A Randomized, Double-Blind, Single-Dose, Placebo-Controlled, Multicenter, Polysomnographic Study of Gabapentin in Transient Insomnia Induced by Sleep Phase Advance

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Study Objectives: To evaluate the effects of single doses of gabapentin 250 and 500 mg on polysomnographic (PSG) and participant-reported sleep measures in a 5-h phase advance insomnia model.

Methods: Adults reporting occasional disturbed sleep received gabapentin 500 mg (n = 125), 250 mg (n = 125), or placebo (n = 127) 30 min prior to bedtime and were in bed from 17:00 to 01:00, ~5 h before their habitual bedtime. Sleep was assessed by PSG, post-sleep questionnaire, and the Karolinska Sleep Diary (KSD). Next-day residual effects (Digit Symbol Substitution Test [DSST] and Stanford Sleepiness Scale [SSS]) and tolerability were assessed.

Results: Demographics were comparable among groups. Among PSG endpoints, wake after sleep onset (primary endpoint) (135.7 [placebo], 100.7 [250 mg], and 73.2 [500 mg] min) was significantly lower and total sleep time (TST) (311.4, 356.5, and 378.7 min) significantly greater in both gabapentin groups versus placebo. Latency to persistent sleep was not significantly different among groups. Percent slow wave sleep (12.6%, 15.4%, and 17.0%, respectively) was significantly greater and percent stage 1 (15.1%, 11.8%, and 10.8%, respectively) significantly lower relative to placebo. Gabapentin was associated with significantly higher values of KSD Sleep Quality Index and reported TST versus placebo; no other reported outcomes were significant. Neither gabapentin dose produced evidence of next-day residual effects as measured by DSST and SSS. Adverse events were infrequent (< 5%).

Conclusion: Participants with occasional disturbed sleep treated with gabapentin showed significantly longer sleep duration and greater depth (versus placebo) in response to a phase advance manipulation known to disrupt sleep maintenance.

Keywords: Gabapentin, insomnia, polysomnography, sleep phase advance, treatment

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Occasional sleep disturbance (difficulty initiating or maintaining sleep, waking too early, not sleeping long enough, or experiencing non-restorative sleep) is common and generally referred to as "occasional sleeplessness" in over-the-counter (OTC) product labels in the United States.[1] While estimates of prevalence vary due to differences in study population and definition, United States-based surveys reveal that approximately 30% of respondents report occasional sleep disturbances, which are frequently characterized as difficulty maintaining sleep or waking up feeling drowsy or tired.[2,3] The relationship of occasional sleep disturbances to the development of chronic insomnia is not well understood.[4] Individuals with sleep disturbances often seek self-help methods to improve their sleep, including OTC sleep aids,[3] but concerns over safety and efficacy exist, and few treatments have been systematically evaluated in clinical trials, particularly in individuals who report occasional sleep disturbance.[5-7]

Gabapentin, an $\alpha_2\delta$ subunit ligand of L-type voltage-gated calcium channels, is indicated for the management of postherpetic

BRIEF SUMMARY

Current Knowledge/Study Rationale: Adults commonly report occasional disturbed sleep. A 5-h phase advance insomnia model known to impair sleep maintenance was used to evaluate the efficacy of single doses of gabapentin 250 and 500 mg on sleep parameters assessed by polysomnography and participant reports.

Study Impact: Participants with occasional disturbed sleep treated with gabapentin had significantly longer sleep duration and greater depth (versus placebo) in response to a phase advance manipulation known to disrupt sleep maintenance.

neuralgia and restless legs syndrome, and as adjunctive therapy for partial seizures with and without secondary generalization (maximal dose: 600-1800 mg/day depending on indication and gabapentin formulation).[8-10] In addition to its demonstrated efficacy in these indications, patient-reported sleep assessments among a variety of clinical populations suggest that gabapentin has beneficial effects on sleep.[11-18] Polysomnographic (PSG) assessment of sleep further documents gabapentin's positive

effects on sleep.[19-26] One small, open-label study in otherwise healthy individuals with complaints of difficulty initiating and/or maintaining sleep for more than 3 months showed that, compared with baseline, gabapentin increased sleep efficiency, decreased wake after sleep onset (WASO), and increased slow wave sleep, but did not affect sleep onset latency.[27]

Although these studies suggest that gabapentin has favorable effects on sleep, the applicability of these findings to individuals who have occasional difficulty sleeping can be addressed via large, double-blind, placebo-controlled studies evaluating various doses of gabapentin in individuals with occasional sleep difficulties in a validated model of transient sleep disturbance. The primary objective of this study was to examine the dose-dependent (250 and 500 mg) efficacy of gabapentin, using both PSG and participant-reported assessments of sleep in participants with a history of occasional disturbed sleep. Acute sleep disturbance was induced by a 5-h sleep phase advance. The sleep phase advance model is an experimental model of transient insomnia that results in a reliable disruption of multiple sleep parameters. Sleep disturbance (i.e., WASO, total sleep time, and sleep efficiency) appears to be consistently negatively affected, while sleep latency effects are inconsistent.[28,29] One study showed that lengthening the phase advance from 3 to 6 h provoked a greater disruption in sleep maintenance measures.[30] Sedative/hypnotic agents mitigate the disruptive effects of phase advance, supporting the use of this model to assess a drug's effect on transient insomnia.[28,29,31]

The specific objectives of the study were to evaluate: (1) the effects of gabapentin 250 and 500 mg compared with placebo on PSG and participant-reported assessments of sleep maintenance in transient insomnia induced by a 5-h sleep phase advance, and (2) the next-day residual effects of gabapentin using psychomotor performance and subjective sleepiness measures.

METHODS

Study Design

This was a randomized, double-blind, single-dose, placebo-controlled, parallel-group study conducted at 5 United States-based research sites from March 2005 to August 2006 (ClinicalTrials.gov: NCT00674752). The final protocol, any amendments, and informed consent documentation were reviewed and approved by the institutional review board at each of the investigational centers. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice guidelines.

Study Population

Men or women (non-pregnant, non-lactating) ≥ 18 years of age who reported occasional disturbed sleep during the past month were recruited by the clinical research centers using a combination of advertising and existing databases. Once an individual contacted the research center, eligibility was ascertained over the phone by study personnel using a site-generated structured screening questionnaire that contained a query such as, "Have you had instances of occasional sleeplessness

over the past month?" or "Do you occasionally experience problems in going to or staying asleep and have the feeling of sleepiness the next day?" Occasional disturbed sleep was defined by participant report of at least one night (no upper limit) during the past month with problems sleeping, trouble falling asleep, trouble staying asleep, or waking in the middle of the night.

Participants were excluded if they reported any of the following: (1) recent history (within 2 years) of or current treatment for a sleep disorder (including excessive snoring or obstructive sleep apnea) or a chronic painful condition that would interfere with the participant's sleep; (2) current or anticipated use during the study of any of the following: amphetamines, benzodiazepines, cocaine, marijuana, methadone, opiates, propoxyphene, barbiturates, or phencyclidine. Medications taken for chronic medical conditions (e.g., hypertension, diabetes) were allowed; (3) current use of or a known sensitivity to gabapentin; (4) expected travel across ≥ 1 time zone or shift work during study participation; (5) expected use of any other prescription or OTC medication to promote sleep during study participation; or (6) a significant unstable or uncontrolled medical condition that could interfere with participation.

Procedures

The informed consent form was signed at visit 1 before any study procedures were performed; then a routine physical (vital signs, height, and weight) was performed, a urine sample (for pregnancy test and drug screen) was collected, a brief sleep and medical history (including medication use) was obtained, and a sleep diary was provided for at-home use.

Eligible participants were scheduled for visit 2, which occurred 4-16 days after visit 1. Visit 2 procedures included diary collection and review to ensure proper completion, clarity of entries, and compliance with protocol-prescribed sleep times; administration of an alcohol breathalyzer test and urine drug screen; completion of the Epworth Sleepiness Scale (ESS); and a concomitant medication review. Participants were then randomized if they had: (1) a score ≤ 10 on the ESS at visit 2; (2) no use of alcohol within 48 h prior to and a breathalyzer measurement of 0 at visit 2; (3) bedtime between 22:00 and 01:00 and awakening (out of bed) between 05:00 and 10:00 for the 3 days prior to visit 2; and (4) 7-9 h in bed each of those 3 nights. Randomized participants received orally administered gabapentin 250 mg, 500 mg, or matching placebo in a ratio of 1:1:1. Following an afternoon meal, participants were prepared for PSG recording and vital signs were obtained. Participants took study medication at 16:30, went to bed with lights out at 17:00, and were awakened with lights on at 01:00. PSG was conducted during the 8-h lights-out period.

Participants completed self-reported sleep assessments approximately 15 min (8.75 h post drug ingestion) after awakening. These were followed by measurements of sleepiness and psychomotor performance using the Stanford Sleepiness Scale (SSS) and Digit Symbol Substitution Test (DSST), respectively.

Vital signs were obtained, PSG electrodes were removed, and participants were served a meal. The SSS and DSST were again completed at approximately 03:30 and 06:00 (± 10 min), corresponding to 2.5 and 5.0 h after awakening (corresponding to 11.0 and 13.5 h post drug ingestion). Participants were

monitored to ensure they remained awake after lights-on until they were discharged from the study site.

Assessments

Efficacy

The prespecified primary endpoint was PSG-quantified WASO recorded during the 8-h time in bed at visit 2. Secondary endpoints consisted of: (1) other PSG assessments (i.e., latency to persistent sleep, number of awakenings, total wake time plus stage 1 sleep time, total sleep time, percent stage 1, 2, slow wave sleep [stage 3 + 4], and REM sleep); (2) participant-reported sleep assessments (i.e., sleep latency, number of awakenings, WASO, total sleep time, sleep refreshment, quality of sleep); and (3) the Karolinska Sleep Diary Sleep Quality Index (KSD-SQI) and individual item scores for each of the KSD questions.

Next-Day Residual Effects

Subjective sleepiness and psychomotor performance were assessed using the SSS[32] and DSST,[33,34] respectively, following the completion of the sleep assessments after awakening, and at 03:30 and 06:00, corresponding to approximately 2.5 and 5.0 h post-awakening.

Safety

Safety was assessed by monitoring adverse events (AEs), and measuring vital signs (pulse, respiratory rate, and blood pressure) at visit 1 screening and before dosing with study medication and after awakening from the phase advance at visit 2.

Sample Size and Statistical Analyses

The trial was planned to recruit a sufficient number of individuals to enable data to be obtained from approximately 375 completed participants, approximately 125 participants in each treatment group. This sample size was sufficient to provide ≥ 85% power to detect a difference of 35 min in the PSG-derived WASO (primary endpoint), assuming a standard deviation of 80.4 min and a 0.05 level of significance.

The primary analysis was based on the intent-to-treat (ITT) population, which was defined as all randomized participants who received study medication and had any post-treatment efficacy data. The safety population included all participants who received study medication. The ITT and safety populations consisted of all 377 randomized participants—125 in each of the gabapentin-treated groups and 127 in the placebo-treated group.

An analysis of variance with treatment and clinical site terms in the model was used to compare treatments for most endpoints (PSG-derived WASO, number of awakenings, total wake time + stage 1, participant-reported sleep quality and refreshment, KSD assessments, SSS, and DSST). The remaining endpoints were analyzed using the Cochran-Mantel-Haenszel test, stratifying by site, using modified ridit scores.

AEs were coded using MedDRA (version 9.0) and categorized by system organ class and preferred term. AEs were also tabulated by severity (mild, moderate, or severe) and by investigator-judged relatedness to the study medication (related or not related).

Figure 1—PSG-derived WASO was significantly lower in the gabapentin 250 and 500 mg groups compared with placebo.
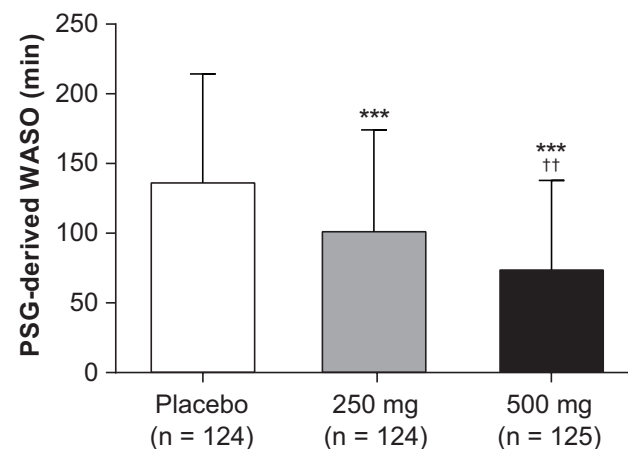
Mean (standard deviation) values are presented. *** p ≤ 0.001 vs. placebo. †† p = 0.003 vs. 250 mg (based on analysis of variance model). PSG, polysomnography; WASO, wake after sleep onset.

RESULTS

Participant Disposition

There were 571 participants screened, of whom 194 were considered screen failures. The remaining 377 participants were randomized: there were 127 participants in the placebo group and 125 participants each in the gabapentin 250 mg and 500 mg groups. One participant in the placebo group discontinued due to an AE, so 376 participants completed the study.

Participant Demographics and Baseline Characteristics

Demographic characteristics and sleepiness (measured by the ESS score at baseline) were comparable among groups (**Table 1**).

Medication use was also comparable among treatment groups. Dietary supplements (22.0%) and hormonal contraceptives (13.5%) were the only medication classes used by ≥ 10% of participants. The treatment groups were also generally comparable with respect to the frequency of participants who reported a medical condition, both overall and within each system organ class.

On average, participants reported having problems sleeping on 3.3 (SD 2.5) nights during the preceding month, trouble falling asleep 2.0 (2.1) times, and trouble staying asleep 1.7 (2.1) times. The participants reported waking up 1.1 (0.9) times during a typical night. The treatment groups were generally comparable with respect to each of these sleep characteristics (**Table 1**).

PSG Assessments

WASO was significantly lower in both active treatment groups than placebo (**Figure 1**), and the magnitude observed at gabapentin 500 mg was significantly greater than that seen at 250 mg (p ≤ 0.01).

Table 1—Demographic characteristics and baseline values.

Characteristic	Placebo (n = 127)	Gabapentin 250 mg (n = 125)	Gabapentin 500 mg (n = 125)
Age, years			
Mean (SD)	42.0 (15.6)	42.2 (17.0)	40.7 (17.1)
Range	18-78	19-85	19-78
Sex, n (%)			
Male	40 (31.5)	47 (37.6)	39 (31.2)
Female	87 (68.5)	78 (62.4)	86 (68.8)
Race, n (%)			
White	69 (54.3)	64 (51.2)	62 (49.6)
Black	43 (33.9)	41 (32.8)	41 (32.8)
Hispanic	13 (10.2)	18 (14.4)	19 (15.2)
Asian or Pacific Islander	2 (1.6)	1 (0.8)	3 (2.4)
Other	0	1 (0.8)	0
Weight, lb			
Mean (SD)	169.8 (37.1)	175.5 (34.6)	167.5 (32.4)
Range	96-276	107-310	106-257
History of sleep problems, mean (SD) [a]			
Problems sleeping	2.9 (2.4)	3.4 (2.5)	3.5 (2.5)
Trouble falling asleep	1.8 (2.2)	2.1 (2.2)	2.1 (2.0)
Trouble staying asleep	1.6 (2.1)	1.7 (1.9)	1.9 (2.4)
Waking up in middle of night	1.0 (0.8)	1.2 (1.1)	1.0 (0.9)
ESS total score, mean (SD)	3.8 (2.7)	4.2 (2.7)	3.8 (2.7)

No significant group effects were observed on demographic characteristics or baseline measures. [a] Values represent number of nights or times in response to the following questions: "Over the past month, how many nights did you have problems sleeping?"; "Over the past month, how many times did you have trouble falling asleep?"; "Over the past month, how many times did you have trouble staying asleep?"; "On a typical night, how many times do you wake up in the middle of the night?" ESS, Epworth Sleepiness Scale.

Table 2—PSG sleep assessments.

Parameter, mean (SE)	Placebo (n = 127)	Gabapentin 250 mg (n = 125)	Gabapentin 500 mg (n = 125)
WASO, min [a]	135.7 (7.0)	100.7 (6.6) ***	73.2 (5.8) ***,††
Latency to persistent sleep, min [b]	43.1 (7.2)	27.7 (4.5)	36.6 (5.1)
Number of awakenings [a]	8.3 (0.4)	8.0 (0.4)	6.5 (0.3) ***,††
Total wake time + stage 1 sleep, min [a]	210.0 (8.3)	162.4 (7.7) ***	138.4 (7.6) ***,†
Total sleep time [b]	311.4 (8.4)	356.5 (7.3) ***	378.7 (7.3) ***,††
Sleep architecture, % [b]			
Stage 1	15.1 (1.0)	11.8 (0.7) ***	10.8 (0.7) ***
Stage 2	56.9 (1.0)	57.5 (1.0)	56.4 (1.0)
Slow wave sleep (stage 3 + 4)	12.6 (0.9)	15.4 (1.0) *	17.0 (1.1) ***
REM sleep	15.5 (0.5)	15.3 (0.4)	15.8 (0.4)

Data presented as observed mean (SE) based on number of participants with non-missing data (n = 124 to 126). [a] Comparisons from the analysis of variance with treatment and site terms in the model. [b] Comparisons from the Cochran-Mantel-Haenszel test, stratifying by site and using modified ridit scores. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, compared with placebo. † $p \leq 0.05$, †† $p \leq 0.01$, compared with gabapentin 250 mg. REM, rapid eye movement; WASO, wake after sleep onset.

PSG endpoints are summarized in **Table 2**. In addition to effects on WASO, both gabapentin doses were associated with significantly less total wake time + stage 1 sleep and significantly greater total sleep time relative to placebo ($p \leq 0.001$). For each endpoint, a significantly greater effect was observed at gabapentin 500 mg versus 250 mg. PSG-measured number of awakenings was significantly lower in the gabapentin 500 mg group than placebo ($p \leq 0.001$).

Gabapentin 250 and 500 mg also affected sleep architecture; percent slow wave sleep (stages 3 and 4 combined) was significantly greater and percent stage 1 significantly lower versus placebo ($p \leq 0.05$). The 2 gabapentin doses were not significantly different from each other. There were no significant differences among treatment groups for percent stage 2 sleep or REM sleep.

Participant-Reported Sleep Assessments

Total sleep time was significantly greater in the gabapentin 500 mg group relative to placebo ($p \leq 0.05$; **Table 3**). There were no other significant differences among groups for participant-reported sleep outcomes (sleep latency, number of awakenings, WASO, refreshing nature of sleep, or sleep quality).

Table 3—Participant-reported sleep assessments.

Sleep Assessment, mean (SE)	Placebo (n = 127)	Gabapentin 250 mg (n = 125)	Gabapentin 500 mg (n = 125)
Sleep Questionnaire			
Sleep latency, min [a]	38.4 (6.7)	42.5 (6.9)	30.7 (3.4)
Number of awakenings [a]	2.6 (0.2)	2.6 (0.2)	2.5 (0.2)
WASO, min [a]	49.4 (5.9)	37.9 (5.1)	41.0 (6.1)
Total sleep time, min [a]	391.5 (8.4)	404.2 (8.4)	407.0 (8.0) *
Sleep refreshment (0-4) [b,c]	1.9 (0.1)	2.1 (0.1)	2.1 (0.1)
Sleep quality (0-4) [b,d]	2.3 (0.1)	2.4 (0.1)	2.5 (0.1)
Karolinska Sleep Diary [b,e]			
Sleep Quality Index	3.3 (0.1)	3.5 (0.1)	3.6 (0.1) *
Sleep quality	3.4 (0.1)	3.6 (0.1)	3.5 (0.1)
Calm sleep	3.3 (0.1)	3.5 (0.1)	3.6 (0.1) *
Ease of falling asleep	3.3 (0.1)	3.4 (0.1)	3.2 (0.1)
Premature awakening (slept throughout)	3.4 (0.1)	3.7 (0.1)	3.9 (0.1) *
Ease of awakening	3.9 (0.1)	4.0 (0.1)	4.0 (0.1)
Well-rested	3.5 (0.1)	3.8 (0.1)	3.8 (0.1)
Sufficient sleep	3.4 (0.1)	3.8 (0.1) *	3.7 (0.1)

Data presented as observed mean (SE) based on number of participants with non-missing data. [a] Comparisons from the Cochran-Mantel-Haenszel test, stratifying by site and using modified ridit scores. [b] Comparisons from the analysis of variance with treatment and site terms in the model. [c] Assessed in response to, "How refreshed do you feel?" 0 = not at all, 1 = a little, 2 = some, 3 = a lot, or 4 = completely. [d] Assessed in response to, "What was the quality of your sleep last night?" 0 = very poor, 1 = poor, 2 = fair, 3 = good, or 4 = very good. [e] Sleep Quality Index is defined as the mean of the following 4 items: sleep quality, calm sleep, ease of falling asleep, and slept throughout; rated from 1 to 5, with a higher value indicating better effects. Three additional scores (ease of awakening, well rested, and sufficient sleep) relate to awakening; rated from 1 to 5, with a higher value indicating better effects. * $p \le 0.05$, compared with placebo. WASO, wake after sleep onset.

Table 4—Stanford Sleepiness Scale and Digit Symbol Substitution Test upon awakening and at 2.5 and 5 h post-awakening.

Test/Administration Time, mean (SE)	Placebo (n = 127)	Gabapentin 250 mg (n = 125)	Gabapentin 500 mg (n = 125)
Stanford Sleepiness Scale [a]			
Upon awakening (~01:00)	2.8 (0.1)	2.6 (0.1)	2.7 (0.1)
2.5 h post-awakening (~03:30)	2.3 (0.1)	2.0 (0.1)	2.3 (0.1)
5 h post-awakening (~06:00)	2.2 (0.1)	1.8 (0.1)	2.0 (0.1)
Digit Symbol Substitution Test [b]			
Upon awakening (~01:00)	66.3 (1.8)	65.1 (1.5)	66.4 (1.7)
2.5 h post-awakening (~03:30)	74.3 (1.9)	74.8 (1.7)	74.6 (1.7)
5 h post-awakening (~06:00)	76.4 (1.8)	75.6 (1.7)	78.2 (1.8)

Data presented as observed mean based on number of participants with non-missing data. There were no statistically significant differences among treatment groups. [a] Based on a score of 1 (feeling active, vital, alert, or wide awake) to 7 (no longer fighting sleep, sleep onset soon, or having dream-like thoughts) [b] Higher scores indicate better performance.

KSD-SQI was significantly greater in the gabapentin 500 mg group, with KSD calm sleep and premature awakening rated higher compared with placebo ($p \le 0.05$; **Table 3**). KSD sufficient sleep was rated significantly higher in the gabapentin 250 mg group than placebo ($p \le 0.05$; **Table 3**).

Next-Day Residual Effects

Participants in all treatment groups showed an average SSS score consistent with normal levels of alertness (2 = functioning at high levels, but not at peak; able to concentrate; 3 = awake, but relaxed; responsive but not fully alert[35]) (**Table 4**). There were no significant differences among groups at any of the 3 time points evaluated.

For the DSST, participants in the 2 gabapentin-treated groups performed similar to placebo-treated participants at all 3 evaluation times (**Table 4**). There were no significant differences among treatment groups.

Safety and Tolerability Assessments

Of the 377 randomized participants, 16 (4.2%) reported at least 1 AE after dosing, with 2 participants (1.6%) in the placebo group, 5 participants (4.0%) in the gabapentin 250 mg group, and 9 participants (7.2%) in the gabapentin 500 mg group. Most events were of mild or moderate severity and were rated by the investigator as having a possible or probable relationship to study medication. One participant (0.8%) in the placebo group discontinued due to an AE (mild nausea and vomiting and a severe headache). There were no serious AEs or deaths. There were no significant differences in the frequency of any individual AE.

Treatment-related AEs are summarized in **Table 5**. The most common AE was headache, reported by 1 participant (0.8%) each in the placebo and gabapentin 250 mg treatment groups and 2 (1.6%) in the gabapentin 500 mg group. An increase in blood pressure was reported in 2 participants (1.6%) in the

Table 5—Summary of treatment-related adverse events.

System Organ Class, number (%)	Placebo (n = 127)	Gabapentin 250 mg (n = 125)	Gabapentin 500 mg (n = 125)
Number of participants with treatment-related adverse events	2 (1.6)	4 (3.2)	5 (4.0)
Nervous system disorders	1 (0.8)	1 (0.8)	3 (2.4)
Headache	1 (0.8)	1 (0.8)	2 (1.6)
Dizziness	0	0	1 (0.8)
Investigations	0	2 (1.6)	0
Blood pressure increased	0	2 (1.6)	0
Gastrointestinal disorders	2 (1.6)	0	1 (0.8)
Nausea	1 (0.8)	0	1 (0.8)
Vomiting	1 (0.8)	0	0
General disorders and administration site conditions	0	0	1 (0.8)
Feeling abnormal	0	0	1 (0.8)
Psychiatric disorders	0	1 (0.8)	1 (0.8)
Anxiety	0	1 (0.8)	0
Euphoric mood	0	0	1 (0.8)
Respiratory, thoracic, and mediastinal disorders	1 (0.8)	1 (0.8)	0
Asthma	1 (0.8)	0	0
Sinus congestion	0	1 (0.8)	0

As assessed by the investigator, events are possibly or probably related.

DISCUSSION

gabapentin 250 mg group. All other treatment-related events were reported once.

Two participants reported AEs that were coded as psychiatric disorders, with 1 in the gabapentin 250 mg group (anxiety of moderate severity), and the other in the gabapentin 500 mg group (euphoric mood of mild severity).

Overall, there were no statistically significant differences among treatment groups in vital sign changes during visit 2 (i.e., before taking study medication compared with upon awakening after taking study medication).

In participants with a history of occasional disturbed sleep who underwent a 5-h sleep phase advance, which is known to produce acute disturbances in sleep maintenance, PSG-determined WASO (primary endpoint) was significantly lower in the gabapentin 250 and 500 mg groups relative to placebo. Significant effects on other sleep maintenance endpoints were also observed. The beneficial sleep maintenance effects of gabapentin in this study are consistent with findings from another phase advance study that examined gabapentin 250 mg following single and multiple day dosing,[36] and a small open-label trial of gabapentin (mean dose 540 mg/day for 4 weeks) in participants with complaints of difficulty initiating and/or maintaining sleep for at least 3 months.[27] Like the present results, neither of these studies demonstrated an effect on sleep latency.

Importantly, the degree of sleep disturbance following the phase advance appears to have been sufficient for detecting drug effects. This is apparent for the PSG endpoints where gabapentin resulted in significant effects, but is also the case for sleep latency where gabapentin had no significant impact. Mean LPS in the placebo group was approximately 43 minutes, which is longer than the comparative value in other phase advance studies in which significant reductions in LPS were observed.[28,29] Thus, the observation that gabapentin did not significantly affect LPS in the present study suggests that this might be an integral property of gabapentin's profile, selectively affecting sleep maintenance and sleep stage distribution but not sleep latency.

With one exception (gabapentin 500 mg vs. placebo for TST), there were no significant effects of gabapentin on post sleep questionnaire endpoints. The reason for the divergence between PSG and these participant assessments is unknown, but the data are inconsistent with the results of a phase advance study of similar design and entry criteria, in which gabapentin 250 mg/day showed significant consistent effects on both PSG and participant-reported sleep maintenance parameters (relative to placebo), including TST, on both Day 1 and Day 28 of treatment.[36]

Gabapentin's positive effects on sleep maintenance were accompanied by less stage 1 sleep and greater slow wave sleep (relative to placebo). This is in agreement with other published reports where the effects of gabapentin on sleep architecture are selective, in that stage 1 is preferentially reduced and slow wave sleep increased,[19,21-25,27,36] although other findings have been reported (e.g., increase in REM sleep).[24,25] A decrease in light sleep (stage 1) with a parallel increase in deeper sleep (stages 3-4) suggests a deepening or consolidation of sleep, which may play a key role in sleep's restorative processes. Slow wave sleep is implicated in waking cognitive behavioral function, particularly memory and peripheral physiological functions that may positively affect physical health.[37,38] Additional well-designed clinical studies examining potential relationships between slow wave sleep and health benefits are needed to better understand the restorative nature of slow wave sleep.

Neither dose of gabapentin had an effect on SSS or DSST (upon awakening or at later times) suggesting a lack of next-day residual effects on these specific measures of sleepiness and psychomotor performance. These are important observations and distinguish gabapentin from various other hypnotic agents, both prescription and OTC, which have been reported to be associated with next-day residual effects.[34,39-41]

Overall, there were no clinically meaningful differences in AE frequency or vital sign changes among the three treatment groups. No new safety concerns were identified during the trial. Notably, the doses used in the present study are appreciably lower than the maximal gabapentin doses indicated for the treatment of approved indications. Because of this lower dose, it may be speculated that the gabapentin regimen used in this study in this essentially healthy population may be even better tolerated than the appreciably larger dosages used to treat individuals with postherpetic neuralgia, epilepsy, or restless legs syndrome.[9,10]

Occasional disturbed sleep is prevalent (frequently in older individuals, who interestingly have less slow wave sleep and more stage 1 sleep[42,43]), yet little is known concerning predisposing factors, possible comorbidities, and long-term health and economic consequences. There is some evidence suggesting that a proportion (10% to 14%) of individuals with symptoms of insomnia (without fulfilling all diagnostic criteria) may in time develop chronic insomnia, and moreover, that even mild symptoms of insomnia are associated with physical and mental health comorbidities, decreases in quality of life, and increases in occupational costs (increased absenteeism and reduced productivity).[44-47] Although individuals with occasional sleep disturbances commonly self-treat with OTC agents, evidence supporting the safety and efficacy of these medications is minimal. Efforts to develop safe and effective sleep aids will allow health care providers, including primary care physicians, nurse practitioners, and pharmacists who commonly encounter these individuals, to recommend evidence-based OTC medications.

Limitations

There are a number of limitations associated with this study that may affect interpretation and generalization. First, the study was powered for PSG assessments and not for participant-reported sleep assessments. Second, there were multiple statistical comparisons, which could increase the likelihood of type 1 errors. Third, the extent and nature of occasional sleep disturbances in the study population were not objectively verified. Fourth, gabapentin was only evaluated following single-dose administration. Fifth, unlike other phase-advance studies, bedtime was not adjusted precisely to the participant's habitual bedtime. However, only those participants who met the criterion of going to bed between 22:00 and 01:00 on the 3 nights prior to visit 2 were included in the study, thus limiting (to some extent) the potential for phase shifts to be substantially different than 5 hours. Finally, although no significant effects were observed on next-day measures of sleepiness (SSS) or psychomotor performance (DSST), the inclusion of a positive comparator (e.g., a sedative/hypnotic known to affect these measures) could have strengthened interpretation of these data.

CONCLUSIONS

Participants with occasional sleep disturbances treated with gabapentin (250 and 500 mg) showed statistically significant benefits on sleep maintenance compared with placebo, as assessed by PSG in a 5-h phase advance insomnia model, without evidence of next-day residual effects.

ABBREVIATIONS

AE, adverse event
DSST, Digit Symbol Substitution Test
ESS, Epworth Sleepiness Scale
ITT, intent-to-treat
KSD-SQI, Karolinska Sleep Diary Sleep Quality Index
OTC, over-the-counter
PSG, polysomnography, polysomnographic
REM, rapid eye movement
SSS, Stanford Sleepiness Scale
TST, total sleep time
WASO, wake after sleep onset

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