A Double-Blind Study in Healthy Volunteers to Assess the Effects on Sleep of Pregabalin Compared with Alprazolam and Placebo

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Study Objectives: To assess the effects of pregabalin compared with alprazolam and placebo on aspects of sleep in healthy volunteers.

Design: Randomized, double-blind, placebo- and active-controlled, 3-way crossover.

Setting: Single research center.

Participants and Interventions: Healthy adult (12 men) volunteers (N = 24) received oral pregabalin 150 mg t.i.d., alprazolam 1 mg t.i.d., and placebo t.i.d. for 3 days.

Measurements and Results: Objective sleep was measured by an 8-channel polysomnograph; subjective sleep was measured using the Leeds Sleep Evaluation Questionnaire. Compared with placebo, pregabalin significantly increased slow-wave sleep both as a proportion of the total sleep period and the duration of stage 4 sleep. Alprazolam significantly reduced slow-wave sleep. Pregabalin and alprazolam produced modest, but significant, reductions in sleep-onset latency compared with placebo. Rapid eye movement sleep latency after pregabalin was no different than placebo but was significantly shorter than that found with alprazolam. Although there were no differences between the active treatments, both pregabalin and alprazolam reduced rapid eye movement sleep as a proportion of the total sleep period compared with placebo. Pregabalin also significantly reduced the number of awakenings of more than 1 minute in duration. Leeds Sleep Evaluation Questionnaire ratings of the ease of getting to sleep and the perceived quality of sleep were significantly improved following both active treatments, and ratings of behavior following awakening were significantly impaired by both drug treatments.

Conclusions: Pregabalin appears to have an effect on sleep and sleep architecture that distinguishes it from benzodiazepines. Enhancement of slow-wave sleep is intriguing, since reductions in slow-wave sleep have frequently been reported in fibromyalgia and general anxiety disorder.

Key Words: Pregabalin, alprazolam, sleep, Leeds Sleep Evaluation Questionnaire, slow-wave sleep, rapid eye movement sleep, healthy volunteers

Abbrevations: NREM, non-rapid eye movement; PSG, polysomnograph ; REM, rapid eye movement; SWS, slow-wave sleep

Citation: Hindmarch I; Dawson J; Stanley N. A double-blind study in health volunteers to assess the effects on sleep of pregabalin compared with alprazolam and placebo. *SLEEP* 2005;28(2):187-193

INTRODUCTION

PREGABALIN, THE S-ENANTIOMER OF 3-ISOBUTYLGABA, IS A NOVEL COMPOUND WITH BROAD-SPECTRUM EFFICACY IN THE TREATMENT OF DIVERSE CONDITIONS, INCLUDING DIABETIC NEUROPATHY,[1] postherpetic neuralgia,[2] and partial seizures.[3] In addition, more-recent preliminary evidence from 2 dose-finding studies[4,5] suggests that pregabalin may also have efficacy in general anxiety disorder.

Disclosure Statement

This was an industry supported study supported by Pfizer. Prof. Hindmarch has participated in studies supported by Pfizer, Merck, UCB, Aventis, Eli Lilly, Lundbeck, Sanofi-Synthelabo, GlaxoSmithKline, and Sepracor; and has participated in speaking engagements supported by Solvay, Pfizer, Sanofi-Synthelabo, UCB, and Servier. Dr. Dawson has participated in studies supported by Sanofi-Synthelabo, Merck, Wyeth, UCB, Aventis, Eli Lilly, Lundbeck, GlaxoSmithKline, and Sepracor. Dr. Stanley has participated in studies supported by UCB, Merck, Aventis, Eli Lilly, Sanofi-Synthelabo, Lundbeck, GlaxoSmithKline, Sepracor, and Pfizer; and has participated in speaking engagements supported by GlaxoSmithKline, Pfizer, and Yamanouchi. The data were analyzed by the authors. The paper was written by the investigators.

Submitted for publication March 2004
Accepted for publication November 2004

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Pregabalin is rapidly absorbed (T_{max} = 1 hour) and has linear kinetics across its therapeutic dose range.[6] Pregabalin is not protein bound. It has an elimination half-life of 6 hours and is primarily (92%) renally excreted (89% as the parent compound). Pregabalin does not inhibit P450-CYP enzymes, nor do CYP-enzyme inhibitors alter its pharmacokinetics.

Pregabalin represents a new class of anxiolytic, with a mechanism of action that is different from benzodiazepines, azapirones (buspirone), monoaminergic antidepressants such as tricyclics, and selective serotonin and noradrenaline reuptake inhibitors. Pregabalin binds to the α_2-δ subunit protein of N- and P/Q-type calcium channels. Pregabalin has no activity at $GABA_A$, $GABA_B$, or benzodiazepine receptors and has shown no discontinuation syndrome following daily doses of up to 900 mg for up to 4 weeks.[7] Pregabalin does not bind to presynaptic or postsynaptic serotonin receptors, nor does it inhibit reuptake of serotonin or norepinephrine.

Pregabalin acts as a presynaptic inhibitor of the release, in stimulated neurons, of excitatory neurotransmitters, including glutamate,[8,9] aspartate, substance P, calcitonin gene-related peptide, and monoaminergic neurotransmitters.[10,11] Voltage-gated calcium channels in the brain and spinal cord provide rapid and fine-tuned modulation of neurotransmitter release by controlling fusion of synaptic vesicles to presynaptic membranes. Pregabalin binding rapidly reduces the influx of calcium, thus preventing synaptic vesicles from fusing and releasing (by exocytosis) additional neurotransmitter. The effect of pregabalin in inhibiting neurotransmitter release appears to be strongly correlated with

the degree of excitation of the presynaptic neuron evident in pathologic states.[12,13]

Data from animal models, which should be generalized to humans with caution, suggest that inhibitory GABAergic and excitatory glutaminergic inputs reciprocally modulate neuronal circuits within brain areas implicated in anxiety and the stress response.[14-17] These areas include the hippocampus, amygdala and related nuclei, and cingulate and prefrontal cortex.[13,16,18] The development of pregabalin offers a novel therapeutic alternative to the benzodiazepines that targets activated excitatory pathways. In rats, pregabalin administration increased the duration of non-rapid eye movement (NREM) sleep and decreased rapid eye movement (REM) sleep after either dark or light onset. Pregabalin also markedly increased the duration of NREM episodes and decreased the number of NREM episodes. Power spectrum analysis revealed pregabalin-induced, dose-dependent increases in relative delta power after administration. In contrast, triazolam, a traditional benzodiazepine, increased the duration of NREM sleep, but had no effect on the duration of REM sleep, and also decreased power density in low-frequency bands.[19] From these findings, the authors suggested that pregabalin is a potential sleep-modulating agent.

The benzodiazepines, such as alprazolam, are among the most widely prescribed class of medications for the treatment of generalized anxiety disorder and sleep disturbance. However, benzodiazepines are known to disturb the sleep architecture of those who take them,[20] and although they improve sleep duration and continuity, the drugs suppress both REM sleep and slow-wave sleep (SWS, sleep stages 3 and 4).

The purpose of this study was to investigate the effects of pregabalin on objective polysomnography (PSG) and subjective Leeds Sleep Evaluation Questionnaire measures of sleep and early-morning function in healthy volunteers. (The results reported here were derived from a larger study investigating the effects of pregabalin on daytime cognitive, psychomotor, and car-driving performance. These results will be presented elsewhere.) Alprazolam was included in the study to act as a positive internal control, or verum, to validate the sensitivity of the psychometrics used in the larger study. However, alprazolam was also expected to produce the classic benzodiazepine effects on sleep, ie, improved sleep efficiency, prolonged total sleep time and duration of stage 2 sleep, decreased wakefulness, more-rapid sleep onset, and suppression of SWS and REM sleep.[21,22]

METHODS

Study Population

Twenty-four volunteers (12 men), aged 18 to 50 years, with a body mass index of 18 to 30 kg/m^2, who were in good health as determined by medical history, 12-lead electrocardiogram, hematology, blood and urine biochemistry, and physical examination, were recruited. Subjects had normal sleep electroencephalograms and an absence of sleep disorders or lifestyle patterns, eg, shiftwork, that could prejudice the results of the study. Because of the cross-over design of the study, it was not considered necessary to have subjects sleep at their habitual bed time. All subjects gave written informed consent and had the consent of their general medical practitioner to participate in the trial, which was conducted in accordance with the Declaration of Helsinki and performed to ICH/GCP criteria. Ethical approval was obtained from the South-West Surrey Local Research Ethics Committee.

Study Design

This was a randomized, double-blind, placebo-controlled, 3-way crossover study of the effects of pregabalin compared with alprazolam and placebo on aspects of sleep. Sleep was assessed both quantitatively and qualitatively using sleep PSG and the Leeds Sleep Evaluation Questionnaire, respectively. It has to be emphasized that this investigation formed part of a study that was primarily intended to investigate the effects of pregabalin on daytime cognitive and psychomotor performance. Each volunteer received each of the following treatments, presented orally in identical capsules for each of 3 days. The sequence of administration was randomized, and each subject received pregabalin 150 mg, alprazolam 1 mg, and placebo (all t.i.d.). After the 3 days of treatment, there was a placebo day and night (night 5) to investigate any possible discontinuation effects. At the start of each treatment period, subjects spent 1 night at the study unit for rehabituation and were then randomly assigned to study treatment the following day (Day 1). All medication was administered by study nurses (who witnessed the volunteers take their treatments) at 9:30 AM, 2:30 PM, and 8:30 PM for 3 days. Each treatment period was separated by a washout of at least 7 days. Lights out was at 11:00 PM each night, with a wake-up time at 7:00 AM. Within 15 minutes of being awakened, subjects completed the Leeds Sleep Evaluation Questionnaire .

Volunteers were not to work overnight before the study, were to go to bed at their usual time the night before they came to the unit, and were not allowed to drink alcohol or caffeine-containing beverages for 24 hours before attending the study unit and for the duration of the treatment period. Smoking and the use of other nicotine products were also prohibited for the duration of the study. Subjects were prohibited from taking other medications during the study, except for oral contraceptives and nonsteroidal analgesics. Subjects remained in the unit for the duration of each treatment period. Prior to the start of the experimental phase of the study, subjects underwent an adaptation night in the sleep laboratory.

Sleep Measurement Procedures

Sleep PSG

Eight channels of data were recorded (4 electroencephalography [C4-A1, C3-A2, O2-A1, O1-A2], 2 electrooculography, and 2 submental electromyography) using Ag/AgCl electrodes connected to an Medilog® recorder (Oxford Medical, Abingdon UK). Electroencephalographic data were transferred to UltrasomTM (Nicolet Biomedical, Madison ,WI) to facilitate manual staging by an experienced sleep stager, blinded to treatment allocations, according to standard criteria.23 Variables analyzed included sleep efficiency; total sleep time; latency to sleep stages 1, 2, 3, 4, and REM; number of awakenings and percentages and total amounts of wakefulness in each sleep stage; and the distribution of REM and SWS throughout the night.

The Leeds Sleep Evaluation Questionnaire

The Leeds Sleep Evaluation Questionnaire assesses the effects of psychoactive compounds on sleep and early-morning behavior using visual analogue scales.[24-26] Subjects mark a series of 100-mm lines, indicating the direction and magnitude of any changes in behavioral state experienced following drug administration.

More specifically, the Leeds Sleep Evaluation Questionnaire considers 4 factors[27] related to the perceived ease of getting to sleep, the quality of sleep, the ease of awakening, and the integrity of behavior following awakening. Scores are represented in millimeters, with the higher numbers representing a more positive subjective evaluation of sleep.

Statistical Analysis

The number of subjects admitted to this study was determined from power calculations performed on data on alprazolam obtained on the battery of psychometric tests used in previous pharmacodynamic studies. Because the primary aim of this study was to determine the pharmacodynamic profile of pregabalin with regard to daytime performance, the sleep data derived from this trial must be considered exploratory, although sleep studies of this type have been performed with a smaller number of volunteers than were used in this instance.[28-32] The per-protocol population used in the analyses of sleep data consisted of all subjects who completed the full course of treatment and had a full set of data.

The sleep variables used to measure the effects of treatment on sleep architecture, as measured by PSG, were SWS as a percentage of total sleep-period time and sleep-onset latency. Other variables included sleep efficiency; total sleep time; latency to sleep stages 1, 2, 3, 4 and REM; and number of awakenings. Each of these sleep variables was also assessed for each third of the night, together with measures of time awake and SWS.

Sleep measurements from 11:00 PM to 7:00 AM were examined for the nights of days 2, 3, and 4, and active treatment was to be compared to placebo. These PSG data were analyzed using an analysis of variance model with the main factors subject, treatment, and day as a repeated measure and treatment by day interactions. If the latter interaction was found to be significant, an analysis was performed for each night. An analysis of any withdrawal effects on night 5 was effected by comparing the change on night 5 compared to the mean of nights 2, 3, and 4.

Data from the Leeds Sleep Evaluation Questionnaire performed on days 2, 3, and 4 were also analyzed using analyses of variance. The model contained the main effects, subject, treatment, and day (the last as a repeated measure), and treatment by day interaction. If the latter interaction was significant, then separate analyses were performed for each night. All significance testing was 2-tailed and used the 5% probability level; Bonferroni-adjusted significance levels were employed to correct for multiple comparisons. (Effect size compared with placebo is listed in parenthesis)

RESULTS

Subject Disposition

Twenty-three subjects completed each of the study periods (1 subject withdrew before taking any study medication) and were evaluable for the per-protocol analysis; of these, 11 (48%) were men. Subjects had a mean age of 29 years and a mean body mass index of 24.4kg/m^2.

Sleep PSG

Although there was no statistically significant difference between the 2 active treatments, overall (nights 2, 3, and 4), both drugs produced a significant increase in total sleep time compared to placebo (Table 1). Overall, pregabalin produced a significantly higher proportion of SWS (stages 3 and 4) in the total sleep period compared with both placebo and alprazolam, while, at the same time, SWS in the total sleep period was significantly lower for alprazolam compared with both placebo and pregabalin (Table 1). This significantly augmented level of SWS with pregabalin was evident in all thirds of the night and for each night of treatment compared with both placebo and alprazolam (Table 1). Overall, no significant difference in SWS was noted between alprazolam and placebo in the first third of the night, but those subjects treated with alprazolam had a significantly lower proportion of SWS in the second and final thirds of the night compared with those who took placebo. The proportion of stage 2 sleep in the total sleep period was significantly higher for those taking alprazolam than for those taking either placebo or pregabalin, but there was no statistically significant difference between results of subjects taking pregabalin and placebo (Table 1).

For each assessment, sleep-onset latency was modestly, but significantly, shorter with both pregabalin and alprazolam compared to placebo. Overall both drugs produced significant improvements in sleep efficiency compared with placebo, and there were significantly fewer awakenings of less than 1 minute in duration compared with placebo (Table 1). Notably, there were fewer awakenings of longer than 1 minute in duration with pregabalin compared with both placebo and alprazolam (Table 1).

Although pregabalin was not different from placebo, alprazolam caused a significantly longer REM latency compared with placebo (Table 1). Pregabalin and alprazolam produced significantly lower amounts of REM sleep as a proportion of total sleep period compared with placebo, although there were no differences between the active treatments. Pregabalin and alprazolam both produced a significantly lower proportion of REM sleep in the first third of the night compared with placebo (Table 1). In those who received pregabalin, the proportion of REM sleep was significantly higher than alprazolam in the second third of the night and significantly lower than alprazolam in the final third of the night (Table 1). For variables in which the treatment by day interaction was significant, the differences ($P < .05$) from placebo, alprazolam, or both placebo and alprazolam are also indicated in Table 1. On night 5 (withdrawal), there was no significant difference between placebo values and those obtained with either of the active substances on any PSG variable (Table 2).

Leeds Sleep Evaluation Questionnaire

Treatment with both pregabalin and alprazolam resulted in significant improvements in the mean subjective assessments of the ease of getting to sleep and the perceived quality of sleep compared with placebo. These improvements were significantly greater for alprazolam than for pregabalin (both P values $< .05$). Perceived behavior following awakening was significantly impaired by both active treatments (pregabalin, 40.4 mm on the visual analog scale; alprazolam, 39.6 mm) with respect to placebo, but neither active treatment had any significant effect on awakening from sleep.

DISCUSSION

The benzodiazepines are widely used as anxiolytics, anticonvulsants, and muscle relaxants, as well as for sleep induction and maintenance as hypnotic agents, but they are known to suppress

Table 1—Effect of Pregabalin, Alprazolam, and Placebo on Polysomnographic Variables for Each of 3 Nights*

	Pregabalin, 450 mg			Alprazolam, 3 mg			Placebo		
Night	**2**	**3**	**4**	**2**	**3**	**4**	**2**	**3**	**4**
		***			***				
Stages 3 & 4, % of SPT	41.81 ± 9.77#+	36.22 ± 8.55#+	36.37 ± 8.8#+	19.61 ± 4.8#	19.1 ± 5.65#	18.23 ± 4.42#	25.93 ± 8.09	25.68 ± 7.27	25.31 ± 7.91
		***			***				
SOL, min	4.41 ± 3.69#	6.83 ± 6.24#	9.24 ± 6.72#	3.7 ± 2.58#	4.39 ± 2.28#	8.61 ± 8.39#	10.98 ± 7.68	17.25 ± 14.9	13.63 ± 9.75
		***			***				
SE, %	96.97 ± 1.42	96.03 ± 2.83	95.32 ± 2.14	95.41 ± 1.61	94.84 ± 1.72	93.69 ± 3.08	91.7 ± 4.57	90.1 ± 5.99	90.07 ± 4.65
		***			***				
TST, min	465.78 ± 6.81	461.41 ± 13.56	458 ± 10.29	458.41 ± 7.74	455.67 ± 8.28	450.17 ± 14.78	440.64 ± 21.96	433.02 ± 28.78	432.7 ± 22.41
		***			***				
SPT, min	475.91 ± 3.59#	473.67 ± 6.24#	471.14 ± 6.85	476.8 ± 2.58#	476.25 ± 2.24#	471.87 ± 8.37	469.4 ± 7.85	463.25 ± 14.9	466.59 ± 9.89
		***			***				
REM latency, min	130.09 ± 60.59	103.91 ± 42.96	102.3 ± 38.12	151.37 ± 50.32	157.76 ± 48.32	151.91 ± 47.35	99.5 ± 49.94	105.61 ± 45	97.2 ± 36.48
		***			***				
Awakenings, no.									
< 1 min	7.35 ± 4.12	7.83 ± 4.93	8.45 ± 4.24	11.78 ± 4.39	11.89 ± 3.95	13.43 ± 4.96	15.95 ± 6.24	17.77 ± 7.18	18.64 ± 5.72
		***							
> 1 min	1.26 ± 1.57	1.22 ± 1.68	1.41 ± 1.26	3.43 ± 2.35	3.83 ± 2.53	4.09 ± 2.73	3.67 ± 3.01	3.41 ± 3.36	4.45 ± 3.66
REM sleep, %		***			***				
First third	5.67 ± 5.63	6.41 ± 3.79	6.3 ± 6.67	4.93 ± 5.93	2.27 ± 3.51	4.73 ± 6.07	9.76 ± 5.82	9.35 ± 7.77	9.82 ± 5.68
					*				
Second third	19.19 ± 7.6	24.65 ± 7.65	24.86 ± 9.79	18.43 ± 9.54	19.08 ± 7.79	20.82 ± 6.5	22.65 ± 9.51	20.46 ± 8.87	26.77 ± 10.12
		***			**				
Third third	27.23 ± 8.92	27.17 ± 6.37	25.06 ± 6.1	30.97 ± 9.04	30.29 ± 9.47	33.24 ± 10.3	31.2 ± 8.61	34.71 ± 9.18	30.55 ± 8.2
SWS, %									
		***			***				
First third	70.15 ± 10.31#+	65.63 ± 9.43#+	64.12 ± 11.32#+	47.31 ± 11.02	41.83 ± 9.51	43.97 ± 12.68	46.85 ± 13.49	47.78 ± 13.2	45.32 ± 12.23
		***			***				
Second third	38.34 ± 14.29#+	27.64 ± 13.41#+	27.34 ± 16.96#+	7.96 ± 6.77#	9.22 ± 7.58#	8.1 ± 7.33#	20.46 ± 10.4	19.78 ± 10.67	18.68 ± 9.04
		***			***				
Third third	17.27 ± 6 11.9	15.63 ± 10.93	17.86 ± 9.51	3.66 ± 6.02	6.38 ± 7.36	2.75 ± 3.9	10.63 ± 6.76	9.64 ± 8.22	12.14 ± 10.84
		***			***				
Sleep stage, % of SPT REM	17.32 ± 5.19	19.36 ± 4.17	18.7 ± 4.63	18.07 ± 5.03	17.18 ± 4.55	19.55 ± 4.61	21.16 ± 4.93	21.46 ± 4.65	22.32 ± 4.46
		***							
1	1.95 ± 1.25	2.18 ± 1.3	3.13 ± 2.13	3.68 ± 1.85	3.88 ± 1.46	4.7 ± 2.23	4.31 ± 1.59	4.76 ± 2.22	5.26 ± 2.54
		*			***				
2	36.77 ± 6.37	39.62 ± 5.81	39.01 ± 7.21	54.8 ± 5.06	55.52 ± 4.59	52.93 ± 6.26	42.47 ± 4.72	41.53 ± 5.97	39.81 ± 8.03
		*			**				
3	11.8 ± 4.08	10.69 ± 3.89	10.99 ± 3.11	6.29 ± 2.07	7.01 ± 2.23	7.8 ± 3.19	9.96 ± 3.89	8.86 ± 2.95	8.96 ± 3.15
		***			***				
4	30.00 ± 8.17#+	25.53 ± 5.95#+	25.39 ± 7.38#+	13.3 ± 4.72	12.09 ± 5.76#	10.42 ± 5.22#	15.98 ± 5.41	16.8 ± 5.65	16.36 ± 6.33

*: $p < 0.05$ versus placebo
**:$p < 0.01$ versus placebo
***:$p < 0.001$ versus placebo
Interaction of treatment and day p value equal to or less than 0.05 #versus placebo +versus alprazolam.

*Data are presented as mean ± SD.
SPT refers to total sleep period; SOL, sleep-onset latency; SE, sleep efficiency; TST, total sleep time; REM, rapid eye movement; SWS, slow-wave sleep.

SWS and REM sleep. It is important to demonstrate the absence of a disturbance of sleep architecture with new central nervous system compounds because such disturbance could be countertherapeutic. However, to reveal the effects of the drug alone, it is equally important that such data be collected in young healthy individuals with normal sleep cycles, sleeping for a fixed time in bed. Results from patient studies indicate not only the pharmacodynamics of the drug per se, but also the interaction between the effects of the drug on sleep and the disturbed sleep present in the individual patient. Any effects observed in a well-controlled study such as the present investigation would, therefore, be a reflection of the drug's true pharmacologic effects on sleep rather than its therapeutic effects on any symptoms of sleep disturbance or psychological disorder.

In contrast to alprazolam, which significantly reduced SWS compared with placebo, pregabalin significantly increased the proportion of SWS, both as a proportion of the total sleep period and in each third of the night. However, while this finding was reflected in a significant increase in stage 2 sleep with alprazolam, the level of stage 2 sleep observed with pregabalin was not different from that with placebo. Although pregabalin had no effect on REM latency, alprazolam significantly increased it. However, both active treatments, compared with placebo, caused a statistically significantly shorter duration of REM sleep.

Although both pregabalin and alprazolam significantly decreased the number of awakenings of less than 1 minute in duration compared with placebo, pregabalin also significantly reduced the number of awakenings of greater than 1 minute in duration compared with both placebo and alprazolam. Both pregabalin and alprazolam, compared with placebo, significantly increased total sleep time, reduced sleep-onset latency, and improved sleep efficiency.

Alprazolam exhibited the classic benzodiazepine effects on sleep, whereas the profile of effects of pregabalin is novel, although not unique: gaboxadol, a direct-acting, GABA-A receptor-agonist with a high potency for α_4-containing $GABA_A$ receptors, is currently under development as a hypnotic and is also reported to increase SWS.[33,34] The 5-HT_{2A} antagonists, ritanserin and seganserin, have also been shown to augment SWS, although they are certainly not classic hypnotic agents.[35,36] While SWS is physiologically very important, not only being involved in the restitution and repair of the body,[37,38] but also playing a crucial role in the consolidation of memory and learning,[39,28] its functional significance, or the clinical benefit of its augmentation, has yet to be elucidated. Also, while SWS is considered as the deepest, most restful part of sleep, its relative contribution to a subjective perception of "a good nights sleep" is uncertain.

Analysis of the Leeds Sleep Evaluation Questionnaire data showed that both pregabalin and alprazolam significantly improved the subjective ease of getting to sleep and the quality of sleep compared with placebo, although these improvements were significantly greater for alprazolam than pregabalin. Both active treatments, compared with placebo, significantly impaired subjective behavior following awakening, which could be either due to hangover associated with the pharmacodynamics of the treatment or a result of sleep inertia due to the increased "intensity" of sleep as a result of increased SWS in the final third of the night, as seen with pregabalin.[41]

Overall, pregabalin had significant effects on the sleep electroencephalogram of healthy humans, specifically, an increase in SWS and sleep continuity as measured by the number of awakenings longer than 1 minute. However, there is evidence of the discontinuation of medication on night 5, on all PSG variables, for both drugs. Given the design limitations of this study with the

Table 2—Effects of Pregabalin, Alprazolam, and Placebo on Polysomnographic Variables for the Mean of Nights 2, 3, and 4 Compared to Night 5*

	Pregabalin, 450 mg		Alprazolam, 3 mg		Placebo	
Night	**2, 3, 4**	**5**	**2, 3, 4**	**5**	**2, 3, 4**	**5**
SOL, min	6.83 ± 5.55	28.07 ± 24.52	5.57 ± 4.42	21.26 ± 22.36	13.95 ± 10.78	16.70 ± 10.83
SE, %	96.11 ± 2.13	84.63 ± 6.81	94.65 ± 2.14	85.67 ± 8.92	90.62 ± 5.07	89.55 ± 4.26
TST, min	461.73 ± 10.22	406.63 ± 32.72	454.75 ± 10.27	411.55 ± 42.87	435.45 ± 24.39	430.23 ± 20.64
SPT, min	473.57 ± 5.56	452.98 ± 25.02	474.97 ± 4.40	459.21 ± 22.34	466.41 ± 10.88	463.41 ± 10.98
REM latency, min	112.10 ± 47.22	104.05 ± 45.97	153.68 ± 48.67	108.26 ± 47.28	100.77 ± 43.81	99.34 ± 43.69
Awakenings, no.						
< 1 min	7.88 ± 4.43	21.20 ± 12.83	12.37 ± 4.43	18.05 ± 7.4	17.45 ± 6.38	19.82 ± 4.82
> 1 min	1.30 ± 1.50	5.90 ± 3.18	3.78 ± 2.54	6.38 ± 4.22	3.84 ± 3.34	4.68 ± 3.08
REM sleep, %						
First third	6.13 ± 5.36	8.42 ± 7.74	3.98 ± 5.17	7.45 ± 5.12	9.64 ± 6.42	9.75 ± 7.77
Second third	22.90 ± 8.35	24.61 ± 11.84	19.44 ± 7.94	28.39 ± 7.92	23.29 ± 9.5	24.32 ± 8.47
Third third	26.49 ± 7.13	29.96 ± 9.89	31.50 ± 9.60	24.98 ± 9.58	32.15 ± 8.66	30.25 ± 9.26
SWS, %						
First third	66.63 ± 10.35	39.86 ± 15.18	44.37 ± 11.07	33.57 ± 13.58	46.65 ± 12.97	47.95 ± 13.11
Second third	31.11 ± 14.89	15.26 ± 9.35	8.43 ± 7.23	9.05 ± 7.88	19.64 ± 10.04	20.87 ± 10.65
Third third	16.92 ± 10.8	7.45 ± 6.97	4.26 ± 5.76	4.64 ± 6.29	10.80 ± 8.61	9.02 ± 7.26
Sleep stage, % of SPT						
REM	18.46 ± 4.66	20.95 ± 5.66	18.27 ± 4.73	20.23 ± 5.12	21.65 ± 4.68	21.39 ± 5.16
1	2.42 ± 1.56	7.16 ± 3.43	4.09 ± 1.85	7.62 ± 2.82	4.78 ± 2.12	5.20 ± 1.7
2	38.47 ± 6.46	40.88 ± 7.99	54.42 ± 5.30	46.12 ± 7.81	41.27 ± 6.24	40.35 ± 7.39
3	11.16 ± 3.69	7.51 ± 2.59	7.03 ± 2.50	6.27 ± 3.34	9.26 ± 3.33	9.66 ± 2.88
4	26.97 ± 7.17	13.29 ± 5.26	11.94 ± 5.23	9.46 ± 5.13	16.38 ± 5.80	16.23 ± 6.8

*Data are presented as mean ± SD.
SPT refers to total sleep period; SOL, sleep-onset latency; SE, sleep efficiency; TST, total sleep time; REM, rapid eye movement; SWS, slow-wave sleep.

lack of a pretreatment baseline PSG data, it is difficult to determine if such effects are due to rebound, and further investigations are required to fully document the nature of these observed effects. Because reductions in SWS have been reported in patients with fibromyalgia,[42,43] and reports of nonrestorative sleep and increased nocturnal awakenings are a characteristic of patients with generalized anxiety disorder,[44] pregabalin might prove to be beneficial in the treatment of patients with these and related disorders. The exact mode of action of pregabalin is at the moment unknown; however the fact that it has no activity at $GABA_A$, $GABA_B$, or benzodiazepine receptors must, to a large degree, account for the difference between its affects on sleep architecture and that seen with alprazolam.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contributions of Mark Versavel, MD; Hans Mikkelsen, MD; Capucine de Meynard, MD; and Timothy Hsu, MD, toward the preparation of this manuscript.

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