ). Although there was a significant difference between patients on one cardiac medication versus zero cardiac medications (62.8 and 71.2, respectively,  $p=0.0076$ ) there was no significant difference between the groups on one, two, or three cardiac medications.

**Conclusions:** Sleep efficiency among patients on cardiac medications was lower when compared to those not on cardiac medications. It is possible that this observation is a direct result of the medications. However, it is also plausible that increasing number of cardiac medications is a surrogate marker for underlying cardiac disease.

**713.P**

**LOWER BOWEL SYMPTOMS PREDICT SYMPATHO-VAGAL BALANCE DURING REM SLEEP**

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**Introduction:** Susceptibility to stress and psychological abnormalities are felt to be important co-morbid factors in irritable bowel syndrome (IBS) patients. IBS patients were previously found to have a physiological marker, elevated sympatho-vagal dominance during REM sleep, when compared to controls (1,2). Previous studies have demonstrated that IBS patients have a higher amount of sleep complaints as measured by the Pittsburg Sleep Quality Index (PSQI) than healthy controls (3). IBS patients also have more psychological disturbances as measured by the Symptom Checklist (SCL-90-R) than controls. The present study used a linear regression model to determine if gastrointestinal symptoms, psychological factors, or subjective sleep quality predicted the physiological findings of sympatho-vagal dominance during REM sleep.

**Methods:** Forty-two IBS patients and 21 controls participated in an overnight sleep study. Standard polysomnography was utilized to detect the various stages of sleep. The SCL-90-R determined the presence of psychological disturbances. A GI symptom questionnaire was completed by each participant and the responses were categorized into dyspeptic symptoms (DS) e.g., heartburn, nausea, vomiting and lower bowel symptoms (LB) e.g., constipation, diarrhea, passing mucous or gas. Autonomic activity was investigated by heart rate variability analysis. The low frequency band/high frequency band (LF/HF) ratio is the indicator of sympatho-vagal balance. Subjective sleep quality was assessed utilizing the PSQI.

**Results:** The stepwise linear regression model utilized the following predictors: global severity index (GSI) and positive symptom distress index (PSDI), LB symptoms and DS symptoms to predict the LF/HF ratio. LB symptoms ( $r = .33$ ) significantly ( $p=.02$ ) predicted the LF/HF ratio during REM sleep while excluding DS symptoms, GSI and PSDI from the model. LB symptoms were also significantly correlated ( $p<.05$ ) with the amount of psychological disturbances (GSI and PSDI). The PSQI was significantly ( $p<.05$ ) correlated with both LB symptoms and psychological disturbances (GSI and PSDI).

**Conclusions:** 1. LB symptoms account for a low but significant percent of variance in sympatho-vagal balance during REM sleep. 2. Autonomic functioning during REM sleep remains an important source of independent variance in IBS patients. 3. PSQI also correlates significantly with LB symptoms, but it does not account for unique variance in the predictive model.

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## 714.P

### GASTROESOPHAGEAL REFLUX IN HEARTBURN PATIENTS WITH AND WITHOUT SLEEP COMPLAINTS

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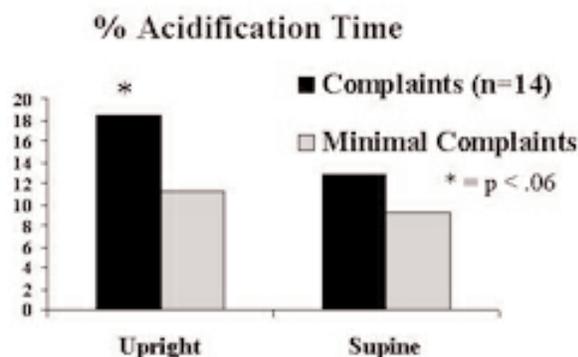
(1) Lynn Institute for Healthcare Research

**Introduction:** Sleep complaints are common in patients with symptomatic gastroesophageal reflux disease (GERD). Recent epidemiological studies have suggested that individuals with complaints of nocturnal heartburn at least twice a week have a significantly greater risk of various sleep complaints (1, 2). It is not known whether these sleep complaints are directly related to sleep disruptions secondary to sleep related gastroesophageal reflux (GER), or an indirect consequence of reflux and heartburn. The aim of this study was to identify heartburn sufferers with and without sleep complaints and compare their sleep patterns and frequency of (GER).

**Methods:** A questionnaire was initially sent to a database of 852 individuals with complaints of heartburn. Questionnaires addressed both the frequency and timing of heartburn (day vs. night), as well as sleep complaints and complaints of daytime sleepiness. Total number of responders was 364. All respondents with heartburn at least 4 days per week and one night per week were identified. From this group of responders, 14 with complaints of poor sleep and/or daytime sleepiness at least 2-3 times per week were compared to 10 individuals without sleep complaints with regard to 24-hour esophageal pH parameters and one night of polysomnography (PSG).

**Results:** Subjects with sleep complaints had more esophageal acid contact time in both the upright (waking) and supine (during the sleeping interval) positions. This was statistically significant only in the upright position (Figure 1). In addition, the group with sleep complaints also showed a larger number of prolonged reflux events, but again this was statistically significant only in the upright position. Subjects with sleep complaints had a strong trend towards greater awakenings from sleep ( $p < .08$ ).

Figure 1



**Conclusions:** 1) Individuals with significant heartburn complaints (including nocturnal heartburn) do have a greater degree of GER, and this was most notable during waking as opposed to sleep. 2) Subjects with sleep complaints also exhibited greater awakenings from sleep. Effective treatment of heartburn with potent acid suppression should result in improved sleep and daytime performance and heartburn sufferers with concomitant sleep complaints. 3) Increased GER may lead to disrupted sleep as well as enhanced sensitivity to the effects of poor sleep or the perception of poor sleep.

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## 715.P

### PREVALENCE OF SLEEP DISORDERS IN FIBROMYALGIA

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**Introduction:** Various sleep anomalies have been reported in patients with fibromyalgia. These include: alpha electroencephalographic (EEG) sleep i.e., phasic alpha (alpha delta sleep), tonic alpha; frequent cyclic alternating pattern (CAP)(i.e., k-alpha, or periodic polyphasic bursts), periodic limb movement disorder (PLMS) and restless legs, and sleep apnea. The objective of this study was to determine the prevalence of sleep anomalies in a community sample of people with fibromyalgia.

**Methods:** Thirty-two consecutive subjects who responded to an advertisement and were confirmed to fulfill the American College of Rheumatology criteria for fibromyalgia entered the study. Subjects were female (mean age 42.3 yrs, s.d. = 11.8 yrs) and free of all medications for at least 2 weeks prior to their overnight sleep study. Two subjects who withdrew their consent and one subject who had evidence of a coincident cardiac abnormality were not entered into the study. Sleep recordings (C3A2 and C4A1, OzA2 EEG, right and left oculogram, submental electromyogram, electrocardiogram, right and left anterior tibialis, respiratory effort, airflow and oximetry) were performed on 29 subjects. The sleep studies were staged according to standard criteria (Rechtschaffen and Kales, 1968). Two raters, previously shown to have high inter-rater reliability, scored alpha EEG sleep according to stage of sleep (MacLean et al., 1995). Alpha EEG sleep disorder was rated if alpha (7.5-11.5 Hz) occurred in 60% or more of NREM stages 2, and stages 3 and 4 or slow wave sleep (SWS). Subjects were classified as having tonic alpha EEG sleep disorder if their alpha ratings remained unchanged across NREM stages 2, and SWS. Subjects whose alpha ratings differed between stage 2 sleep and SWS were classified as having phasic alpha EEG

sleep disorder. CAP (periodic K-alpha or polyphasic EEG bursts) 10 per hour of sleep or greater were rated as significant (MacFarlane et al. 1996).

**Results:** No sleep pathology occurred in 2 subjects (7%). Alpha EEG sleep disorder occurred in 26 subjects (90%). See Table for the prevalence of the varieties of alpha EEG sleep and other coincident sleep disorders.

**Table 1**

Sleep Disorders in Fibromyalgia Subjects	Number of Subjects (n)	Prevalence (%)
Phasic Alpha EEG Sleep: SWS alpha > Stage 2 alpha	1	3
Phasic Alpha EEG Sleep: Stage 2 alpha > SWS alpha	14	48
Tonic Alpha EEG Sleep	11	38
CAP	16	55
Periodic Limb Movement Disorder (≥10/hr)	6	21
Sleep Apnea/Hypopnea (≥10/hr)	1	3

**Conclusions:** 1. Phasic and tonic alpha EEG sleep disorders occur in 90% of subjects with fibromyalgia. 2. Coincident sleep disorders in subjects with fibromyalgia include CAP (periodic K-alpha or polyphasic EEG bursts) in 55%, PLMS in 21%, and sleep apnea in 3%.

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**716.P**

**WHAT IS NORMAL SLEEP? A COMPARISON OF HEALTHY, AVERAGE, AND SLEEP DISORDERED INDIVIDUALS**

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**Introduction:** There exists a considerable amount of polysomnographic data on normal sleep, but very little self-reported data. Those epidemiological studies that do assess self-report sleep usually ask respondents about characteristics of their sleep (e.g., total sleep time, sleep onset latency, etc.) but fail to account for health or psychological factors when determining means. Several studies have shown both physical and health problems to either increase or decrease duration and quality of sleep. Therefore the values these studies give for normative sleep may be skewed because of underlying factors that affect sleep. The present study was performed in an attempt to determine if there are differences in the sleep of normal healthy adults (no medical problems), the sleep of

average adults without sleep disorders, and the sleep of individuals with either insomnia or other sleep disorders.

**Methods:** We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Volunteers were paid for completing 14 sleep diaries and seven questionnaires evaluating associated daytime functioning, such as fatigue and sleepiness.

**Results:** We have collected and analyzed data from 772 people. The sample is composed of 243 men and 279 women, ranging from 21 to 98 years of age. The racial breakdown is 70.0% White, 26.8% Black, and 3.2% Asian and Hispanic. We separated these individuals into four groups; 1) healthy sleepers (not taking medications, no self-reported health problems, mental problems, or sleep disorders), 2) average sleepers (not included in healthy sleepers with no self-reported sleep disorders), 3) people with self-reported insomnia, and 4) people with other self-reported sleep disorders. We will report analyses on eight sleep variables: SOL, # of awakenings, WASO, TST, TIB, SE, sleep quality and nap time. Table 1 reports means of each group on each dependent variable. First, a MANOVA was performed comparing the four groups on the set of eight sleep variables and was found to be significant, Wilks' Lambda = .68, F(24, 2205) = 12.99, p < .001. Follow-up univariate tests indicated significant differences between groups on all dependent variables (all p's < .001). Therefore, Tukey's post-hoc tests were performed comparing groups to each other. These tests revealed that while healthy sleepers had better scores than average adults on all measures, these differences were only significant in # of awakenings. However, both normal sleepers and average sleepers scored better than people with other sleep disorders on SOL, WASO, Sleep Efficiency, and Sleep Quality. Further, normal and healthy sleepers also scored better than people with insomnia on all measures except time in bed. Finally, people with other sleep disorders scored better than people with insomnia on all measures but time in bed and nap time.

**Table 1**

Variable	Healthy	Average	Other Sleep	Insomnia
SOL (min)	17.35	18.37	23.68	32.77
Awakenings	1.09	1.40	1.58	2.01
WASO (min)	13.02	17.47	29.79	41.09
TST (min)	428.27	431.71	420.70	396.32
TIB (min)	476.73	486.43	496.53	494.32
SE (%)	89.77	88.87	84.54	80.17
SQ	3.59	3.67	3.33	2.98
Nap (min)	13.60	15.59	27.96	22.72

**Conclusions:** While people without any health problems do sleep better on the whole than those with health problems, these differences are not significantly different. However, the means presented here are based on a sound self-report process and should possibly be considered when describing normal sleep in the future.

**Research supported by National Institute on Aging grants AG12136 and AG14738.**

## 717.Q

## SUBJECTIVE ASSESSMENT OF SLEEP QUALITY ACROSS THE MENSTRUAL CYCLE IN WOMEN WITH PREMENSTRUAL DYSPHORIC DISORDER

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**Introduction:** Existing evidence demonstrates that sleep structure varies across the menstrual cycle in healthy women (1). These variations could be more severe in women suffering from premenstrual dysphoric disorder (PMDD) (2). In a previous study of healthy women, subjective sleep quality was shown to be constant across both phases of the menstrual cycle (3). The current study aims to test whether there exists a variation in subjective sleep quality of PMDD sufferers across the follicular and luteal phases of the menstrual cycle.

**Methods:** Five women (ages 28-41) with a clinical diagnosis of PMDD maintained regular sleep/wake habits over one entire menstrual cycle. Sleep/wake times outside of the laboratory were kept constant and confirmed by wrist actigraphy. Daytime napping was prohibited during the entire study. Every third night of one entire menstrual cycle, sleep was polysomnographically recorded in the laboratory using a standard montage. Intrinsic sleep disorders were ruled out during the first sleep recording. Participants also assessed the quality of their prior sleep episode, upon waking using a 10 cm visual analog scale.

**Results:** Mean sleep length in the laboratory was 8h12min + 10 minutes. A Wilcoxon signed ranks test was performed to compare subjective sleep quality scores of the early follicular (first week) and the late luteal (last week) phases of the menstrual cycle. During the early follicular phase, subjective sleep quality was 6.43 (SD= 2.89), while that of the late luteal phase was 5.41 (SD = 3.43) (Figure 1). The scores were found to vary significantly between the phases of the menstrual cycle ( $p = 0.041$ ). Furthermore, participants' assessment of sleep quality was positively correlated with polysomnographic measures of sleep efficiency ( $r = 0.550$ ,  $p = 0.02$ ) (Figure 2).

Figure 1

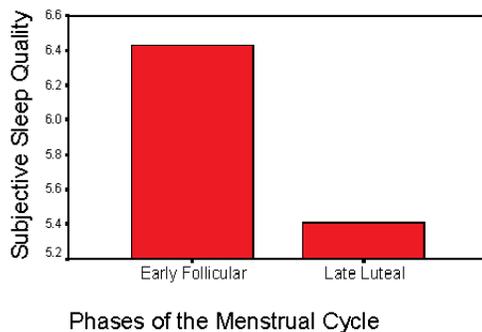
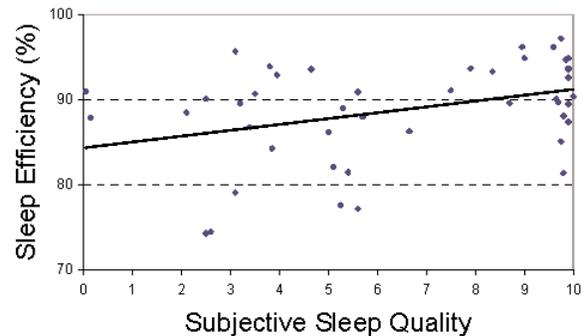


Figure 2



**Conclusions:** The present study indicates that subjective sleep quality deteriorates significantly during the late luteal phase in women with PMDD. This is not surprising since sleep disturbances are an important diagnostic criteria of PMDD. These results are different from what has been reported in healthy women (3). Elucidation of the factors mediating changes in sleep during menstruation in participants with PMDD may have key implications in developing new and innovative treatments.

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## 718.Q

## MODAFINIL FOR TREATMENT OF THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA AND ANTIPSYCHOTIC-INDUCED SEDATION

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**Introduction:** Schizophrenia is characterized by positive and negative symptoms, changes in mood, and disturbances in cognition. Augmentation strategies are frequently utilized when monotherapy with antipsychotics fails to adequately improve symptoms (especially negative symptoms) or induces sedation. Many of the sympathomimetic agents, notably the amphetamines, are generally not prescribed to psychotic patients because of abuse potential and the potential for worsening psychosis. Modafinil, a novel wake-promoting agent, is effective for improving wakefulness in narcolepsy<sup>1</sup> and obstructive sleep apnea.<sup>2</sup> The pharmacological profile of modafinil differs from that of the stimulants. Modafinil is not

a dopamine receptor agonist, has less potential for abuse, and has not been associated with significant changes in weight. Modafinil may be useful for treating the negative symptoms of schizophrenia and antipsychotic-induced sedation.

**Methods:** Modafinil treatment of the negative symptoms of schizophrenia and antipsychotic-induced sedation was evaluated in two patients.

**Table 1**  
Patient characteristics/medication histories.

Characteristic	Case 1	Case 2
Sex	Male	Male
Age (yr)	41	43
Race	White	White
Duration of schizophrenia (yr)	17	21
Hospitalized for schizophrenia	Yes	Yes
Medication history *	Clozapine Haloperidol Olanzapine <sup>†</sup> Quetiapine Risperidone Thiothixene	Clozapine <sup>†</sup> Dextroamphetamine Olanzapine <sup>†</sup>
Modafinil dose		
Starting	100 mg	200 mg
Current	200 mg	200 mg
Current concomitant medication	40 mg olanzapine	10 mg olanzapine

\* Ineffective unless otherwise noted. <sup>†</sup> Partial positive response.

**Results:** Case 1 had failed numerous trials with different antipsychotic medications. He also experienced a marked gain in weight when novel antipsychotic medications were started, and became obese (BMI = 31.3). He had a partial response to olanzapine 20 mg/d, but was still mildly paranoid and exhibited significant negative symptomatology (eg, alogia, anhedonia, amotivation, hypersomnia, restricted affect, poor grooming). Olanzapine was increased to 30 mg/d, but induced sedation. Modafinil 100 mg/d was then added to the treatment regimen. Sedation was reduced, and negative symptoms improved within one week, resulting in brightened affect, increased quantity of speech, increased energy, less need for sleep, decreased fatigue, more socialization in group activities, and decreased isolation. After 1 month, modafinil was increased to 200 mg/d and olanzapine was increased to 40 mg/d. Over the next 4 months, negative symptoms continued to improve, enabling the patient to participate routinely in an exercise program. He lost 20 lbs during this period. Over the next 6 months, the patient's weight was maintained at 210 lb (BMI = 28.5), and his psychiatric condition stabilized. Case 2 was started on clozapine with good amelioration of positive symptoms, yet remained very "flat," nonspontaneous, and unmotivated. He also exhibited other negative symptoms (eg, poor personal hygiene, long, unkempt, dirty hair, poor grooming). After developing persistent leukocytopenia, the patient was switched to olanzapine 10 mg/d, but continued to exhibit negative symptoms. Dextroamphetamine 30 mg BID failed to improve his negative symptoms and was discontinued. Treatment with modafinil 200 mg/d was started, and within 1 month the patient was observed to be slightly more spontaneous in conversation. Daytime wakefulness and energy level increased

slightly, and there was a slight decrease in the need for sleep. Additionally, grooming and personal hygiene were noticeably improved. No changes in weight were noted at this early time.

**Conclusions:** These two case studies suggest that modafinil may be efficacious for improving the negative symptoms associated with schizophrenia and minimizing the sedating side effects associated with antipsychotic medications. The first case also suggests the possibility that these improvements may lead to increased patient activity and reversal of weight gain.

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### 719.Q

#### GENDER AND AGE EFFECTS ON SLOW-WAVE ACTIVITY IN CHILDHOOD AND ADOLESCENT DEPRESSION

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**Introduction:** There is evidence to suggest that the amplitude and time course of slow-wave activity (SWA) during NREM sleep is abnormal in men, but not women, with depression. Moreover, the gender differences in depressed adults are 2-3 times larger than those observed in healthy controls (1-2). To date, it is not clear whether depressed children and adolescents also exhibit SWA abnormalities and if large gender differences also characterize younger depressed patients (3).

**Methods:** The present study evaluated SWA in 150 depressed outpatients 11-23 years of age (73 females, 76 males) compared to 97 healthy controls in the same age range (52 females, 45 males). All patients were symptomatic and unmedicated at the time of study. All study participants maintained regular sleep/wake cycles at home for 5 days, verified by actigraphy, and followed by 2 consecutive nights in the lab. Power spectral and period amplitude analysis was used to quantify SWA in each consecutive NREM period, and across the night. MANOVA tested interactions and repeated measures effects on SWA amplitude and power. Exponential regression analyses evaluated the SWA time course. Linear regressions assessed age-related changes in SWA separately for each group.

**Results:** Significant gender by group by age interactions were obtained for SWA amplitude and power in the first NREM period ( $p < .02$ ). Overall, depressed males had the lowest SWA amplitude and power, particularly in those aged 16 and older. Moreover, the time course was abnormal in adolescent and young adult depressed males, with a lower accumulation of SWA in the first NREM period and the slowest dissipation across all NREM time. By contrast, the depressed females

showed no evidence of reduced SWA amplitude or power or an abnormal time course. Interestingly, the adolescent and young adult depressed girls showed the highest accumulation of SWA with the fastest dissipation compared to all other groups. All groups showed robust developmental declines in SWA amplitude and power ( $p < .0001$ ), with the largest age-related change in depressed males. However, only depressed males showed a significant decline in the accumulation of SWA with increasing age ( $p < .03$ ). None of the other groups showed significant age-related changes in the time course of SWA, although the exponential function was stronger after puberty in healthy males and females and in depressed females.

**Conclusions:** As reported in depressed adults, SWA abnormalities were evident in post-pubertal males with depression but not in females of the same age. Further, the time course of SWA appears to show an age-related decline only in this group. The findings suggest that early onset depression is associated with homeostatic abnormalities but it is strongly gender-dependent.

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## 720.Q

### SLEEP PATTERNS OF BATTERED WOMEN IN TRANSITIONAL HOUSING PROGRAMS

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**Introduction:** Battered women are subject to repeated deliberate, often severe abuse from their intimate male partners. Increasingly transitional housing programs are being offered to battered women as structured and supportive environments after they leave emergency shelters. However, clinical practice in transitional housing programs suggests that like women in emergency shelters, these battered women also have disturbed sleep. Sleep is a basic physiologic need and essential for healthy human functioning. Yet, previously there were no studies that described the sleep patterns of battered women in transitional housing programs. The purpose of this study was to describe the sleep patterns of battered women in transitional housing programs and the personal and environmental variables (e.g., age, health status, motherhood status, number of children, pregnancy status, spiritual, family and financial resources, ethnicity, employment status, and battering experience) that influence them. Research questions: (a) What are

the sleep patterns of battered women residing in transitional housing programs? (b) What is the relationship between personal and environmental variables and the sleep patterns of battered women residing in transitional housing programs?

**Methods:** A convenience sample ( $N = 29$ ) of ethnically diverse battered women residing in transitional housing programs were recruited to the study. Sleep disruption, manifested subjectively as initiation insomnia or maintenance insomnia was assessed in the transitional housing program for 2 consecutive days and nights using the wrist actigraphy to estimate total sleep time and sleep maintenance. Participants also completed the General Sleep Disturbance Scale (GSDS), Spiritual Perspective Scale (SPS), Symptom Checklist-90-Revised (SCL-90R), Conflict Tactics Scale (CTS), Sleep Behavior Scale (SBS) [children's sleep], and a demographic sheet.

**Results:** Participants reported disturbed sleep an average of 3 out of 7 nights ( $2.77 \pm .84$ ). The most common complaints were (1) frequent wakings, (2) feeling tired or fatigued during the day, (3) and waking too early. Objective sleep maintenance ranged from 98.6% to 56.5% ( $87.4\% \pm 9.4\%$ ). Both personal and environmental variables were found to significantly affect sleep patterns. Objective sleep as measured by average total sleep time was significantly and inversely correlated with the number of children sleeping in the same room. ( $r = -.42$ ,  $p < .05$ ). Average number of wakings was significantly and inversely correlated with SPS score ( $r = -.37$ ,  $p < .05$ ). Finally, participants who experienced a high degree of physical and psychological distress including PTSD as measured by the SCL-90R ( $r = .36$  to  $.52$ ), also reported more troubled subjective sleep (GSDS).

**Conclusions:** Project findings increase the body of knowledge of battered women's sleep patterns and provide baseline data for the development of specific management strategies that could reasonably be implemented by transitional housing agencies and the women themselves.

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## 721.Q

### THE EFFECTS OF VAGUS NERVE STIMULATION (VNS) ON SLEEP IN DEPRESSION

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**Introduction:** Recent work has demonstrated the efficacy of vagus nerve stimulation (VNS) in treatment-resistant depression (1). Moreover, a preliminary study showed improved sleep architecture and enhanced strength of sleep EEG rhythms after 8 weeks of VNS treatment (2). The purpose of the present study was to extend these findings to a larger sample of treatment-resistant patients and to examine long-term effects on sleep

**Methods:** Eight treatment-resistant, severely depressed patients participated in study. Sleep studies were performed at

baseline, after 8 weeks of VNS delivered by a NeuroCybernetic Prosthesis (NCPTM). To date, four of the patients have returned for an additional study after 1-2 years of continuing treatment. All patients remained on medication throughout the study. Changes in sleep macroarchitecture, based on standard stage scoring (i.e. total sleep time, % sleep stages, REM characteristics, etc.) and microarchitecture, based on quantitative EEG analyses (i.e. temporal coherence, periodicity and amplitude of EEG rhythms) were compared with repeated-measures MANOVA.

**Results:** Significant treatment effects were obtained for both macro- and microarchitectural measures and on symptom severity. Hamilton depression scores were decreased by more than 50% ( $p < .0001$ ) and subjective, patient-rated sleep quality was significantly improved ( $p < .001$ ). Decreased Stage 1 sleep and intermittent wakefulness, accompanied by increased Stage 2 sleep were evident after 8 weeks of VNS ( $p < .01$ ). Total sleep time was also significantly reduced whereas REM sleep was unaffected. Although the period length and temporal coherence of sleep EEG rhythms was unchanged by VNS, the strength or amplitude of beta, theta and delta rhythms increased dramatically with VNS ( $p < .001$ ). The largest effect was observed in the strength of delta rhythms, increasing the amplitude by 200%. Most of the sleep effects of VNS persisted into long-term treatment, although effect sizes were reduced.

**Conclusions:** VNS treatment improved symptom severity and both subjective and objective sleep characteristics in treatment-resistant depressed patients. VNS also restored the strength of ultradian sleep EEG rhythms to near normal levels, effects that largely persist into long-term treatment. Since our previous work has not shown dampened amplitude rhythmicity to be a characteristic of non-resistant patients (3) it appears that sleep is more disturbed in treatment-resistant patients.

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**722.Q**

**SLEEP-WAKE TRANSITION VARIABILITY IN DEPRESSED AND NON-DEPRESSED PARTICIPANTS**

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**Introduction:** The majority of sleep-related studies in unipolar depression have used self-report sleep measures and polysomnography (PSG) to document sleep activity. However, self-report measures are subjective and vulnerable to a variety of response biases, and PSG cannot usually be conducted in the home environment over multiple nights. Actigraphy, on the other hand, allows for the objective assessment of sleep that can be used to test the variability of sleep patterns within the natural environment. To date, research studies using actigraphy have documented increased nighttime motor activity in individuals with depression <sup>Begin 1</sup> End . However, few studies have characterized the differences between depressed outpatients, whose schedule is not subject to a hospital routine, and control subjects in the variability of sleep disturbances over multiple nights. Consistent with a social rhythm model of depression <sup>Begin 2</sup> End , we hypothesize that depressed individuals experience greater variability in sleep parameters than normal controls, which may be a contributing factor to the maintenance of the disorder.

**Methods:** Twenty outpatient individuals diagnosed with Major Depressive Disorder (MDD) and six individuals with no current or past history of depression participated in the ongoing study. Subjects were screened for bipolar disorder, current substance abuse/dependence, sleep disorders, and recent (6 weeks) changes with any medications. Normal controls had no current or past history of MDD and no current psychiatric disorders. Subjects received the Structured Clinical Interview for the DSM-IV (SCID), the Hamilton Depression Rating Scale (HRDS), and various self-report measures over a period of two-weeks. They received an Actillum wrist activity monitor (Ambulatory Monitoring, Inc., Ardsley, NY) to wear on the second week for 3-7 nights.

**Results:** Two measures of sleep parameter variability, the standard deviation of WASO (M Dep = 35.19; M Con = 14.21) and the standard deviation of nighttime awakenings (M Dep = 4.13; M Con = 1.86), discriminated depressed from non-depressed participants (WASO  $\chi^2$  <sup>Begin 2</sup> End =7.11;  $p = .04$ ; awakenings  $\chi^2$  <sup>Begin 2</sup> End =8.44;  $p = .03$ ). Logistic regression analyses suggested that depressed individuals were more likely than normal controls (M=19.79) to have a larger amount of WASO (M Dep = 66.51; M Con = 19.79;  $\chi^2$  <sup>Begin 2</sup> End =9.58;  $p = .05$ ) and a larger number of nighttime awakenings (M Dep = 8.82; M Con = 2.22;  $\chi^2$  <sup>Begin 2</sup> End =13.37;  $p = .03$ ). Average minutes and standard deviation of each awakening did not differ between the two groups (M  $p = .89$ ; SD  $p = .99$ ).

**Conclusions:** Sleep associated with depression is characterized by greater frequency and variability of sleep-wake transitions, rather than by the duration of each awakening. The variability in sleep-wake patterns tentatively supports a social rhythm theory of depression. The lack of consistency in sleep

patterns may suggest that homeostatic functions related to circadian rhythms are disrupted in depressed individuals. In general, these findings highlight the importance of variability indices in research investigations of sleep quality with psychiatric disorders.

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### 723.Q

#### SLEEP ELECTROENCEPHALOGRAPHIC CHARACTERISTICS IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

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**Introduction:** While many investigators report various sleep abnormalities in schizophrenic patients, not all studies confirm this (1). These inconsistencies can partly be explained by major methodological shortcomings in studies evaluating sleep in schizophrenia, and inconsistencies themselves also would represent the heterogeneity of schizophrenic syndrome. To minimize these shortcomings, it is necessary to conduct sleep studies limited to specific subtypes of schizophrenia. The author attempted to investigate the sleep electroencephalographic (EEG) characteristics and the correlation of psychotic symptoms with sleep variables (especially slow wave sleep) in a specific subtype of schizophrenia - chronic negative symptom schizophrenia. The author also tried to correlate the etiologic pathophysiology of chronic negative symptom schizophrenia through this study.

**Methods:** The author analyzed the EEG sleep patterns of 15 male schizophrenic patients who were drug-free for at least 14 days, and those of age- and sex-matched 15 healthy controls. Patients were assessed by the Positive and Negative Symptom Scale, Brief Psychiatric Rating Scale and Hamilton Rating Scale for Depression. Polysomnography was performed on 2 consecutive nights and second night data were analyzed.

**Results:** The sleep continuity and structure of schizophrenic patients were more disturbed than those of normal controls: delayed sleep latency, decreased sleep efficiency, SWS deficits (especially stage 4 sleep), delayed REM latency, increased arousals and awakenings, and more fragmented. Slow wave sleep (SWS) was negatively correlated with negative symptoms. The correlation, however, failed to reach statistical significance ( $r=-0.44$ ,  $p<0.1$ ). Mean time of REM latency was significantly later in schizophrenic patients ( $p<0.05$ ), but there were no significant differences in REM amounts and REM sleep percentage compared to controls.

**Conclusions:** The results of the present study indicate that sleep structure and continuity are disturbed in patients with chronic negative symptom schizophrenia. The findings support the view that SWS deficits may be related to negative symptoms of schizophrenia and may perhaps be mediated by

neurodevelopmental error, CNS neurotransmitters including serotonin dysfunction, and prefrontal lobe dysfunction of schizophrenia as suggested in previous studies (2). Also, SWS deficits may be a trait-related marker of schizophrenia. Lack of SWS, therefore, may have some important clinical and pathophysiological implications in chronic negative symptom schizophrenia.

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### 724.R

#### VALIDATION OF A COMMERCIALY AVAILABLE RODENT POLYSOMNOGRAPHIC SCORING ALGORITHM

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**Introduction:** We have assessed the sensitivity and specificity of a commercially available rodent scoring plug-in module (Rodent scoring module Ver 1.0, BioAutomatix, San Francisco, CA) that integrates seamlessly into the Somnologica/Addlife® polysomnography platform (Flaga Medical Systems, Iceland). This plug-in module performs auto-regressive spectral analyses (ARS) in three signals simultaneously: a) cortical EEG, b) hippocampal theta EEG, and c) EMG. During ARS, the frequency containing the most power, as well as the total power across all frequencies, is determined. A decision-making matrix then assesses these power frequency components to determine sleep-wake state.

**Methods:** Polysomnographic data was collected from six neonatal rats, each over a 24-hour period. A single observer then scored each record in 30-second epochs as either wake (W), non-slow wave (NSW), slow wave (SW), or REM sleep. Wake was defined by the presence of low amplitude fast frequency EEG in conjunction with moderate to high amplitude EMG. Non-slow wave sleep was defined by the presence of high amplitude low frequency delta wave activity that occupied at least 20%, but no more than 50%, of the epoch in conjunction with low amplitude EMG. Slow wave sleep was defined by the presence of high amplitude, low frequency delta wave activity that occupied greater than 50% of the epoch. REM sleep was defined by the presence of hypersynchronous theta wave activity centered near 6.5 Hz, low amplitude fast frequency EEG and EMG activity at its nadir. Once each polysomnographic record had been manually scored, the rodent scoring plug-in module was used to score each file. Kappa coefficients were used to determine levels of agreement between these two scoring methods for each rat's 24-hour data file.

**Results:** Levels of agreement between the six hand-scored and automated scored files were: 1) 84.4%, 2) 85.1%, 3) 86.1%, 4) 87.3%, 5) 92.1%, and 6) 93.1%, yielding a mean agreement level of 88%. We determined the automated scoring program's

specificity for determining W to be 89.4%, NSW-52.5%, SW-96.5%, and REM-88.8%.

**Conclusions:** A significant level of agreement between polysomnographic variables was achieved from data scored both manually and automatically with the scoring plug-in module. In addition, we found that manual editing of computer-scored data was achieved in less time than that required to manually score an entire polysomnographic record. We conclude that this automated scoring algorithm, which seamlessly interfaces with a commercially available software platform, can reliably score rodent polysomnographic data. However, manual editing of files is necessary to ensure that absolute accuracy is achieved, particularly with regards to NSW. Ongoing validation of newly developed features such as: a) user selectable epoch length, b) computation of bout length, and c) output of EEG and EMG power/frequency components, will better define the applicability of this automated analysis program for scoring rodent polysomnographic data.

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## 725.R

### AUTOMATIC DETECTION OF RAPID EYE MOVEMENT EVENTS

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**Introduction:** Evidence suggests that REM count abnormalities exist in several psychiatric syndromes when compared to normal controls [1]. However, REM count information has been largely ignored, probably because manual scoring of eye-movements (EMs) is a tedious and time-consuming task that is subject to significant scorer bias. There is a need for an objective automatic detection method.

**Methods:** The method was developed using five randomly selected all night polysomnograms recorded at Hôpital Sacré-Coeur (Montreal, Canada) using Stellate Systems polysomnography analysis and acquisition system with a sampling rate of 128 Hz. Sleep technicians marked individual REMs in the first fifteen minutes of the second REM period. The method attempts to incorporate the various EM features that have been used in previously published techniques without explicitly using an EM model. Two salient features of REMs are their rapid change in amplitude and the phase-reversed synchrony in the left and right EOG channels. Thus, the method uses two channels. The detection rationale is that REMs must occur in synchrony in the two EOG channels, must be phase-reversed and must have fast deflections with sufficient amplitudes. This is accomplished with a two-step process. In the first step, both EOG channels are bandpass filtered with cutoff frequencies of 1 and 5 Hz to eliminate slow EMs. REM detection criterion,  $\rho$ , is generated as the negative instantaneous cross product (NICP) of the data in the two filtered sequences. Candidate REMs (CREMs) are determined to be the peaks in  $\rho$ , where no two CREMs are allowed to be closer than 0.25 seconds. In the second step, CREMs are filtered to exclude those that do not meet REM criteria. For each CREM, the following features are evaluated: 1) cross correla-

tion coefficient ( $\rho$ ) of the two EOG channels in the staging epoch; 2) NICP; 3) a measure of the slope of the EM deflections (determined using best-fit straight lines through data on the left and right side of the CREMs). In order for a CREM to be a valid REM,  $\rho$ , NICP must be greater than 120 and slope must satisfy a minimum criterion.

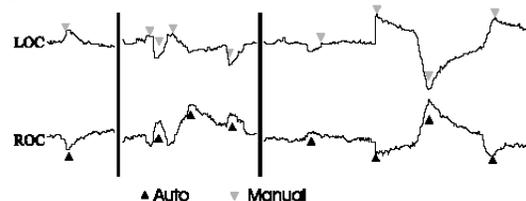
**Results:** Figure 1 shows the results of training data of five subjects. Overall sensitivity and specificity are approximately 84% when compared to manual scoring. A detected REM was considered a good detection if within a window of  $\pm 0.25s$  there was a manually marked REM.

Figure 1

Sub	Total Manual	Auto detections	GD	FD	Sens.	Spec.
A	110	108	96	12	87.3%	88.9%
B	190	211	158	53	83.2%	74.9%
C	199	184	160	24	80.4%	87.0%
D	26	22	22	0	84.6%	100.0%
E	41	52	36	16	87.8%	69.2%
					84.7%	84.0%

Training set: automatic REM detection results (GD, good detection; FD, false detection).

Figure 2



Examples of auto and manually scored REMs.

**Conclusions:** To the best of our knowledge this is the first report on the performance of an automatic REM detector based on comparison of individual REMs. Initial performance is very encouraging as evidenced by the results in Figure 1. We feel that automatic REM detection will provide consistent and objective results, in contrast to significant inter and intra-scorer variations (likely due to unclear definition of REMs). Figure 2 illustrates examples of auto and manually scored REMs with varying morphologies. An important aspect of the presented method is the unique and simple detection criteria that can be easily changed to accommodate the user preferences and control sensitivity/specificity tradeoffs.

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## 726.R

## AUTOMATIC VIGILANCE STATE CLASSIFICATION OF RATS AND MICE USING COMMERCIAL SLEEP ANALYSIS SOFTWARE

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**Introduction:** Traditionally, sleep stage classification has been a labor intensive process requiring highly trained personnel. The process is also open to observer bias, which often adds additional burdens by requiring re-analysis to reduce variability. Several attempts at automating the process of sleep stage scoring have been made over the last 3 decades, but most of those programs were either not widely available or were designed for custom applications. Recently a commercial software application for automatically scoring sleep records has been released. The system was used to acquire and score 6, 12 and 24 hr recordings from both rats and mice. Initial results agree well with expert manual scorers, and indicate that the system, although designed for human studies, is flexible enough to be used in animal studies.

**Methods:** SleepSign software (Kissei Comtec America, Irvine, CA) running on a standard Pentium-class PC was used to acquire (skull EEG and nuchal EMG) and automatically score sleep records from both rats and mice. The software suite consists of data acquisition and off-line analysis software modules, either of which can be used independently. The analysis module employs digital filtering and fully customizable waveform recognition algorithms and state logic tests to identify sleep stages. Up to 6 frequency bands are available for waveform recognition, although it was almost always found that a maximum of 3 bands, including delta (0.1-3.0 Hz) and theta (3.0- 9.0 Hz), were sufficient. 1 channel of EEG and 1 channel of EMG were recorded using standard Grass polygraph amplifiers. Up to 4 animals were recorded simultaneously; digitization of signals took place at 125 Hz.

**Results:** Screening of sleep records using an initial set of parameters in both rats and mice resulted in an accuracy rate of approximately 80-85%, compared with manual (visual) scoring. The time required to set up and perform the initial analysis was on the order of minutes, resulting in a significant savings over manual methods. Further refinement of the analysis parameters provided additional increases in sleep stage identification accuracy, although returns began to diminish as accuracy approached 100%.

**Conclusions:** A commercially-available software suite was used to automatically score sleep records from rats and mice. The analysis program uses a graphical user interface and highly customizable analysis routines to facilitate the automatic identification of sleep stages. This system offers several advantages over alternative methods such as custom or proprietary systems, including the availability of "factory support" and the absence of development time. Using the system on a laptop computer system confers an added benefit by reducing the amount of space necessary for conducting sleep studies. The software requires training to use properly, but future enhancements to the system should lessen the amount of learning required to use the system effectively and efficiently.

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## 727.R

## INFLUENCE OF PULSE OXIMETER TECHNOLOGY ON HYPOPNEA DIAGNOSIS USING THE NEWLY PROPOSED DEFINITION OF A RESPIRATORY HYPOPNEA

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**Introduction:** New guidelines for scoring a respiratory hypopnea proposed by AASM<sup>1</sup> have recently been adopted by Medicare in consideration of coverage of nasal CPAP therapy, replacing the 30-apnea rule (Coverage Decision Memorandum for CPAP, October 30, 2001). These guidelines require a measurable desaturation of 4% or greater in conjunction with a minimum of a 30% reduction in airflow or effort to qualify the respiratory event as a hypopnea. The aim of this study was to establish if the fidelity of different pulse oximeter technologies could influence the scoring of hypopneas.<sup>2</sup>

**Methods:** Twenty nine patients referred to the sleep disorders laboratory for evaluation of possible sleep disordered breathing were studied using three different oximeters, a Masimo Radical with SET V3 technology (M), a Nellcor N-395 (N3), and a Nellcor N-200 (N2). The N-200 was placed in Mode 2 configuration, which has a stated data averaging time of 2 to 3 seconds. The Radical was configured in the 2-second data averaging mode. The N-395 does not have a user-selectable averaging mode. All three oximeters were turned on simultaneously at the beginning of the study and turned off simultaneously at the termination of the study. The data from all three oximeters were downloaded into PROFOX oximetry analysis software (version PFWS 08/99). Two saturation indices, mean saturation and number of desaturations  $\geq 4\%$ , were extracted from the report and analyzed.

**Results:** There were no differences in mean saturation between M, N3, and N2 ( $95.8 \pm 1.7\%$ ,  $95.9 \pm 1.8\%$ ,  $95.9 \pm 1.5\%$  respectively). There was a large difference in the number of desaturations greater than or equal to 4% between the three oximeters. The mean number of desaturations were  $81 \pm 89$ ,  $48 \pm 55$ , and  $31 \pm 35$  for M, N3, and N2 respectively. The Masimo Radical detected 69% more desaturations  $\geq 4\%$  than the Nellcor N-395 and 161% more desaturations  $\geq 4\%$  than the Nellcor N-200. The Nellcor N-395 identified 55% more desaturations  $\geq 4\%$  than the Nellcor N-200.

**Conclusions:** In this population of patients, three different pulse oximeter technologies gave significantly different results for the number of desaturations  $\geq 4\%$  while overall mean saturation was the same for all oximeters. This difference between pulse oximeter technologies in detecting the degree of desaturation from baseline could have an important impact on qualifying patients for nasal CPAP coverage under the new Medicare reimbursement rules.

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**728.R**

**ASSESSMENT OF THE PHASE SHIFTING ABILITY OF A PORTABLE LIGHT DELIVERY DEVICE**

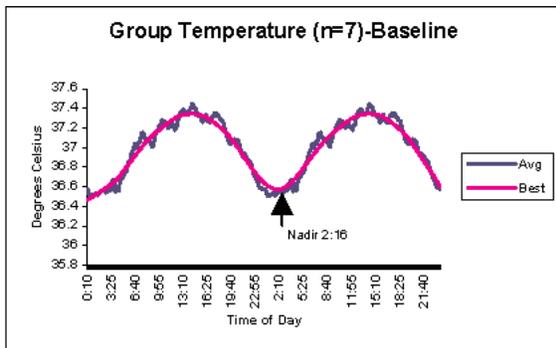
Orbeta LI,<sup>1</sup> Ortiz RJ,<sup>1</sup> Boudjenah D,<sup>1</sup> Benloucif S,<sup>1</sup> Goldman N,<sup>1</sup> Zee PC<sup>2</sup>

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**Introduction:** Sleep disturbances affect approximately 50% of Americans over the age of sixty-five years. Common in this age group is an advance in sleep phase, accompanied by sleep maintenance insomnia and early morning awakening. Previous studies have shown that timed bright light exposure from natural and artificial sources may be useful in the treatment of sleep-wake cycle disorders. However, the available methods for treatment of sleep-wake cycle disorders include the use of light boxes that are cumbersome, physically restrictive and decrease compliance due to practicality of use. Therefore, a more mobile and convenient device is being investigated for use in the treatment of circadian phase disorders. The goal of this study was to assess the effects of a novel bright light delivery system on circadian rhythms in older people.

**Methods:** The Somnavue™ is a portable fiber-optic bright light delivery system worn like a pair of glasses. This unit emits approximately 3,000 to 4000 lux close to the pupil and permits the individual the ability to have sufficient visual acuity to read and move around safely. Eleven subjects (mean age 71 years ± 2 years) were recruited from assisted care living facilities and residential homes. All subjects were advanced in phase (early morning awakening and advance core body temperature nadir) and were exposed to bright light (3000 - 4000 lux) by using this fiber-optic system in the evening (20:00 – 22:00) for 14 days. Light exposure and activity were monitored during the 7-day baseline period and throughout the 14 days of intervention through the use of the Actiwatch. During the last two days of the baseline period and for two days following the intervention, core body temperature was measured.

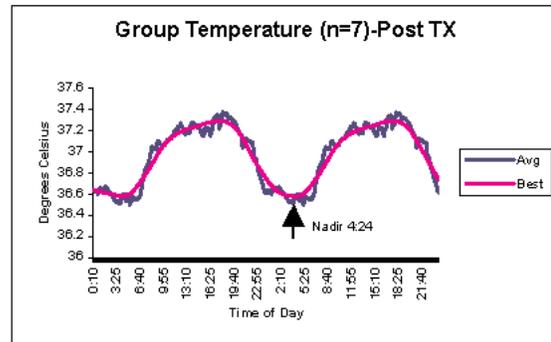
**Figure 1**



**Results:** The average baseline nadir of core body temperature for this study group (n=7) was 2:16 ± 0.55 hours. Light exposure for 14 days delayed the average post treatment core body temperature nadir to 4:24 ± 0.62 hours. Analysis of tempera-

ture data on this relatively small sample by repeated measures ANOVA resulted in a significant phase shift of their circadian rhythm (p=0.04).

**Figure 2**



**Conclusions:** The results of this study indicate that a mobile bright light delivery system is effective in shifting the circadian temperature rhythms of older adults. A portable bright light delivery system that is convenient to use and physically less restrictive may increase light treatment compliance in patients with sleep-wake cycle disorders.

**Research supported by R43 AG 13826-01A2, P01 AG 11412-03, K01 AG00810**

**729.R**

**VALIDATION STUDY OF PAPERLESS COMPUTER CADWELL EASY II SLEEP SYSTEM.**

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**Introduction:** Technological advances in the recording and scoring of sleep studies (Polysomnographs) has progressed rapidly in recent years (ASDA, 1994). New systems have replaced standard paper equipment in many of the top sleep institutes. The following study was conducted to compare the quality and consistency of recordings and scorings between the paperless computer Cadwell Easy II Sleep System with the standard paper equipment (Nikhon Kohden).

**Methods:** Twenty subjects (6 healthy and 14 with sleep disorders) were recruited at the Sleep and Behavior Medicine Institute in Skokie Illinois and agreed to participate in a validation study. The subjects ranged in age from 16 to 55 years old and consisted of 6 females and 14 males. Polysomnographs (PSG) and Multiple Sleep Latency Tests (MSLT) were recorded simultaneously on the Cadwell Easy II Sleep system and the Nihon-Kohden paper equipment using two separate sets of electrodes connected to each system. An identical standard montage was used (four channels of EEG, EOG, chin and leg EMG, nasal airflow, chest and abdominal respiration, pulseoxymetry). The recordings were scored by a certified sleep technician with partial rescoring by a Board Certified sleep specialist. The quality of the records were evaluated independently by two Board Certified sleep specialists. Statis-

tical analysis of the correlation between the records from two sleep systems was conducted using the Pearson's r correlation coefficient in SPSS 8.0 for Windows.

**Table 1**

**Correlation Between Cadwell and Paper Polysomnographs**

Indicators	Cadwell	Paper	Pearson's r
	Mean	Mean	
Total Sleep Time (min)	344.82	344.10	.996**
Sleep efficiency Index	0.89	0.87	.981**
Sleep Latency (min)	13.12	11.48	.719**
REM Latency (min)	111.19	109.9	.997**
Stage 1	39.33	38.13	.967**
Stage 2	183.01	184.14	.987**
REM	61.73	60.08	.986**
SWS	60.16	59.46	.992**
Apnea Index	1.73	1.91	.995**
Hypopnea Index	4.07	4.21	.997**
RDI Total	5.83	5.97	.998**
PLM Arousal	9.65	13.50	.767**
PLM Index	13.63	12.95	.855**

\*\* Significance at  $p < 0.001$

**Results:** There was a high degree of correlation between the Cadwell and paper PSG and MSLT (Table 1). All variables except Sleep Latency, PLM Index, and PLM Arousal, had correlation coefficients that were greater than .96. A more modest correlation was observed between the Cadwell and Paper system on the remaining variables (.70 - .85). Thus, the study shows a high degree of consistency between the two methods. Qualitative reports from scorers indicated that the quality of the EEG recordings by the Cadwell Easy II Sleep system and paper system was comparable and adequate. Disagreements of the manual scoring between these two systems were minimal and acceptable. Disagreements between the manual and automatic scoring of paperless recordings were minimal in the analysis of stages and respiratory events, but significant in evaluation of periodic limb movements.

**Conclusions:** The quality of the polysomnographic recordings and scorings of the Cadwell Easy II Sleep System is comparable with the standard paper equipment and adequate for clinical and research polysomnographic evaluations.

**References:**

(1) American Sleep Disorder Association. Practice parameters for the use of portable recording in the assessment of Obstructive Sleep Apnea. American Sleep Disorders Association and Sleep Research Society 1994, 17(4): 372-7.

**Research supported by the Sleep and Behavior Medicine Institute, Skokie, IL.**

## 730.R

### EPWORTH SLEEPINESS SCALE SCORES AMONG NORMAL SLEEPERS: AN ANALYSIS FROM A RANDOMIZED SAMPLE

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**Introduction:** The Epworth Sleepiness scale was developed as a subjective measure of daytime sleepiness. It measures an individual's tendency to fall asleep in 8 situations that are rated on a scale of 0-3 (0-would never doze- 3 high chance of dozing). Attempts have been made to establish norms for this measure within populations of normal sleepers and people with sleep disorders. These attempts have led to mixed results due to the use of cut-points. Cut-points have varied widely across studies. Past research has reported mean scores ranging from 4.6 to 7.7 in normal sleepers. There has also been mixed results with regard to gender differences and age differences on the ESS. Lastly, ESS scores among a large sample of normal sleeping African Americans have not been examined. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diary data and ESS data. This paper will focus on the ESS results among the normal sleepers in this sample.

**Methods:** We used random-digit dialing to collect data from 772 participants from 20 to 98 years old in the metropolitan Memphis (TN) area. Participants completed sleep diaries and questionnaires evaluating health, mood, and daytime functioning, including sleepiness and fatigue. For this analysis we examined scores on the Epworth Sleepiness Scale (ESS). Participants that were classified as having insomnia as measured by sleep diaries, or admitted to some other sleep disorder were excluded from this analysis. Also, 8 individuals were excluded from the analysis due to ethnicity because we felt the sample was not large enough to be representative. Lastly, 3 people were omitted due to missing data. This left us with a sample of 592 people who were characterized as normal sleepers.

**Results:** Of this sample 294 (49.6%) were male and 298 (50.4%) were female. Furthermore, 178 participants were classified as African American (30%) and 414 were classified as Caucasian (70%). There were relatively equal numbers of individuals in each age group (defined by decade). After conducting a series of ANOVAs we concluded that there was not a significant gender difference on the ESS, nor was there a difference between age groups. However, the ANOVA was significant for ethnicity with African Americans reporting significantly higher ESS scores than Caucasians ( $F=14.74, p<.001$ ). The mean ESS scores for the total sample of normal sleepers, the African Americans, and the Caucasians in that order are as follows:  $M=8.43, SD = 4.09$ ;  $M= 9.40, SD = 4.45$ ;  $M=8.01, SD = 3.84$ . ESS scores for this sample of normal sleepers were considerably higher than previous reports evaluating ESS in normal sleepers.

**Conclusions:** Based upon sleep diaries and ESS ratings in this randomized sample, these results find that normative scores on the ESS may be considerably higher than previously thought, for some populations without sleep disorders. Also, these

results do not support a significant relation between age or gender to ESS scores. However, within this sample of normal sleepers we had a notable sample size of African Americans and a significant difference between ethnicity on ESS ratings emerged. African Americans self-reported their probability of falling asleep as measured by the ESS to be significantly higher than Caucasians did.

Research supported by National Institute on Aging grants AG12136 and AG14738

731.R

A MODIFIED EPWORTH SLEEPINESS SCALE TO ASSESS SLEEPINESS AT DIFFERENT TIMES OF THE DAY: PRELIMINARY REPORT

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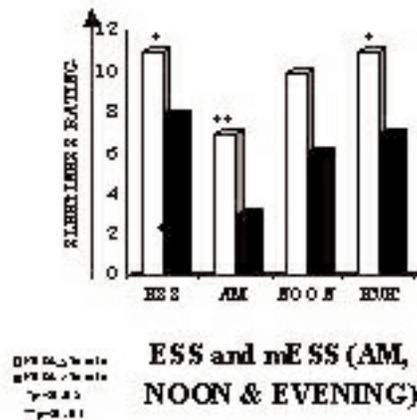
(1) Sleep Medicine Associates of Texas, P.A.

**Introduction:** Availability of self-reported sleepiness measures has facilitated the evaluation of clinic populations affected by disorders of sleepiness/alertness. The Epworth Sleepiness Scale (ESS) and the Sleep-Wake Activity Inventory have been shown to correlate with polysomnographic measures of sleepiness. Both scales assess patients' likelihood to fall asleep in activities of daily living. However, the scales do not inquire about the propensity to fall asleep at specific times of the day. The accessibility of such sleepiness measures would aid clinicians to identify, for individual patients, critical times of the day. From a research perspective, this tool would help characterize levels of sleepiness/alertness across different populations. In an effort to assess the viability of such an instrument, the ESS was modified from the usual one column format to a three-column format to assess patients' likelihood to fall asleep during their morning, afternoon and evening activities among patients attending a Sleep Medicine consultation.

**Methods:** Data from 69 consecutive patients are reported. Patients completed the ESS, a sleep questionnaire inquiring about their sleep habits and symptoms, and a modified ESS (mESS). The latter consisted of the same items and format of the ESS but asked subjects to rate each item based on their estimates of sleepiness in the morning (AM, before noon), afternoon (PM, noon to 18:00 hrs) and evening (EV, after 18:00 hrs). The group was divided by their subjectively reported nocturnal sleep onset latency (SOL < 30 min and > 30 min) as a means to differentiate sleepiness/alertness levels. The group with a normal SOL (SOL<30) consisted of 42 patients with complaints of snoring and/or EDS, 3 with Insomnia and 2 with parasomnia. The group with SOL of > 30 min (SOL>30) consisted of 15 patients with snoring and/or EDS and 7 with Insomnia. Similar proportion of male and female patients was encountered in both groups (32 and 40 % were female patients respectively), their ages were comparable (49 ±10 and 52 ±16) and both groups were overweight (BMI= 34 ±9 and 33 ±10). They reported similar bedtimes (range 20:30 to 02:00 hrs), arising times (range 04:00 to 12:00 hrs) and total sleep times (SOL<30=6.4 ±1.4 hrs and SOL>30=6.2 ±1.9 hrs). **Results:** The ESS scores based on the dichotomy of reported nocturnal sleep onset latency were different (SOL<30= 11+5

and SOL>30= 8 ±5, p< .05). For the mESS scores, there was a main effect of SOL grouping with no evidence of an interaction. The mESS scores in the AM (SOL<30=7 ±6 and SOL>30=3 ±3, p< .01), PM (SOL<30=10 ±6 and SOL>30=6 ±4, p< .05) and EV (SOL<30=11 ±6 and SOL>30=7 ±5, p< .05) are shown in the figure. Interestingly, there was a main effect of time with the AM mESS revealing the most alert scores (6 ±6, p< .05) when compared to the PM (8 ±5) and EV scores (9 ±6). The latter two scores were comparable. Consistent with these results are the relatively high correlations between the mESS and the ESS (AM r=0.69, p< .01, PM r=0.78, p< .01, and EV r=0.74, p< .01).

Figure 1



**Conclusions:** The results of this study confirm the viability of a modified ESS to assess sleepiness at different times of the day. The high correlations between the mESS and the ESS strongly suggest that patients' reports of sleepiness at different times of the day are consistent with their overall experience of sleepiness on the ESS. Yet, the mESS seems able to provide additional information on the changing nature of sleepiness levels across the day. Consistent with the view of an accumulating homeostatic sleep need across the day, patients reported significant increases in sleepiness levels in the afternoon and evening. An additional finding of this study relates to the apparent sensitivity of the reported nocturnal sleep onset latency to reflect a state of CNS arousal. Pointedly, this differential level of arousal seems to permeate the subjective experience of sleepiness/alertness across the day even among patients who do not necessarily complain of difficulty initiating and/or maintaining sleep.

732.R

EPWORTH SLEEPINESS SCALE CORRELATION WITH THE MULTIPLE SLEEP LATENCY TEST IN PATIENTS WITH OSAS

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**Introduction:** The Epworth Sleepiness Scale (ESS) is a brief subjective questionnaire that assesses daytime sleepiness. The

MSLT is a labor and time intensive polysomnographic tool that objectively evaluates an individual's sleepiness. Daytime sleepiness is a well-described symptom of OSAS and other sleep disorders such as Periodic Limb Movement Disorder of Sleep (PLMDS) and narcolepsy. The literature has reported both positive and negative correlations of the ESS with the MSLT. (1,2) Due to the conflicting data in the literature, we further pursued the question of whether or not the ESS results correlate with the MSLT findings.

**Methods:** As a brief screen of daytime sleepiness, we routinely administer the ESS at the time of initial evaluation. If the ESS reveals a score greater than ten, this supports our clinical decision to perform a MSLT as part of the diagnostic testing. We retrospectively analyzed the data on every adult patient that had been diagnosed with OSAS and who had also completed the ESS and underwent an MSLT in a four month period between April and July 2001. We then compared the results of the ESS to the MSLT findings.

**Results:** There were a total number of 45 patients (32 males and 13 females) in this sample. The average age was 46.4; median age was 46 and the ages ranged from 19 to 79. At the time of data collection, patients were undergoing diagnostic testing for OSAS and all of the patients included in this sample met the criteria for OSAS. Thirteen of the 45 patients (28%) also met the criteria for PLMDS. Average TST=336.0 minutes ( $\pm 60.5$ ); average SE%=77% ( $\pm 12.8$ ); average AHI= 24.7 ( $\pm 40.5$ ); average RAI=40.7 ( $\pm 28.2$ ); average Arousal Index=46.8 ( $\pm 30.43$ ), average SL on the MSLT=9.0 minutes ( $\pm 5.42$ ); average ESS score was 10.9 ( $\pm 5.7$ ). Multiple regression analysis did not reveal any statistically significant correlation between the ESS scores and the MSLT sleep latencies ( $B=-.00$ ). No statistically significant values were found when comparing the ESS scores to the TST, SE%, AHI, RAI, Arousal Index, and PLM arousal index. Separating the sample by gender did not affect the outcome. Separating the sample into two groups based on level of sleepiness determined by the ESS ( $ESS <=10$  vs.  $ESS >=10$ ) also did not change the outcome.

**Conclusions:** In our limited sample of patients with OSAS, the findings showed that the ESS scores did not correlate with the results of the MSLT. Our conclusion is that patients may subjectively underestimate or overestimate their level of sleepiness when completing the ESS. Obtaining an objective measure of daytime sleepiness should be considered when evaluating patients with OSAS or other sleep disorders associated with hypersomnia.

#### References:

- (1) Johns M W: Reliability and Factor Analysis of the Epworth Sleepiness Scale; *Sleep*, 1992, 15(4): 376-381
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### 733.S

#### THE USE OF PUBLIC SERVICE ANNOUNCEMENTS TO QUANTIFY SLEEPINESS IN THE POPULATION

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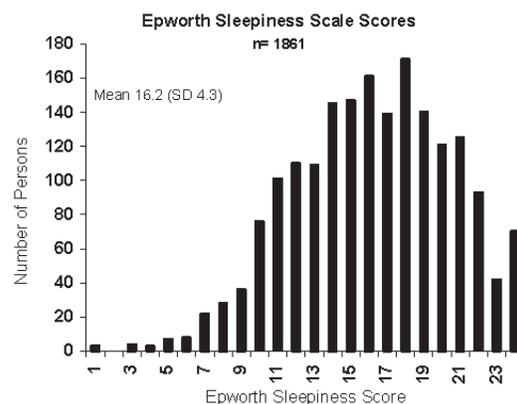
**Introduction:** Recent 'Sleepiness in America' surveys con-

ducted by the National Sleep Foundation (NSF) have included the Epworth Sleepiness Scale (ESS) as a validated measure to assess levels of sleepiness in the general population. In the first such survey, the NSF found that 32% of adults (approximately 63 million) over the age of 18 scored  $>10$  on the ESS, and 6% (approximately 12 million) scored  $>15$ , suggesting severe levels of sleepiness potentially indicative of an undiagnosed sleep disorder. <sup>1</sup> Experts have estimated that 95% of individuals suffering from sleep disorders go undiagnosed and untreated. <sup>2</sup> Thus, there is a need for increased awareness of sleepiness as a potential sign of a sleep disorder. We implemented a public awareness program to encourage people who thought they might be suffering from excessive daytime sleepiness (EDS) to call a central information center. Through this center they could either receive additional information on sleep disorders or take the ESS to quantify their level of sleepiness. We present the results of the ESS scores from these patients who responded to the public service announcement (PSAs).

**Methods:** We developed a series of PSAs highlighting situations described in the ESS. These situations are normal daily activities in which people suffering from EDS might fall asleep. These messages were disseminated via multiple mechanisms, including public service TV; print media; national, regional and local news and radio programs; and in-flight airline shows. At the end of these announcements, people who thought they may be suffering from EDS were encouraged to call a toll free number (1-888-41-AWAKE) to receive more information on EDS. Upon calling the EDS hotline, persons were presented with two options. They could either 1) directly enter their zip code to receive addresses of the 3 American Academy of Sleep Medicine (AASM) accredited sleep centers closest to their home, or 2) take the ESS test to determine their level of sleepiness. The ESS was administered via a voice-automated system, and scores were calculated immediately.

**Results:** Data from 3,347 people who called the EDS hotline during a 9-month period (March – November 2000) were collected and analyzed. 90% of all respondents requested information on AASM accredited sleep centers in their area. 56% ( $n=1,861$ ) of callers chose to take the ESS. In these individuals the mean ESS score was 16.16 (SD 4.3). 94% ( $n=1,750$ ) of these individuals had sleepiness levels  $>10$ , and 65% ( $n=1,210$ ) had sleepiness levels  $>15$ .

Figure 1



**Conclusions:** More than 90% of individuals responding to PSAs for sleepiness were pathologically sleepy, according to their ESS scores. Most (65%) had severe sleepiness at the level of untreated narcolepsy or obstructive sleep apnea. These data suggest that PSAs may be a valuable method to reach the approximately 12 million people with severe sleepiness previously identified by the Sleepiness in America Poll.

**References:**

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Research supported by Cephalon, Inc., West Chester, PA.

**734.S**

**SLEEP KNOWLEDGE IN A SAMPLE OF LATIN-AMERICAN MEDICAL STUDENTS**

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**Introduction:** Failure of adequate training or education in sleep medicine for health care professionals is main concern in the sleep medicine community.(1) Activities in medical schools show a large percentage of no structured teaching time on sleep medicine.(2) In the same way reliable instruments to measure knowledge on the topic are scarce. It has recently been published “The ASKME Survey” a reliable, consistent and discriminative test between samples with varied levels of education, experience and specialty training (3)Up to the best of our knowledge this approach has never been used to survey Latin American medical students. This report describes the findings among a sample of medical schools in two countries in Latin America using a translated version of “The ASKME survey”

**Methods:** A committee of Latin American’s sleep medicine experts from the “Red Latinoamericana de Educación en Medicina del Sueño” (REDLADES) were selected. All members of the committee were bilingual, some trilingual. Two translations were done, one to Spanish and the other to Portuguese. After discussion all members of the committee agreed in one final version in each language. An official translator Independently translated the original english survey to Portuguese and Spanish, and then back translated to English those versions translated by the committee. Over 90% agreement among all translated versions and english original paper was found.A group of medical students of the academic year immediately previous to internship from different universities of Brazil and Peru were invited to participate. The questionnaire was handed out as self-administered and paper printed.

**Results:** The percentage of acceptance to participate was 85 %. Responders were 95 medical students from three universities of Brazil and one from Peru. Results from Brazilians and Peruvians medical students, were not different in total per-

centage of correct answers among questions grouped by topics A second comparison was done combining the results of the original report(3) with our group of study. One-way analysis of variance among means of the results of 75 American sleep specialists, 213 American, 51 Brazilian and 44 Peruvian medical students found significant differences between sleep specialists and all medical students group, however no significant differences among medical students from different countries were reached. Table 1.

**Table 1**

Comparison of Percentage Correct among groups				
Category/	A	B	C	D
Sleep *	US Med	Brazil Med s	Peruvian Med	
	Specialists	Students	Students	Students
	(N=75)	(N=213)	(N=51)	(N=44)
Overall correct	85,3	56,3	42,35	40,56
Basic Sleep	82,0	63,8	41,90	46,54
Circadian S/W	94,0	56,3	56,48	40,24
Sleep Architecture	92,1	59,5	46,91	36,58
Sleep-dis breathing	92,7	68,3	63,89	75,61
Narcolepsy	86,0	36,4	12,96	48,78
Insomnia.	85,9	56,4	48,15	24,88
Parasomnias.	78,5	49,0	33,70	27,64
Effects Drugs/Alcoh	80,5	54,4	39,50	25,61

Anova between groups p<0.05. Tukey A≠ B=C=D

**Conclusions:** The translated versions to Spanish and Portuguese of “The ASKME survey” could be useful for evaluating sleep knowledge in Latin American medical students. Its discriminative values might be the same as in the original english version. Although we did not find differences among results of medical students, we think bias in selection of sample and small number of participants limits more firm conclusions.

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Research supported by Study sponsored by REDLADES from Sanofi-Synthelabo

**735.S**

**SLEEP AWARENESS AMONG HEALTH CARE PROFESSIONALS**

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**Introduction:** Sleep Disorders are very common in clinical practice. Even so, adequate emphasis has not been placed to incorporate teaching in this field in the curricula of medical schools and residency programs. Not surprisingly, many physicians do not obtain a detailed history about sleep which can lead to under-diagnosis of these disorders.

**Methods:** A simple questionnaire (19 items) was sent to all attending physicians, residents and medical students (M3 & M4s) at the University of Missouri. The questions pertained to medical speciality, training in the field of sleep medicine and knowledge of symptoms associated with sleep apnea. Questionnaires were sent via the university e-mail system or by regular institutional mail (printed copies). Printed replies were obtained in an anonymous fashion.

**Results:** 104 questionnaires were completed. Of these, 27 (25.9%) were attending physicians and the rest were fellows, residents and medical students. Most respondents- 47 (45%) - were physicians in the field of internal medicine or an internal medicine subspecialty. There were 33 medical students (31.7%), 10 neurologists (9.6%), 5 surgeons (4.8%), 6 family physicians (5%) and 3 pediatricians (2.8%). 77 respondents (74.1%) did not receive any training in sleep medicine. 27 (25.9%) did get some training- 17 (16.3%) had attended lectures, 12 (11.5%) participated in clinical discussions and 13 (12.5%) had formal rotation in sleep medicine. 7 (6.7%) participated in Journal club on sleep medicine. Only 50 respondents (48%) routinely asked questions regarding the patients sleep and 41 (39.2%) referred patients for sleep studies. Snoring, excessive daytime sleepiness and obesity were the most frequent features (95% of respondents) to raise the index of suspicion for sleep apnea. However, 61 (58.6%) were not aware that erectile dysfunction may be associated with sleep apnea. 88 respondents (84.6%) thought that training in sleep medicine should be increased.

**Conclusions:** Most physicians and medical students do not seem to receive adequate training in the field of sleep medicine. Although most of them were aware that snoring, excessive daytime sleepiness and obesity may be associated with sleep apnea- yet, majority did not know that erectile dysfunction can be associated with sleep apnea. More importantly, 52% of the respondents did not routinely obtain a sleep history in their patients. While this is a small, single center study, it does suggest the need to increase the exposure to sleep medicine in the medical school and residency program curricula.

**Research supported by Sleep Disorders Center, University of Missouri-Columbia**

**736.U**

**SLEEP, MOTOR VEHICLE ACCIDENTS, AND THE ENVIRONMENT: CONSIDERATION OF AN IMPORTANT, BUT UNDER EXPLORED RELATIONSHIP.**

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**Introduction:** Inadequate sleep leads to impaired performance in cognitive and motor skill tasks. Studies demonstrate that after 17-19 hours without sleep individuals perform on tests at a level equivalent to that of a BAC of 0.05% and after longer periods up to 0.1%. Yet, while the hazardous effects of alcohol are widely recognized and addressed through legislation and campaigns, only two American States have laws addressing excessive daytime sleepiness. The hazards of sleep deprivation are well documented as the direct cause of many environmental disasters, including: the Exxon Valdez oil spill, the Challenger explosion, and in the meltdown at Chernobyl. Inadequate sleep also directly impacts the environment through motor vehicle accidents. Accidents are the fourth leading cost of mortality in the United States, and motor vehicle accidents are responsible for 51% of these deaths. Previous estimates indicate that fatigue may be responsible for 1% to 60% of all motor vehicle accidents. These statistics translate to a conservative estimate of 100,000 sleep related crashes, 17,689 deaths, and 769,184 disabling injuries annually (Leger 1994). Poor sleep hygiene, shift work or medical disorders (the most common being sleep apnea syndrome) are often contributing factors to these social and environmental disasters that result from inadequate sleep.

**Methods:** From 1996-2000, 347 drivers involved in Motor Vehicle Accidents (MVA) were taken to St. Mary Medical Center's trauma ward. Of these patients, 179 were considered in a motor vehicle accident chart review; where information on accident description, demographic characteristics, and past medical history were obtained. This information was considered with relation to sunrise/sunset tables and weather conditions to assess the extent to which sleep, or sleep debt, was a cause of the accident based on a scale from 1-(directly attributed to sleep) to 4-(no role played by sleep).

**Table 1**

	Number of Accidents	% of Total
1 (completely)	28	15.64
2 (possibly)	21	17.32
3 (probably not)	64	35.74
4 (definitely not)	44	24.58
Total	167	93.28
*Judgment of 12 cases is currently pending		

**Results:** In 28 of these cases evidence directly indicated or the driver stated, "I fell asleep" (Table 1). For another 31 cases,

the potential role of sleep or fatigue in the accident is high. In only 25% of the cases could we confidently assess that sleep did not play a role. In total, sleep directly played a role in 16% of the MVA's and possibly was a component in up to 32% of the accidents.

**Conclusions:** These figures reveal the importance of addressing the relationship between sleep and motor vehicle accidents-from both a social and environmental standpoint. Two of the key approaches for reducing these preventable accidents include driver reeducation and identification and treatment of patients with sleep disorders such as sleep apnea syndrome. Obstructive sleep apnea (OSA) has been found to be the most prevalent sleep disorder referred to sleep clinics, occurring in approximately 34% of the general population and 87% of Truckers (Stoohs et al. 1995). Studies demonstrate that patients with sleep-disordered breathing have accident rates two to seven times higher than patients without OSA, and that these accident rates diminish to control levels after CPAP treatment (Young et al. 1997). Base on the current study, addressing the causes of excessive daytime sleepiness and driver fatigue awareness has the potential to reduce the environmental and social consequences of motor vehicle accidents by 32%.

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**737.U**

**SLEEP IN SOUTH AFRICAN UNIVERSITY STUDENTS: CONSEQUENCES OF SLEEP BEHAVIOR FOR DAYTIME FUNCTIONING.**

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**Introduction:** Very little is yet known about sleep behavior and daytime alertness of South African university students. A large proportion of university students in other countries, however, are sleep deprived and consequently are sleepy during the day<sup>1,2</sup>. Sleep debt may have serious consequences for students' daytime alertness, academic performance and general psychological well being<sup>2</sup>. Sleepiness also affects driving behavior and often may predispose students to potentially serious driving accidents<sup>2</sup>.

**Methods:** As part of a larger investigation about sleep in South African students, we conducted a questionnaire-based study to investigate the influence of sleep habits and daytime alertness on academic performance, emotional state and sleep-related vehicle accidents in 986 South African university students

(21±3years, 53% female) over the previous month.

**Results:** The students reported a mean (SD) time in bed of only 7hr22min (1hr12min) on weeknights and a large majority (61%) reported that their sleep was of moderate to very poor quality. The students were excessively sleepy during the day, as indicated by a mean score of 9.7 on the Epworth Sleepiness Scale, which is far higher than that reported for American adults (5.9) and approximates scores reported for American adults with Obstructive Sleep Apnea (11.7) 3. Time in bed and sleep quality also influenced the students' daytime performance. Those students who spent a significantly longer time in bed (F(2,693)=14.4,P<0.0001) and reported better sleep quality ( $\chi^2(2)=10.6$ , P<0.01), also reported putting more effort into their university work. Although time in bed was not associated with better grades on the students' most recent examinations, the likelihood of obtaining better grades was greater for those who reported better perceived quality of sleep ( $\chi^2(2)=9.4$ , P<0.01). Sleep also affected the psychological well being of the students; poorer sleep quality ( $\chi^2(1)=57$ , P<0.0001) and greater daytime sleepiness (F(1,918) = 17.4,P<0.0001) was associated with little or no energy during the day. Similarly, poorer sleep quality was more likely to be reported by the students who were very or fairly unhappy ( $\chi^2(1)=20.7$ , P<0.0001) and by those who were fairly or very stressed ( $\chi^2(1)=24$ ,P<0.0001). Finally, 55% of the students reported feeling sleepy, at least occasionally, while driving. 20% of this group had fallen asleep at the wheel and 2% had already had an accident because they fell asleep. Those students who reported feeling sleepy while driving spent less time in bed (F(2,693)=7.6,P<0.001), had lower sleep quality ( $\chi^2(2)=13.6$ , P<0.01), and were sleepier during the daytime (F(2,826)= 5.6,P<0.005).

**Conclusions:** South African university students get relatively little sleep and are pathologically sleepy during the day, which puts them at risk for poor ability to perform at university, poor mood and increased likelihood of fatigue-related automobile accidents.

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**738.U**

**SPATIAL MEMORY AND WINDOWS OF LEARNING**

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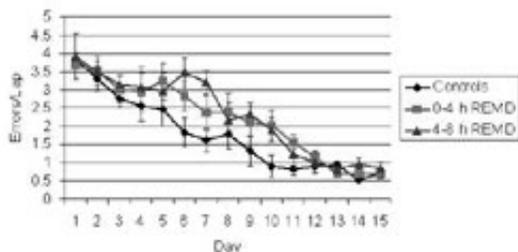
- (1) University of Michigan

**Introduction:** We tested the hypothesis whether animals deprived of REM sleep in the 1st vs. 2nd sleep "window" (4 h period) are impaired in their performance compared to controls on a spatial learning task over an extended period of time. In a prior study, rats deprived of REM sleep during hours 4-8 after learning a task never reached the same level of perform-

ance efficiency as controls and as rats deprived of REM sleep in hours 0-4 after learning. We replicated the 6-d study and extended the number of days recorded to 15 to determine the asymptote for the learning curve of each group.

**Methods:** Two groups of rats were selectively deprived of REM sleep for 4 h, using the inverted multiple flower pot method. The first group was deprived immediately following training, the second group was returned to their home cage for 4 h before REM deprivation. A third group of controls (non-deprived) were trained on the same maze then returned to their home cage. For motivation, rats were only fed on the maze. The spatial task required rats to learn locations of food placement in 3 of 8 available box choices. Three types of errors were possible: commission - in which rats investigated a non-baited box, hesitation - in which rats paused beside a non-baited box, and omission - in which rats failed to investigate a baited box. We controlled for a number of non-spatial strategies, such as procedural or simple cue learning, with a variety of tactics. A repeated measures ANOVA was used to determine if the learning curve was different between groups. We analyzed the types of errors committed each day between groups. **Results:** The repeated measures ANOVA showed no difference between the two REM-deprived groups, but a significant difference between control and REM-deprived rats at the middle of the learning curve on days 6, 7, 9, and 10. The control group learning curve shifted 2-3 days ahead of the deprived rats. The performance of all groups reached asymptote at the same level, on average < 1 error/lap. The learning curves of the rats from this experiment were different than those of the previous experiment. These rats needed 13 days to reach asymptote, compared with 6 days on the prior study. In the first 4 days the rats could eat their bedding, before we switched from corncob to recycled paper bedding, and therefore did not lose weight as quickly and ran fewer laps in the first week.

Figure 1



**Conclusions:** REM deprivation delayed spatial learning by 2 to 3 days, however repeated exposure eventually compensated for this impairment. Different types of errors may reveal the learning process. Errors of omission diminished rapidly in the first days in all groups, and may indicate a growing familiarity with the procedure. Errors of commission comprised the largest discrepancy between groups and, together with errors of hesitation, reveal the REM-deprivation dependent impairment in specific place learning.

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## 739.U

### EXCESSIVE DAYTIME SLEEPINESS IN THE URBAN ADULT GENERAL POPULATION OF CAMPO GRANDE, BRAZIL

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**Introduction:** Excessive daytime sleepiness is a fairly usual complaint in general population. The present report is part of a larger population study to determine sleep characteristics and sleep disorders in Campo Grande city, Brazil.

**Methods:** We evaluated the prevalence of excessive daytime sleepiness in a sample of Campo Grande city. The sample was composed by 408 adults evaluated at home interviews; this at random sample was stratified by sex, age and social status. Excessive daytime sleepiness was considered in those who achieved scores (11 or more) in the Epworth Sleepiness Scale. Statistical analysis was performed using chi-square, Fisher, Pearson and inferences based on binomial distribution parameters; the significance level was 5%; and the confidence level, 95%.

**Results:** Excessive daytime sleepiness was detected in 18.9% of the population, using the Epworth Sleepiness Scale (SD=1.9%; IC 15.1% to 22.7%). There was no significant correlation between excessive daytime sleepiness and any of the following studied parameters: age, sex, school educational years, social status, marital status, job, insomnia, hypnotic drug use, other alternative sleep inducing methods.

**Conclusions:** There was a high excessive daytime sleepiness index observed on Campo Grande urban adult population. Further studies will focus on affected sub-groups.

## 740.U

### SLEEP-DEPENDENT MOTOR SKILL LEARNING

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**Introduction:** Motor-skill learning is known to continue across 24-hours post-training, yet the relative contributions of wake and sleep are unknown.

**Methods:** Experiment One: Eighteen subjects were assigned to two experimental groups. All subjects received training on a sequential finger-tapping task and were retested twice over the next 24-hours. The "wake-1st" group was trained at 10 AM, and retested at 6PM that evening and 10 AM the next morning. The "sleep-1st" group underwent training at 10PM, and was retested at 8 AM the next morning, and 6 PM that evening. Experiment Two: Ten additional subjects were trained on the same motor-skill task at 10 PM, having their sleep monitored using polysomnography, and were retested at 8AM the following morning.

**Results:** Experiment One: Although practice within the training session improved performance for all subjects equally, the wake-1st group demonstrated no significant improvement when retested 8-hours later at 6PM. Only at 10AM the next

morning, after a night of sleep, was a dramatic 22% improvement seen, compared with the post-training session 24-hours earlier ( $p=0.0003$ ). In contrast, the sleep-1st group demonstrated a similar 21% improvement over night, just 10-hours post-training ( $p=0.001$ ); no further improvement was seen at 6PM despite an additional 10-hours of wake. Experiment Two: Again, an average 21% improvement occurred overnight. Furthermore, a significant correlation was evident between %-improvement and the total amount of stage2-NREM sleep ( $r=0.61$ ;  $p=0.04$ ), increasing to  $r=0.77$ ;  $p=0.009$  when focused on the last 8th of the total nights sleep.

Figure 1

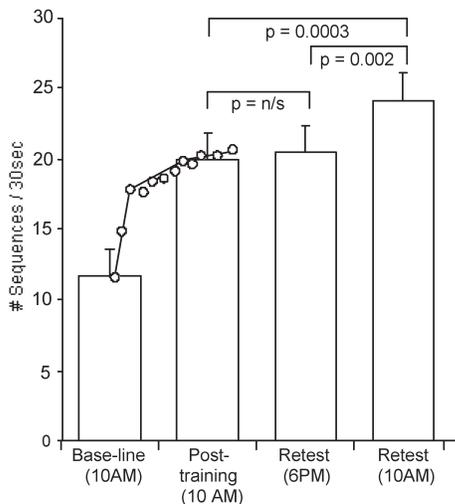
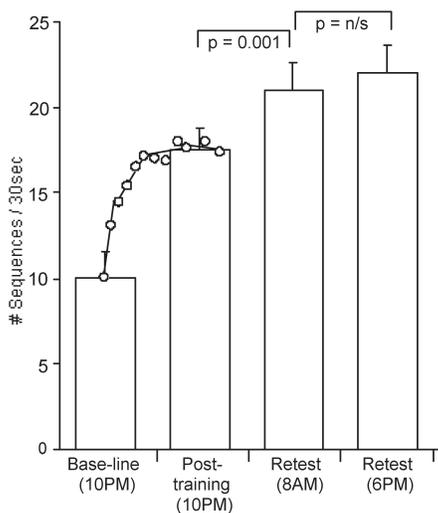


Figure 2



**Conclusions:** This represents the first clear case of sleep-dependent improvement on a motor task, with implications regarding the mechanisms of motor-skill learning.

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741.U

**POWER NAPPING AND BURNOUT: THE RESTORATIVE EFFECT OF NAPS AFTER PERCEPTUAL LEARNING**

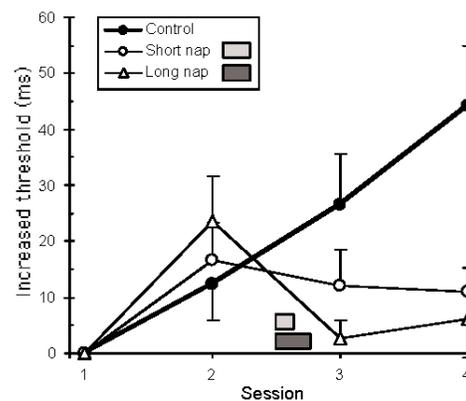
Stickgold R,<sup>1</sup> Mednick S,<sup>1</sup> Cantero JL,<sup>2</sup> Atienza M,<sup>1</sup> Pathak N,<sup>1</sup> Nakayama K<sup>1</sup>

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**Introduction:** Studies of the effect of strategic naps on the psychomotor performance of night workers have found improvement in performance and alertness. But no studies have examined the effect of day-time naps on perceptual learning. We tested the effect of day-time naps on perceptual learning with a visual texture discrimination task (TDT) (Karni & Sagi, 1991) whose learning is known to be sleep dependent (Stickgold et al., 2000).

**Methods:** Subjects were tested on the TDT four times in one day (9 AM, 12 PM, 4 PM and 7 PM). Five groups of subjects were tested. Controls took the four tests without intervention; subjects in the Short Nap group were allowed to sleep for 30 min at 2 PM, and subjects in the Long Nap group were allowed 60 min of sleep at the same time. Subjects in the Switch group were treated the same as Controls, except that the location of the target stimuli were switched to the opposite visual quadrant (from lower left to lower right or vice versa) for the fourth and final test session. Subjects in the Incentive group were treated the same as Controls, except that at the start of their third session they were offered a monetary incentive to improve their performance back to baseline (first test) levels.

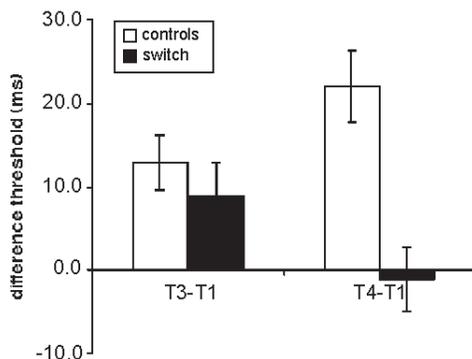
Figure 1



**Results:** Control subjects (N=10) showed a 52% slowing of perceptual processing across the four test sessions (Figure 1, filled circles) ( $p = .0003$ ). As predicted, napping significantly improved subsequent performance, with 30 min naps preventing the normal deterioration seen during sessions 3 and 4 (Fig. 1, open circles), and 60 min naps reversing the deterioration evident in the second session (Fig. 1, open triangles). Thus, while controls showed a 14.1 ms increase in threshold between the second and third sessions, the short nap group showed a

4.5 ms decrease in threshold, and the long nap group showed a 20.9 ms decrease ( $p = .0002$ ). Performance of the Switch group did not differ significantly from the Control group across the first three sessions, but, unlike the control group, the Switch group showed significant improvement in the fourth session (Fig. 2) ( $p = .002$ ), performing as well or better than during the first, 9 AM test session. Finally, the Incentive group showed only minimal ability to improve their performance when offered a monetary incentive, and showed no ability to regain baseline performance levels during the final two test sessions.

**Figure 2**



**Conclusions:** Repeated testing on the TDT across a day leads to a continued decrease in performance. This apparent fatigue can be prevented by a 30 min nap or reversed by a 60 min nap. However, the deterioration in performance is not due to a generalized fatigue, since switching the visual quadrant in which the stimuli are presented abolishes the fatigue effect. Thus, the "fatigue" is retinotopically specific, suggesting a use-dependent fatigue of local neural networks.

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#### 742.U

##### **FMRI BASED ANALYSIS OF AFFECT OF REM SLEEP ON THE ORGANIZATION OF NEURAL CIRCUITS IN MEMORY CONSOLIDATION**

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**Introduction:** It is known that most of the long term memory

processing occurs during the REM sleep. One of the first theories in support of this concept was by Roffwarg, Musio and Dement in 1966. They suggested that repetitive firing of neurons during REM sleep in human fetuses was associated with neuron growth and development, and recent synaptic reinforcement continued in adult life during REM sleep. Performance of a basic visual discrimination task improved after a normal night's sleep [1,2]. In recent years, sleep deprivation has been shown to impair high-level executive thinking.

**Methods:** Hippocampus has shown to play an important role in memory consolidation during REM sleep. Therefore, we try to answer the question: whether the cortical neural networks work differently during memory consolidation in individuals with REM sleep compared to those who were not allowed to go into REM sleep. We proceeded with following questions: Whether the quality of sleep effects memory consolidation. If yes, what is the association of quality of sleep (type of sleep pattern as seen in EEG) with the way neural circuits are organized in memory consolidation? In our research study, four healthy individuals were selected who had no previous complaints of sleep disturbance. They were given text and numbers to memorize before going to sleep. They were monitored during their sleep using Telefactor Video EEG system. Two individuals were not allowed to go into the REM sleep by disturbing their sleep, and the other two were allowed to continue their regular sleep with continuous video EEG monitoring. fMRI frames were recorded for a fixed time interval for analysis purpose

**Results:** fMRI based analysis were performed on all four individuals using 1.5 T GE Horizontal Echospeed MR system using conventional BOLD sequences. This was done for 3 consecutive days. The subjects were asked to repeat the text and the numbers presented to them previous day. Using fMRI data we tried to analyze the difference in cortical activities in these two groups of individuals using artificial neural networks based model. The volume of area activated significantly differed in two groups. The patterns of cortical activity, which was analyzed, using fMRI images, differed between individuals with REM sleep in comparison to those with little or no REM sleep.

**Conclusions:** We try to analyze effect of REM sleep on cortical activity and also on the way neural networks are organized in memory consolidation using fMRI information. Initial results of analysis are very encouraging and we are able to say that REM sleep does play significant role in memory consolidation. We plan to study and evaluate the difference in neural network organization in these individuals and compare them to neural network analysis using artificial neural network. Further investigations are being undertaken to get more results.

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743.U

PETS AND SLEEP

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**Introduction:** Snoring and body movements are considered capable of disrupting the sleep of bedpartners (1). Infants and children co-sleeping with their parents may also disrupt sleep. The present survey was conducted to determine the frequency and severity of sleep disruption that may result from family pets.

**Methods:** Between February and September 2001, a total of 300 patients seen in routine consultation were surveyed. If they currently had any pets, the number and type were recorded along with whether or not the pet(s) slept in the patients bedroom and/or on the bed. If the pet(s) slept in the bedroom, the average number of nights per week that the pet disrupted their sleep to any extent was recorded. Patients were also asked whether their pets snored and to estimate the average number of minutes per night that their sleep was disrupted by their pet. The following scale was used. 0 = no disruption, 1 = <20 min, 2 = 20-40 min, 3 = >40 min.

**Results:** One hundred and fifty-seven (52%) of the patients had one or more pets. They were almost exclusively dogs, cats or both. Of the 157 patients with pets, 92 (59%) only had dogs, 38 (24%) only had cats and 27 (17%) had both. Table 1 shows the number and percentages of patients with dogs, cats or both that slept in their bedroom and on their bed. The number of nights per week that their sleep was disrupted by their pet(s) followed a highly bimodal distribution. In contrast to the 40% who felt that their sleep was never disrupted, 53% considered their sleep to be disrupted to some extent every night. However, only 1% of patients felt that their sleep was disrupted for more than 20 minutes per night on average. Snoring was reported in 32 (21%) of dogs and 6 (7%) of cats. In only 1 dog was the snoring considered louder than that of the spouse and for whom a veterinarian recommended a palatoplasty.

Table 1

Number of Patients with Pets			
	#	In Bedroom	On Bed
Dogs	92	46 (50%)	26 (28%)
Cats	38	24 (63%)	22 (58%)
Both	27	21 (78%)	17 (63%)
Total	157	91 (58%)	65 (41%)

**Conclusions:** Approximately 50% percent of patients referred for sleep consultation will have pets. Of the patients with pets, 58% of them allowed the pet(s) to sleep in their bedroom with 41% permitting the pet(s) to sleep on the bed. Despite 53% of the patients reporting that their sleep was disrupted to some extent 7 nights per week, only 1% considered this disruption to average greater than 20 minutes per night. Cats were more likely than dogs to be allowed in the bedroom and on the bed. It remains to be determined if this is due to the higher frequency of snoring reported in the dogs compared to the cats.

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744.U

FATIGUE AND FITNESS FOR DUTY IN THE SOUTH AUSTRALIAN MINING SECTOR

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**Introduction:** Fatigue that results from inadequate restorative sleep is now the focus of Occupational Health and Safety (OH&S) legislation in Australia. The Duty of Care aspect of the OH&S legislation assigns responsibility to both employers and employees for maintaining safe workplaces. For the employer, the responsibility exists to provide and maintain a safe and healthy workplace and system of work. For the employee, the responsibility exists to undertake lifestyle management that ensures fitness for duty (preparation and recuperation). Fitness for duty can be defined as the capacity of an individual to perform their job safely and competently. Thus, the onus is on the employee to present themselves at their place of work in a fit state. Fitness for duty (FFD) policies are introduced to enforce the duty of care of both the employer and employee. Factors that impair an individual's ability to perform their job are the focus of workplace FFD policies. For the most part, FFD policies cover short-term 'reasons' for impaired ability, which manifest quickly and can be treated immediately and relatively easily.

**Methods:** A qualitative approach that involved face-to-face and/or focus group semi-structured interviews was used to assess the understanding and effectiveness of FFD policies and legislation as it applies to the Mining and Quarrying industry. Potential participants were identified by the Mining and Quarrying Occupational Health and Safety Committee (MAQOHSC) and included managers, OH&S representatives, employees and Union delegates.

**Results:** From a potential 132 mining and quarrying organisations in South Australia, we have sampled 23 with the remainder currently under review. Data collected to date indicates a broad range of understanding and compliance by mining personnel to Fitness for Duty policies especially regarding drugs and alcohol in the workplace. However, while fatigue was recognised by most mining personnel as a workplace problem this was not reflected in policy documents. Anecdotal report from miners suggests that work napping was not uncommon (30% of sample), near miss fatigue-related incidents went largely unrecorded if there were no visible signs of damage to equipment or personnel (43%), and where policies do exist they are generally not implemented especially if disciplinary action is required (18%).

**Conclusions:** The preliminary data indicates that while sleep and fatigue related incidents are not uncommon in the Mining and Quarrying Industry, they are generally under-reported. Indeed while policies may exist, they are not targeting the underlying psycho-social factors that may determine compliance with FFD policies. It is now considered socially unacceptable for employees to work while under the influence of drugs and/or alcohol, in the same way it is becoming evident that tired workers may place themselves and others at risk.

Therefore, it is important to determine the extent of the problem within the mining sector and to determine how policies that influence workplace practices are developed and implemented such that employers and employees fulfil their responsibilities under the OH&S legislation. At the conclusion of the study we hope to have achieved an extensive survey of policies and practices within the mining sector that can act as a benchmark for best practice guidelines nationally.

**Research supported by the Mining and Quarrying Occupational Health and Safety Committee, South Australia.**

