Sleep-related Outcomes in Persons with Mild to Moderate Alzheimer Disease in a Placebo-controlled Trial of Galantamine

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Study Objectives: To recognize the potential effect of acetylcholinesterase-inhibiting medications on sleep quality when used for the treatment of mild to moderate Alzheimer disease and describe sleep outcomes for patients treated with galantamine.

Design: This study examined sleep quality among individuals with mild to moderate Alzheimer disease using data from a 3-month, double-blind, flexible-dose trial of galantamine. The hypothesis was no difference in sleep quality between galantamine- and placebo-treated subjects.

Patients: 136 patients treated with galantamine 24 mg per day and 125 patients treated with placebo.

Measurements: Based on caregiver reports, the sleep-related outcome measures were the Pittsburgh Sleep Quality Index and the sleep disorders item from the Neuropsychiatric Inventory. Using a P-value of 0.05 (2-tailed), analysis of covariance was used to compare treatments on mean change from baseline to month 3 (Pittsburgh Sleep Quality Index) or mean score at month 3 (Neuropsychiatric Inventory), adjusted for baseline score and investigator.

Results: Both patient groups had an average age of 75 years and a mean Mini-Mental Status Examination score of 20. There were no significant differences between groups on the Pittsburgh Sleep Quality Index total (P=0.59) or subscales. For galantamine and placebo, the mean adjusted changes from baseline on the total Pittsburgh Sleep Quality Index were 0.01 and –0.17, respectively. There also was no difference on the Neuropsychiatric Inventory sleep score at month 3 (P=0.51).

Conclusions: Medications to treat Alzheimer disease should maintain sleep quality and have a neutral effect on sleep. These results further confirm the lack of sleep problems associated with galantamine treatment.

Key Words: Acetylcholinesterase inhibitors, sleep quality, Alzheimer disease, galantamine

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INTRODUCTION

SLEEP PROBLEMS AMONG PEOPLE WITH ALZHEIMER DISEASE (AD) ARE COMMON AND TEND TO WORSEN AS THE DISEASE PROGRESSES.[1,2] Changes include more time awake during the night and less rapid eye movement and slow wave sleep.[2,3] Moreover, because reduced sleep quality is associated with aging, the sleep problems linked to AD occur among a population subgroup whose sleep already is vulnerable or compromised.[4] Poor sleep among persons with AD may lead to increased daytime irritability and may decrease attention, motivation, and cognitive performance.[2,5] Another concern is that sleep disruption among persons with AD also disrupts the sleep of their caregivers and leads to high levels of distress.[1] Consequently, any evidence linking medication treatment for AD to sleep problems requires consideration and further investigation.

In recent years, the introduction of acetylcholinesterase inhibitor (AChEI) medications has brought new energy and hope to the treatment of people with AD. Comparisons to placebo demonstrate that treatment with these medications leads to slower progression of cognitive dysfunction, preserved function on performance of activities of daily living, and less behavioral disturbance.[6-13] In addition, it appears that caregivers may experience indirect benefits from treatment through diminished time spent in caregiving[14,15] or a reduction in the perceived difficulty of their caregiving responsibilities.[16,17]

At least one AChEI may have adverse sleep effects on a small, but significant, proportion of patients who are treated with this medication. In 2 placebo-controlled clinical trials, donepezil was found to be associated with elevated rates of insomnia based on adverse-event reports.[6,9] For patients treated with donepezil at a dose of 10 mg per day and placebo, respective rates of insomnia were 18% and 5% in 1 study[9] and 8% and 4% in another study.[6] In contrast, there was no indication of insomnia based on adverse-event reports during trials of rivastigmine or galantamine.[7-13] The rates of insomnia for mild to moderate AD patients treated with galantamine at 16 mg per day or 24 mg per day were lower than or similar to rates for placebo-treated subjects.[18]

Adverse-event reporting during clinical trials is one way to gather information on health changes that may be linked to drug treatment. Clinicians are required to provide reports of undesirable health changes reported by subjects (or their caregivers) during clinical trials. Subsequent classification and coding of these events entails use of preferred terms designated by the World Health Organization. Comparisons between drug and placebo groups help identify which specific health problems may be linked to drug treatment.

Systematic reporting of sleep quality, based on a questionnaire, is an additional way to monitor sleep changes that may be influenced by drug treatment. An advantage to this approach is that all subjects are monitored on identical parameters. Thus, the use of a structured questionnaire helps to minimize the differences that may occur based on differential recall, variability among clinicians in reporting adverse events, or the complexity of categorizing responses. In the case of individuals with AD, caregiver reporting typically replaces self report.

Galantamine is an AChEI that became available in the United States in May 2001. It promotes cholinergic function in AD patients through acetylcholinesterase inhibition and modulation of nicotinic receptors.[19] Due to the possible link between donepezil and sleep disturbance, this study evaluated the impact of galantamine on a range of sleep outcomes, based on caregiver reports to well-established questionnaires. The data came from a placebo-controlled clinical trial conducted in patients with mild to moderate AD.[20]

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METHODS

This was a posthoc analysis of data from a 3-month, multicenter, randomized, double-blind, placebo-controlled, flexible-dose trial of galantamine. The performance of the trial, conducted in 43 centers in 6 countries (Australia, Canada, Great Britain, New Zealand, South Africa, and the United States), conformed to the Declaration of Helsinki. The approval of an ethics committee was obtained at each center. The patient (or their representative), as well as the caregiver, provided written informed consent to participate in the study.[20]

Patients were randomized in a 2:1 galantamine to placebo ratio. At baseline, galantamine patients were treated with 4 mg of galantamine twice a day, and the dosage was increased by 4 mg twice a day for 2 consecutive weeks. At the start of week 4, physicians could increase the dose to 16 mg twice a day (GAL 32 mg/day) or maintain the patient at 12 mg twice a day (GAL 24 mg/day). In addition, during week 4, patients increased to the higher dose could be returned to 24 mg per day. After week 4, galantamine doses were fixed for the remainder of the study (2 months). Of note, the 2-week titration to the 24-mg-per-day dose used in this trial was faster than the 2-month titration used in a later trial and currently recommended.[12]

At baseline, patient numbers randomized to the galantamine and placebo groups were 261 and 125, respectively. At the end of week 4, 125 patients were classified as having treatment with galantamine at 32 mg per day, since they were raised to this level at week 4 and maintained at this level. The remaining 136 patients were classified as having treatment with galantamine at 24 mg per day. The latter group consisted of 64 patients who were maintained on 24 mg per day at week 4, 40 patients who were raised to 32 mg per day at week 4 and then returned to 24 mg per day at the end of week 4, and 32 patients who discontinued their study participation prior to week 4.

This analysis was limited to subjects in the galantamine 24-mg-per-day or placebo groups. The 32-mg-per-day dose of galantamine exceeded labeled recommendations; thus, patients maintained at this dose level were excluded. Due to flexible dosing, patients in the galantamine-24-mg-per-day group were randomly assigned to galantamine but not to dose level.

Table 1—Patient Characteristics

Characteristic	Gal24 (n=136)	Placebo (n=125)	P-value
Sex (%)			
Female	66.2	53.60	0.038
Male	33.8	46.40	
Race (%)			
White	94.8	93.6	0.664
Non-white	5.2	6.4	
Age in years (±SD)	75.3 (7.5)	74.6 (7.6)	0.434
Age in years at onset of cognitive problems (±SD)	72.3 (8.1)	71.9 (7.8)	0.691
Cognition (±SD)			
ADAS-Cog	24.3 (9.5)	24.7 (9.5)	0.752
MMSE Total	20.0 (3.7)	19.6 (3.6)	0.420
Other outcome scales			
NPI Total	9.1 (11.5)	8.9 (12.1)	0.894
DAD Total	70.8 (23.0)	73.0 (21.4)	0.423

GAL24, treatment with galantamine 24 mg per day; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; DAD, Disability Assessment for Dementia; NPI, Neuropsychiatric Inventory

Sleep Outcome Variables

The three sets of sleep-related outcome variables used in this study were: (1) the Pittsburgh Sleep Quality Index (PSQI) subscale and total scale scores; (2) the 4-item addendum to the PSQI called Bed Partner Observations; and (3) the sleep disorders item from the Neuropsychiatric Inventory (NPI). Assessments were completed by caregivers, with higher scores reflecting more sleep difficulties. Although measures were conducted at baseline, Week 4, and Month 3, we report only assessments at baseline and Month 3. Because a substantial portion of the galantamine subjects (n=40) received up to 1 week of treatment during Week 4 with a dose that exceeded current recommendations, we did not analyze the Week 4 data in this study.

The PSQI is a widely used measure of sleep quality with good internal consistency (α=0.83) and test-retest reliability (r=0.85).[21] Because it was designed as a self-report measure, its reliability and validity as a caregiver report have not been previously addressed. There are 7 subscale scores, scored from 0 to 3, that cover such domains as habitual sleep efficiency [defined as (hours asleep/hours in bed) * 100], sleep disturbances, and use of sleep medications. The total score, with a range of 0 to 21, is calculated by summing the subscales. The timeframe is the past month.

The Bed Partner Observations that are part of the PSQI are not included in the total scores. The instructions limited these inquiries only to caregivers who were roommates or bed partners of the patient. These

Table 2—Pittsburgh Sleep Quality Index Subscales and Total Scores at Baseline and After Three Months of Treatment with Galantamine or Placebo

	BASELINE[1]					MONTH 3 - CHANGE FROM BASELINE[2]				
	GAL24		PLACEBO		*P*	GAL24		PLACEBO		*P*
MEASURE	N	LS Mean (±SEM)	N	LS Mean (±SEM)		N	LS Mean (±SEM)	N	LS Mean (±SEM)	
Daytime dysfunction	131	0.67 (±0.07)	120	0.66 (±0.07)	0.88	110	0.08 (±0.08)	117	-0.01 (±0.08)	0.34
Habitual sleep efficiency	124	0.57 (±0.09)	115	0.53 (±0.09)	0.77	102	-0.10 (±0.08)	112	-0.06 (±0.08)	0.71
Sleep disturbances	130	1.23 (±0.06)	120	1.24 (±0.06)	0.93	110	0.08 (±0.06)	117	-0.04 (±0.06)	0.12
Sleep duration	127	0.47 (±0.08)	121	0.42 (±0.08)	0.60	107	-0.08 (±0.07)	118	-0.07 (±0.07)	0.92
Sleep latency	129	0.52 (±0.09)	120	0.57 (±0.09)	0.66	109	-0.01 (±0.07)	117	0.06 (±0.07)	0.43
Subjective sleep quality	130	0.50 (±0.06)	120	0.52(±0.06)	0.77	110	0.09 (±0.06)	117	0.03 (±0.06)	0.43
Use of sleep medication	130	0.20 (±0.08)	120	0.29 (±0.08)	0.39	109	0.04 (±0.07)	117	0.06 (±0.07)	0.79
Total PSQI	123	4.16 (±0.32)	114	4.19 (±0.34)	0.94	100	0.01 (±0.26)	111	-0.17 (±0.26)	0.59

[1] Based on analysis of covariance on baseline scores controlling for investigator, there were no significant differences between galantamine and placebo means at baseline
[2] Based on analysis of covariance of change from baseline scores controlling for baseline and investigator, there were no significant differences between galantamine and placebo means at month 3 assessment
GAL 24 MG, treatment with galantamine 24 mg per day; N, number; LS Mean (±SEM), least-square mean ± standard error of the mean; PSQI, Pittsburgh Sleep Quality Index

questions address the presence and frequency of problems while the subject is asleep and include the following items: loud snoring, legs twitching or jerking, long pauses between breaths, and episodes of disorientation or confusion.

The NPI addresses the frequency and severity of 12 behavioral symptoms that are common problems among individuals with AD.[22,23] Prior research has shown that significant decreases in total NPI scores, indicating improvement, may occur during treatment with an AChEI.[24] Ratings are based on a structured interview with the caregiver. The time period covered by the questions is the past 4 weeks. If a symptom is present, the rating of frequency can range from 1 (occasionally, less than once a week) to 4 (very frequently, once or more per day, or continuously) while the rating of severity can vary from 1 (mild) to 3 (severe). Item scores, having a theoretic range from 1 to 12, are calculated by multiplying the frequency and severity ratings. Symptoms that are not present are rated 0. In this analysis, we examined only the sleep disorders item of the NPI.

In addition, all subjects were described with respect to their demographics and baseline scores on scales assessing cognition (Alzheimer's Disease Assessment Scale – Cognitive Subscale [ADAS-Cog] and Mini-Mental State Examination [MMSE]), daily functioning (Disability Assessment for Dementia [DAD]), and psychiatric symptom status (NPI).

Hypothesis

The null hypothesis was that there will be no significant differences between placebo and galantamine on changes from baseline on all of the sleep-related outcome variables at Month 3.

Statistical Analysis

Galantamine- and placebo-treated patients were compared on demographic characteristics and baseline scores of scales that assessed cognition, daily functioning, and psychiatric symptom status. Tests were performed using chi-square and analysis of variance (ANOVA), as appropriate. If demographic differences between subjects and controls were found, we planned to examine the relationship between these variables and the PSQI total scale and the NPI sleep disorder item using one-way analysis of variance. Only variables that varied by group and were related to outcomes would serve as control variables in the multivariate analyses.

Changes from baseline in sleep outcome scores at Month 3 using the Last Observation Carried Forward were the primary outcome variables. Accordingly, postbaseline assessments at Week 4 or any nonscheduled endpoint were used for subjects lacking Month 3 outcome data. All tests of significance were interpreted based on an α level of 0.05 (2-tailed). Least-square mean change from baseline scores, adjusted for baseline, investigator, and other relevant variables, were computed for all PSQI subscale, PSQI total scale, and bed-partner observations. Analysis of covariance (ANCOVA) was used to test between treatment group differences on these sleep outcomes at Month 3.

The frequency distributions of sleep disorder (NPI) scores were displayed at baseline and Month 3. Because of the skewed distribution, Wilcoxon tests were utilized to examine between-treatment-group differences (at the bivariate level) at baseline and Month 3. ANCOVA, as described above, also was used to test between-treatment-group differences on sleep disorder (NPI) change scores.

RESULTS

Table 1 describes the demographics and baseline clinical status of the 136 patients fixed on galantamine treatment at 24 mg and the 125 patients treated with placebo. Compared to placebo-treated patients, galantamine-treated patients were more likely to be female (66.2% vs 53.6%, P=0.038). On all other characteristics, the profiles of the 2 groups were similar. Statistical comparisons on age, age at onset of cognitive problems, race, and baseline levels of cognition, daily functioning, and psychiatric symptoms and problems yielded no significant or near significant differences. Approximately 80% of the caregivers who responded to the PSQI and NPI lived in the same household as the AD patient. Responses to the Bed Partner Observations were provided by caregivers who were roommates or bed partners only. We found no statistically significant relationship between gender and the PSQI total (P=0.929) or NPI sleep score (P=0.929). Therefore, no controls for gender were needed in the multivariate analyses pertaining to outcome.

Ninety-four percent of the combined GAL 24 mg and placebo subjects were white, with a mean age of 75 years (SD=7.5) and a 3-year average duration of cognitive problems. Their mean ADAS-Cog score was 24.5 (SD=9.5), while their average MMSE score was 19.8 (SD=3.6). Their average score on daily functioning as assessed by the DAD was 71.9 (SD 22.2). Thus, the average baseline cognitive and daily functioning scores in this study were similar to the average scores of patients with mild to moderate AD who participated in the 6-month trials of galantamine.[8,13]

Table 2 provides outcome results for the PSQI subscales and total score categorized by treatment group at baseline and Month 3. Adjusted least-square mean scores are presented at baseline along with their standard errors. Adjusted least-square mean-change scores are presented at Month 3. The treatment groups were roughly equivalent on all PSQI baseline variables controlling for investigator, with no findings of significant difference. At Month 3, PSQI scores for both treatment groups were very close to their respective baseline levels. Moreover, there were no significant differences between treatment groups on any of the PSQI sleep-outcome change scores at Month 3, controlling for investigator and baseline. Adjusted least-square mean total PSQI changes from baseline scores at Month 3 were 0.01 for GAL 24 mg subjects and –0.17 for placebo subjects (P = 0.59).

Table 3—Bed Partner Observations at Baseline and After Three Months of Treatment with Galantamine or Placebo

	BASELINE[1]					MONTH 3 - CHANGE FROM BASELINE[2]				
	GAL 24 MG		PLACEBO		*P*	GAL 24 MG		PLACEBO		*P*
VARIABLE	N	LS Mean (±SEM)	N	LS Mean (±SEM)		N	LS Mean (±SEM)	N	LS Mean (±SEM)	
Loud snoring	71	0.95 (±0.18)	72	1.24 (±0.18)	0.17	61	-0.14 (±0.15)	64	0.00 (±0.15)	0.43
Legs twitching or jerking during sleep	70	0.49 (±0.14)	72	0.47 (±0.14)	0.89	61	0.00 (±0.11)	64	-0.06 (±0.11)	0.62
Long pauses between breaths while asleep	71	(±0.09)	72	0.15 (±0.09)	0.92	60	-0.07 (±0.06)	64	-0.02 (±0.06)	0.47
Episodes of disorientation or confusion during sleep	71	(±0.10)	72	0.28 (±0.11)	0.11	61	-0.09 (±0.06)	64	-0.15 (±0.06)	0.43

[1] Based on analysis of covariance controlling for investigator, there were no significant differences between galantamine and placebo means at baseline
[2] Based on analysis of covariance controlling for baseline and investigator, there were no significant differences between galantamine and placebo means at month 3 assessment
GAL24, treatment with galantamine 24 mg per day; N, number; LS Mean (±SEM), least-square mean ± standard error of the mean

Bed-partner observation results are shown in Table 3. Because only caregivers who slept in the same room or bed were instructed to respond, the subject numbers were reduced. On all 4 items, the treatment groups were similar at baseline. Moreover, adjusted change scores were close to 0 at Month 3. There were no significant differences between the treatment groups on any of the bed-partner-observation change-from-baseline scores at Month 3.

Table 4 presents NPI sleep disorder results. There was no significant between-treatment group difference at baseline on the NPI sleep disorder item. At Month 3, there was also no significant between-treatment group difference on the NPI sleep disorder score (p=0.51), controlling for baseline and investigator.

The large majority of caregivers who provided responses to the PSQI and NPI measures lived in the same household as the AD patient. When caregiver co-residence was controlled in ANCOVA (along with baseline and investigator), treatment-group differences on change-from-baseline PSQI and NPI scores continued to be not significant (data not shown).

DISCUSSION

This study found no significant difference between patients treated with galantamine and placebo across a broad range of sleep-related outcomes under double-blind conditions following 3 months of treatment. The results of this study support the absence of sleep problems with galantamine during pivotal clinical trials based on adverse-event reporting.[8,12,13]

The AChEIs are thought to exhibit a positive effect on cognition and global functioning by increasing levels of acetylcholine in neural synapses. Nevertheless, specific drugs differ on multiple features, including drug half-lives, types of cholinergic receptors affected, and modes of binding with acetylcholinesterase. [25] Therefore, drugs may vary on their side-effect profiles, such as their effect on sleep.

There is considerable evidence that the neurotransmitter, acetylcholine, plays a prominent role in the activation of rapid eye movement (REM) sleep. In addition, there are reciprocal interactions between the cholinergic system and REM facilitatory and inhibitory neurons that maintain the cycle between REM and non-REM. [26] For this reason, sleep effects are plausible responses to treatment with an AchEI, and, paradoxically, both positive and negative outcomes have been hypothesized. Donepezil and tacrine, an early AChEI, have been described as treatments for REM-related sleep disorders.[27,28] In contrast, case studies have reported nightmares to be a consequence of donepezil treatment.[29] An open-label study that compared donepezil and rivastigmine also described an elevated incidence of nightmares with donepezil that was not noted with rivastigmine.[30]

The longer half-life of donepezil relative to other AChEIs could contribute to sleep problems.[25] Switching from the recommended evening to a morning administration also could reduce the incidence of the sleep problems observed with donepezil,[29] although the effects of this modification have not been systematically studied.

Patients treated with galantamine 24 mg per day did not differ from patients assigned to placebo treatment on basic demographic and clinical characteristics, with the exception of more females treated with galantamine. Because gender was not related to the outcome measures, no adjustments based on gender were needed.

Differential attrition could have led to an underestimation of sleep problems, since early discontinuers were primarily galantamine-treated patients. Although we cannot rule out such effects, we can consider past analyses of adverse events, which are less subject to attrition bias. The relevant safety analyses showed no increase in sleep-related adverse events in galantamine-treated subjects relative to placebo,[8,12,13] with the possible exception of somnolence.[20]

Due to the prominent role of sleep problems in many cognitively impaired patients, more research is needed to develop valid and reliable sleep-related measures based on informant reports. The PSQI was designed as a self-report, and its completion by caregivers has not been previously studied. The NPI sleep item was designed for caregiver reporting, yet it has received limited validation.[22] Nevertheless, any constraints linked to proxy reporting presumably were shared equally by caregivers of both drug- and placebo-treated subjects. The absence of sleep problems related to galantamine treatment may not generalize to patients whose other medical problems or need for concomitant medication precluded their participation in this study.

The apparent neutral effect of galantamine on sleep is a positive consideration on treatment given the predisposition to sleep problems among individuals with AD. In addition, the variability in responses to AChEIs suggests the need for more systematic investigation of sleep effects, including the use of more robust techniques such as actigraphy or polysomnography. Finally, segments of the AD population with more compromised physical health or preexisting sleep problems require special study because they may be more sensitive to sleep effects.

Table 4—Neuropsychiatric Inventory Sleep Disorders Item Scores at Baseline and After Three Months of Treatment with Galantamine or Placebo

Score[1]	Baseline[2,3]		Month 3[4,5]	
	GAL24 (n=136)	Placebo (n=125)	GAL24 (n=118)	Placebo (n=123)
0	111	101	95	106
1	3	4	3	2
2	0	2	0	3
3	27	6	4	2
4	5	4	9	4
5	10	8	7	6

[1] If problem was not present, item score was 0. If problem was present, item score was the product of the frequency and severity ratings and could range from 1 to 12. Caregivers rated frequency from 1 to 4 (1=occasionally, less than once a week; 4=very frequently, once or more per day or continuously) while severity could vary from 1 to 3 (1=mild, 2=moderate, 3=severe).; [2]Wilcoxon p-value=0.95; [3]Multivariate p-value = 0.98; [4]Wilcoxon p-value=0.24; [5]Multivariate p-value = 0.51; [4]Based on ANCOVA controlling for investigator; [5]Based on ANCOVA controlling for baseline and investigator; GAL24, treatment with galantamine 24 mg per day

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