JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep and Residual Sedation After Administration of Zaleplon, Zolpidem, and Placebo During Experimental Middle-of-the-Night Awakening

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Study Objectives: To assess the efficacy of zaleplon 10 mg and zolpidem 10 mg administered during experimental middle-of-the-night awakenings in patients with sleep-maintenance insomnia using objective polysomnographic measures and to assess daytime residual sedation 4 to 7 hours after dosing using sleep-latency testing.

Design: A randomized, double-blind, placebo-controlled, 3-period, crossover design was used to study 37 adults with insomnia who received treatment during an experimental awakening 4 hours after bedtime. Latency to persistent sleep and total sleep time before and after awakening were recorded. The primary residual sedation measure was a sleep latency test conducted hourly from 4 to 7 hours after treatment. Self-report measure of alertness and concentration and digit symbol substitution tests were examined concurrently.

Setting: Sleep disorders centers.

Patients: Thirty-seven adults with sleep-maintenance insomnia.

Interventions: Zaleplon 10 mg, zolpidem 10 mg, or placebo.

Measurements and Results: Thirty-one patients had efficacy-evaluable data; 37 patients received at least 1 dose of study medication and were included in the safety analysis. Compared with placebo, latency to persistent sleep after both zaleplon and zolpidem was shorter and total sleep time after administration of the drugs was longer (overall $p < .001$, Dunnett $p < .001$ for all posthoc comparisons). Significant differences from placebo were not found with zaleplon in daytime-sedation measures. At 4, 5, and 7 hours after zolpidem, sleep onset on sleep latency testing was shorter than after placebo (overall $p < .001$ for all, Dunnett tests for posthoc comparisons $p < .001$, $p < .001$, $p < .05$, respectively). Self-report measures of concentration (4, 5, and 6 hours, overall $p < .05$, Dunnett $p < .05$ for each time point) and alertness (4 hours, overall $p < .05$, Dunnett $p < .05$), and Digit Symbol Substitution Test scores (4 and 5 hours, overall $p < .001$, Dunnett $p < .01$ for both time points) after zolpidem were also lower than with placebo.

Conclusions: Zaleplon 10 mg and zolpidem 10 mg effectively shorten sleep latency and lengthen sleep duration after dosing, when administered during experimental nocturnal awakening. Residual sedation was not detected as little as 4 hours after zaleplon 10 mg, whereas residual sedation was detected with zolpidem 10 mg up to 7 hours after treatment. These findings suggest that zaleplon may be an appropriate treatment for use when patients awaken during the night and have difficulty reinitiating sleep.

Keywords: Insomnia, treatment, hypnotic, zaleplon, zolpidem, PRN

Citation: Zammit GK; Corser B; Doghramji K et al. Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening. *J Clin Sleep Med*;2(4):417-423.

Disclosure Statement

This was an industry supported study supported by Wyeth Pharmaceuticals. Dr. Krystal has received research support from and/or is a consultant or advisory board member of Sanofi-Aventis, GlaxoSmithKline, King Pharmaceuticals, Inc., Merck & Co., Inc., Cephalon, Inc., Eli Lilly, Neurocrine Biosciences, Inc., Sepracor Inc., Pfizer Inc., Johnson & Johnson, Organon, Takeda Pharmaceuticals North America, Inc., Respironics, Mecta Corporation, Transoral, Neurogen, and Somaxon. Dr. Zammit has received research support from Sanofi-Aventis, maker of Zolpidem; and has received speaking and/or consulting fees from King Pharmaceuticals, owner of Zaleplon, and Sanofi-Aventis. Dr. Corser has participated in speaking engagements supported by Sanofi, Takeda, King Pharmaceuticals, and Cephalon. Dr. Fry has received research support from Aventis Pharmaceuticals, Boehringer Ingelheim, GlaxoSmithKline, Merck & Co., Inc., Sanofi Synthelabo Recherche, Schwartz Biosciences, Inc., and XenoPort, Inc. Dr. Mangano was an employee of Wyeth Pharmaceuticals when this study was conducted. Dr. James worked as a full-time consultant for King Pharmaceuticals. Dr. Doghramji has received research support from Elan Pharmaceuticals and Sanofi; and is a consultant and/or member of the speakers' bureau for King Pharmaceuticals and Sanofi. The data were analyzed by the authors and the company. The paper was written by the principal author, Dr. Zammit.

Submitted for publication January 24, 2006
Accepted for publication May 1, 2006

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Insomnia is defined as the perception by an individual that sleep is inadequate or abnormal.[1,2] This perception can be associated with the experience of difficulty falling asleep (initial insomnia), awakenings during the sleep period (sleep-maintenance insomnia), early awakenings followed by the inability to return to sleep (terminal insomnia), less total sleep time (TST) than desired, or any combination of these forms.[3-6] Insomnia is a common problem. Studies have shown that the prevalence of chronic insomnia in adults is 10% to 15% in the United States,[2,7-10] 21% in Japan,[11] 19% in France,[12] and 18% in Canada.[13]

The occurrence of insomnia is irregular and unpredictable, with significant night-to-night variability. Individuals with oc-

casional insomnia report that symptoms occur an average of approximately 5 nights per month, and those with chronic insomnia report that symptoms occur an average of 16 nights per month.[8] Therefore, insomnia is best characterized as an episodic disorder, even in those with chronic or long-term complaints.

The subtype of insomnia also may change over time. A study of individuals with initial, maintenance, terminal insomnia, or a combination of subtypes of insomnia revealed that the subtype or subtypes reported by patients at the time of initial assessment were not similar to reports obtained 4 months later.[14] Data revealed that only about half of patients with initial insomnia exclusively continued to report just initial insomnia at follow-up, while the balance of that group reported other subtypes of insomnia or combinations of subtypes. The consistency of patient complaints in those with maintenance and terminal insomnia was even lower than in patients with initial insomnia. Therefore, a significant variability in the type of insomnia may be experienced over time.

The night-to-night variability of insomnia and the possibility that symptom presentation may change over time have significant implications for treatment. The traditional model used in the drug treatment of insomnia has been a prophylactic model in which patients are advised to take medication before bedtime, usually on a nightly basis, for the duration of treatment. This model requires that patients take medication prior to the occurrence of symptoms. Consequently, patients may take medication when it is not needed (i.e., on nights when insomnia will not occur), or dosing may be improperly timed relative to the insomnia type and pharmacokinetic profile of the medication used. For example, when the sleep problem is maintenance or terminal insomnia, bedtime dosing of some sleep aids may not result in maximum availability of drug when needed.

Alternative models for the pharmacologic treatment of insomnia have been suggested.[15] Intermittent dosing with hypnotics (i.e., a few nights per week) often is recommended for the treatment of chronic insomnia.[16-21] One recent study showed that patients with insomnia who use medication at bedtime 3 to 5 nights per week report reductions in sleep latency and increases in TST on the nights that drug was administered.[22] Another study demonstrated consistent improvement in subjective ratings of sleep on both drug and nondrug nights for the duration of the intermittent dosing treatment period.[23] However, this model still requires that patients take medication at bedtime, prior to the occurrence of sleeplessness.

Another alternative treatment model is the as-needed (pro re nata [PRN]) dosing model. Patients may take drug at bedtime, later than bedtime, or in the middle of the night in response to symptoms of insomnia. A sleep medication that is used on a PRN basis without causing next-day residual sedation might be of considerable value to the reported 36% of the population who awaken in the middle of the night.[2] Zaleplon (Sonata®/King Pharmaceuticals) is a nonbenzodiazepine compound that undergoes rapid elimination[24] and is not associated with residual sedation or impairment after bedtime-dose administration.[25] Therefore, a middle-of-the-night dosing strategy was tested preliminarily as part of the clinical investigation of zaleplon.[26] In the first study, zaleplon 10 mg was compared with flurazepam 30 mg, using the long-acting benzodiazepine as an active control under the hypothesis that it (and its slowly eliminated metabolite) would produce next-day sedation. Indeed, flurazepam not surprisingly caused significant sedation on all measures up to 6.5 hours after dose administration. However, zaleplon showed no difference from placebo on any measure of residual sedation as few as 5 hours after middle-of-the-night administration to patients with maintenance insomnia.[26]

Zolpidem 10 mg (Ambien®/Sanofi-Aventis) is a nonbenzodiazepine hypnotic that represents a more pharmacologically similar active comparator to zaleplon, given that the mean half-lives of these 2 compounds are 1.0 hours and 2.5 hours, respectively. The present study was undertaken to determine if zaleplon 10 mg and zolpidem 10 mg are more effective than placebo in reducing sleep latency after nocturnal awakenings in patients with sleep-maintenance insomnia. The study also assessed TST after nocturnal awakenings and residual sedation after the middle-of-the-night administration of study medication using a self-report measure, the Digit Symbol Substitution Test, and a sleep-latency testing (SLT) protocol.

METHODS

Ethics

This study was conducted according to the Declaration of Helsinki and its amendments. The protocol received institutional review board approval before the study began.

Patients

Patients were men and women between the ages of 18 and 65 years who reported a history of primary sleep-maintenance insomnia for at least 1 month. Patients underwent 2 screening phases prior to initiation of the study period.

PROCEDURES

First Screening Phase

Patients were recruited by soliciting clinical patients who were likely to meet criteria for the study and by advertisement. Patients were screened by telephone prior to the initial office visit to determine if they were likely to meet inclusion and exclusion criteria for the study. At the time of the initial office visit, the study protocol was explained orally to patients, who then read and signed an informed consent form. Following consent, patients underwent a 7- to 21-day screening period during which they were given a routine physical examination including measurement of vital signs and weight, a neurologic assessment, and a 12-lead electrocardiogram. Blood and urine samples were obtained for laboratory testing and drug screening.

Patients were excluded from the study if they reported a history of transient insomnia, situational insomnia, insomnia associated with changes in sleep-wake schedules, illness-induced insomnia, or insomnia associated with the use of alcohol or drugs. Patients with a history of clinically important or unstable medical illness or major psychiatric disorder, which in the opinion of the investigator was likely to affect the study, were also excluded. Finally, patients were excluded if they had either a history or presence of any of the following: recent illicit drug use or daily alcohol consumption; positive urine drug screen; clinically important abnormalities on prestudy physical examination, 12-lead electrocardiogram, or laboratory-test results; concurrent use of medications known to interfere with study-drug absorption or metabolism; excessive consumption of beverages or foods containing caffeine;

routine or habitual napping; use of any investigational drug within 30 days of entry into the study; or hypersensitivity or paradoxical response to benzodiazepines or other sedatives. Nursing or pregnant mothers were also excluded.

Patients were given a sleep log to complete at home for at least 7 days after enrollment. In order for a patient to be included in the study, sleep logs were required to indicate both 45 minutes or more of wakefulness after initial sleep onset and 7.0 to 8.5 hours in bed on at least 4 of the last 7 consecutive nights before the beginning of the second screening phase. Patients also were required to have bedtimes that did not vary by more than 2 hours during the week when sleep logs were recorded.

Second Screening Phase

During the week prior to randomization, all patients underwent a second screening phase that consisted of 3 nights of polysomnographic (PSG) recording with administration of single-blind placebo. PSG recordings included measurement of electroencephalographic, electromyographic, electrooculographic, and electrocardiographic activity. On the first PSG screening night, respiratory airflow, oxygen saturation, and bilateral anterior tibialis muscle electromyographic readings were obtained. PSG-related inclusion criteria included a latency to persistent sleep (LPS) of 20 minutes or more after an experimental middle-of-the-night awakening for administration of the placebo on at least 2 of 3 screening nights, 10 or fewer apneas or hypopneas per hour, oxygen saturation not less than 85%, and no more than 10 periodic lower-limb movements with greater than 3-second arousals (the latter during the first PSG screening night).

Double-blind Treatment

Within 14 days of starting the second screening phase, patients were assigned to a random-treatment sequence that included zaleplon 10 mg for 2 nights, zolpidem 10 mg for 2 nights, and placebo for 2 nights. Each 2-night treatment period was separated by a 5- or 12-day washout period. Patients reported to the sleep laboratory at least 1 hour before lights out on each night and were prepared for PSG recording. PSG recording began at the patients' habitual bedtimes (as determined by sleep-diary entries) and continued for 460 minutes. Patients were awakened 4 hours after lights out, and they were kept awake for approximately 40 minutes. During the experimental awakening with lights turned on, patients got out of bed, were allowed to use the bathroom, were presented with a word list, completed an immediate word-recall test, received double-blind treatment, remained awake for 30 minutes after receiving the dose, completed a delayed word-recall test, and completed a questionnaire. The delayed word-recall test and questionnaire were used only to promote wakefulness, and the results were not analyzed. Thirty minutes after dose administration, patients returned to bed for an additional 3 hours. Patients who already were awake 4 hours after lights out followed the same procedure. Patients who awakened spontaneously at times other than the scheduled experimental awakening remained in bed while the PSG recordings continued.

An SLT procedure began approximately 30 minutes after the end of the PSG recording, allowing nap opportunities at 4, 5, 6, and 7 hours after the dose of study medication. The SLT was based on the guidelines for the Multiple Sleep Latency Test developed by the Association of Sleep Disorders Centers Task Force on Daytime Sleepiness.[27] Patients removed shoes, loosened constricting clothing, and were prepared for SLT recording by 5 minutes prior to the start of each test. Patients were then given instructions to lie quietly with their eyes closed and to allow sleep to occur. Each SLT was terminated 20 minutes after lights out if there was no sleep, after 3 consecutive 30-second intervals of stage-1 sleep, or after the first 30-second interval of any other sleep stage. Sleep onset was defined as the time elapsed between the lights being turned off and the first 30-second interval recorded as sleep.

A memory test (4-hour delayed-word recall) was administered each morning 25 minutes after awakening. A 90-second Digit Symbol Substitution Test and subjective assessments of sedation were administered after each SLT. The subjective assessment asked patients to rate both their level of alertness and their ability to concentrate on a scale of 1 to 7, ranging from excellent to extremely poor.

Statistical Analysis

PSG, LPS , LPS-AFTER, TST, TST-AFTER and primary and secondary daytime-sedation outcome variables were calculated for each treatment condition by averaging data for each patient's 2-day treatment period. Overall treatment differences among the 3 conditions were assessed via analysis of variance for a crossover design. If overall treatment difference was significant, a Dunnett test was used to determine which active treatment was different from placebo. Nonparametric procedures were used to confirm basic analysis of variance results. Primary analysis was performed on data from all randomly assigned patients who had no major protocol violations and who had data from at least 1 night of each of the 3 treatment periods (efficacy-evaluable population). All patients who enrolled in the study and had data from at least 1 dose of study medication were included in the safety analysis.

RESULTS

Twenty-five (68%) of the patients enrolled in the study were women, and 12 (32%) were men. The mean age, height, and weight (± standard deviation [SD]) of the patients were 44 ± 10.9 years (range, 25-65), 170 ± 9.3 cm, and 74 ± 16.17 kg, respectively. Twenty-seven patients were white, 7 were black, and 3 were Hispanic. All 37 patients enrolled in the study received at least 1 dose of study medication and were thus included in the safety analysis. However, only 31 had data from each of the 3 treatment periods and were included in the outcome analyses (n = 31 for all analyses of variance).

LPS was defined as the time (in minutes) from the beginning of the recording (lights turned off) to the first epoch of the first 20 consecutive 30-second epochs of sleep (stages 1, 2, 3/4, or rapid eye movement [REM]). LPS-BEFORE, recorded prior to administration of study medication (during the first 4 hours of PSG), was not different between groups. Mean latencies for patients in the zaleplon 10 mg, zolpidem 10 mg, and placebo groups were 21.5, 26.91, and 19.6 minutes, respectively (overall $p = .393$). LPS-AFTER, recorded after the administration of zaleplon 10 mg, zolpidem 10 mg, and placebo was 14.9, 11.7, and 42.2 minutes, respectively (overall $p < .001$), which made the LPS with active agents shorter by approximately 27 minutes and 31 minutes (Dunnett $p < .001$ for both posthoc comparisons) (Figure 1).

TST was defined as the total time (minutes) of stages 1, 2, 3/4,

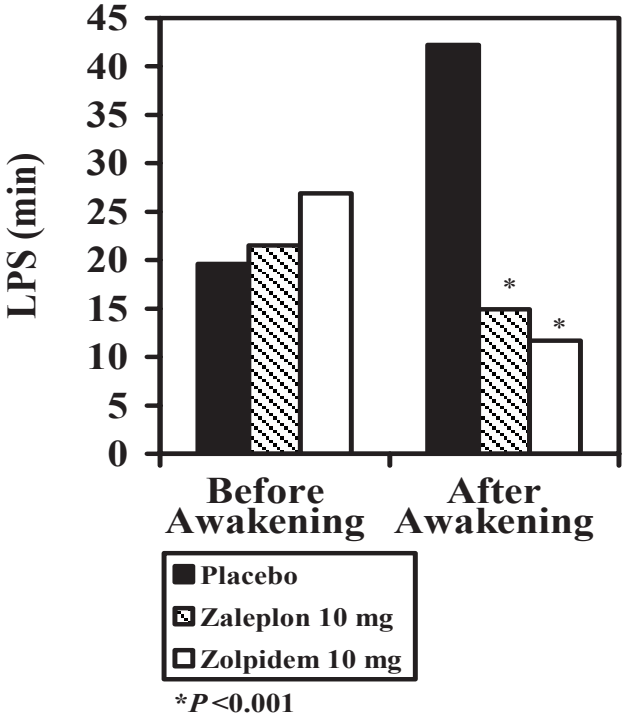

Figure 1—Latency to persistent sleep (LPS) for each group before and after experimental awakening. Both agents produced a significant decrease in the time for patients to fall asleep after an experimental middle-of-the-night awakening, as compared with placebo.

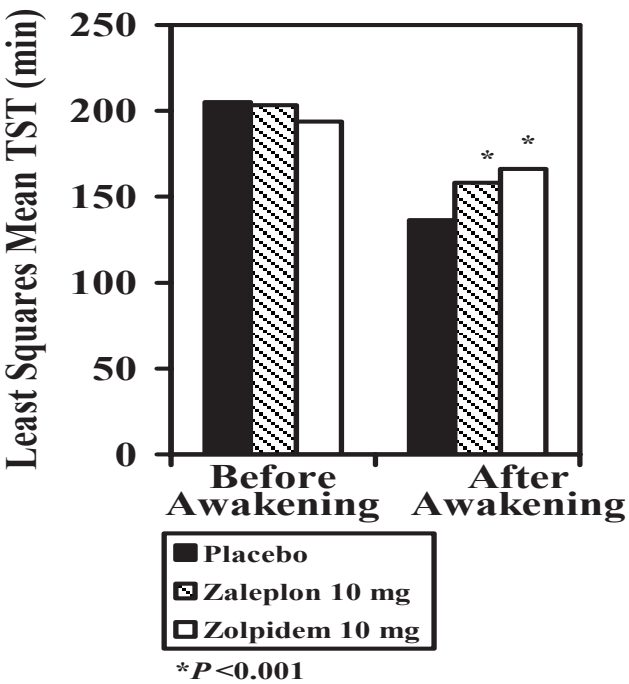

Figure 2—Total sleep time (TST) of each group before and after experimental awakening. Compared with placebo, both agents significantly increased sleep time after administration following an experimental middle-of-the-night awakening.

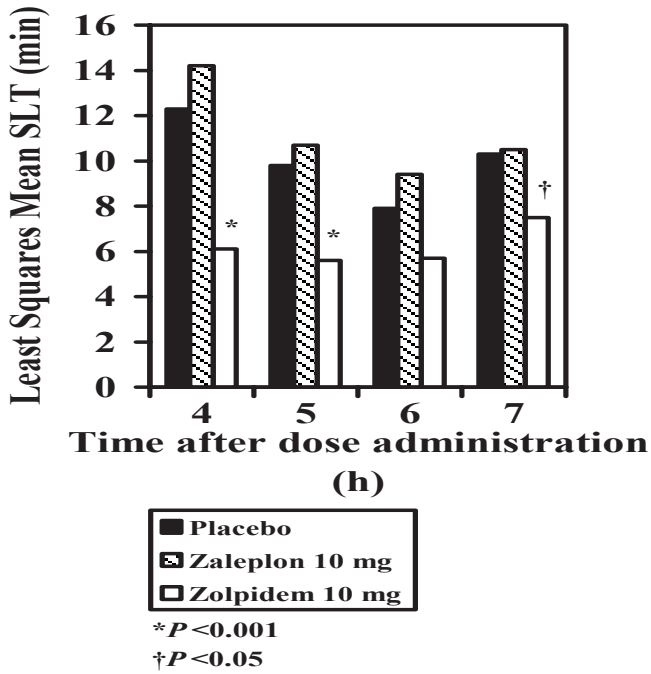

Figure 3—Next-day sleep-latency testing (SLT) after experimental middle-of-the-night awakening. Zolpidem resulted in significant sedation for up to 7 hours after administration following an experimental middle-of-the night awakening, as compared with placebo, whereas zaleplon resulted in no significant sedation at any time point evaluated on the day after administration.

and REM sleep combined. TST-BEFORE, recorded in the first half of the night (during the first 4 hours of PSG), was not different between groups. Mean TST values for patients in the zaleplon 10-mg, zolpidem 10-mg, and placebo groups were 203.4, 193.7, and 205.2 minutes, respectively (overall p = .128). TST-AFTER was recorded in the second half of the night (following dosing) with zaleplon 10 mg and zolpidem 10 mg was significantly longer than placebo by approximately 22 minutes and 30 minutes, respectively (overall p <.001, and Dunnett p < .001 for both posthoc comparisons) (Figure 2).

Daytime sleep latency was not significantly different between the zaleplon 10-mg and placebo conditions when SLT assessments were performed 4 to 7 hours after dose administration (Dunnett p > .136 for all posthoc comparisons). Daytime sleep latency with zolpidem 10 mg was approximately 6.0, 4.0, and 3.0 minutes shorter than with placebo (overall p < .001 for all comparisons) when tested at 4 (Dunnett p < .001), 5 (Dunnett p < .001), and 7 (Dunnett p < .05) hours, respectively, after dose administration (Figure 3).

On the questionnaire completed after each SLT, no statistically significant difference between the zaleplon 10-mg and placebo conditions was reported in patients' subjective level of alertness or ability to concentrate. However, patients reported significantly less alertness after the SLT performed at 4 hours after dosing with zolpidem 10 mg relative to reports after dosing with placebo (overall p = .005, Dunnett p < .05). Daytime subjective reports of ability to concentrate following zolpidem 10 mg were significantly worse than following placebo when tested after the SLT at 4, 5, and 6 hours after treatment (overall p < .05 for all comparisons, Dunnett p < .05 for each time point, Figure 4).

On the Digit Symbol Substitution Test, there were no significant differences between zaleplon 10 mg and placebo in the total number of symbols completed at any time point after dose administration. Patients completed significantly more symbols correct-

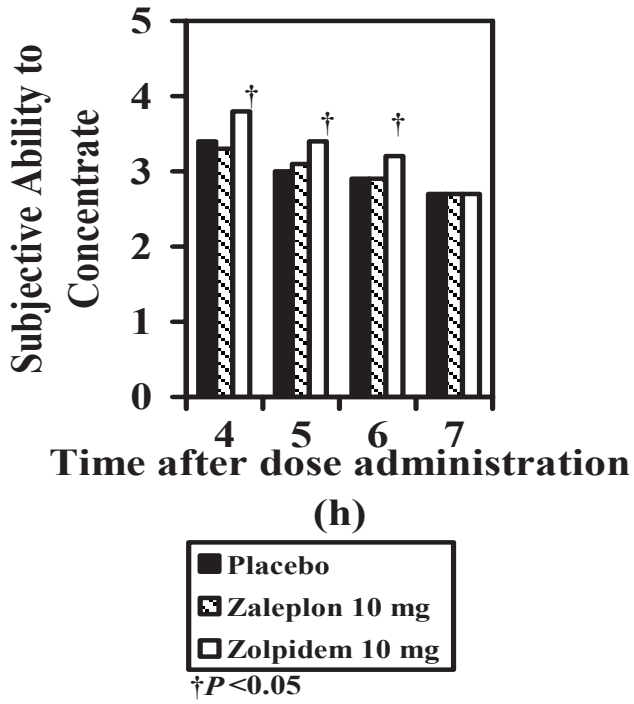

Figure 4—Next-day subjective measure of concentration after experimental middle-of-the-night awakening. Compared with placebo, zolpidem resulted in a significant decrease in the self-reported level of concentration for up to 6 hours after administration following an experimental middle-of-the night awakening, whereas zaleplon resulted in no significant difference relative to placebo on the day after treatment administration.

ly 7 hours after dosing with zaleplon 10 mg compared with after placebo (overall p = .002, Dunnett p < .05). In contrast, patients completed both significantly fewer symbols and significantly fewer symbols correctly following zolpidem 10 mg compared with placebo when tested 4 (overall p < .001, Dunnett p < .001) or 5 (overall p < .001, Dunnett p < .01) hours after dose administration (Figure 5). There were no significant differences between placebo and active treatment in the number of words recalled or the number of words recalled correctly when assessments were performed immediately after word presentation (immediate word recall) or 4 hours after dose administration (delayed word recall).

As shown in Table 1, 1 or more adverse events (AEs) were reported by 12 patients (33%) who were exposed to treatment after receiving zaleplon 10 mg (n = 36), 12 patients (32%) after receiving zolpidem 10 mg (n = 37), and 17 patients (46%) after receiving placebo (n = 37). AEs were defined as any negative event experienced by a patient during the study. Treatment-emergent adverse events were defined as those that started or worsened during a treatment or washout period. Treatment-emergent AEs were reported by 10 patients (28%) after receiving zaleplon 10 mg, 9 (24%) after receiving zolpidem 10 mg, and 12 (32%) after receiving placebo. The most common treatment-emergent AEs were headache, nausea, vomiting, and somnolence.

The number of patients who received some type of concomitant therapy during the double-blind treatment period with placebo, zaleplon 10 mg, and zolpidem 10 mg were 24 (65%), 25 (69%), and 24 (65%), respectively. Table 2 provides a summary of concomitant medications taken by at least 5% of patients in at least 1 group.

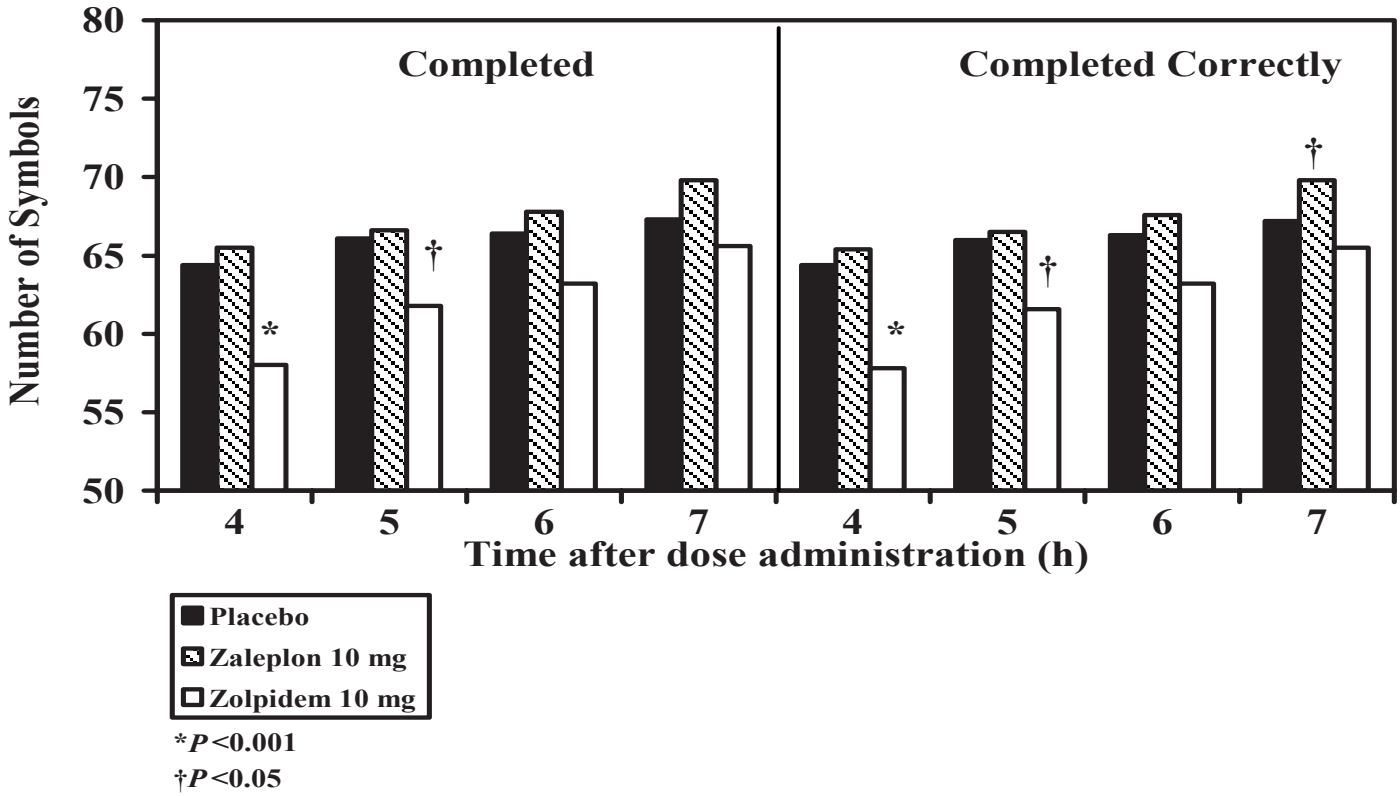

Figure 5—Next-day Digit Symbol Substitution Test after experimental middle-of-the-night awakening. Dosing with zolpidem after a middle-of-the-night experimental awakening significantly decreased both the total number of symbols completed and the number of symbols completed correctly at 4 and 5 hours after treatment administration. In contrast, dosing with zaleplon showed no difference in psychomotor skills, with the exception of an improvement in function relative to placebo at 7 hours after treatment.

Table 1—Patients Reporting Adverse Events[a]

Body system adverse event	Placebo (n = 37)	Zaleplon 10 mg (n = 36)	Zolpidem 10 mg (n = 37)
Any adverse experience	17 (46)	12 (33)	12 (32)
Body as a whole	8 (22)	9 (25)	7 (19)
Headache	6 (16)	8 (22)	4 (11)
Cardiovascular system	1 (3)		
Digestive system	2 (5)	2 (6)	3 (8)
Nausea		2 (6)	2 (5)
Vomiting			2 (5)
Metabolism and nutrition			1 (3)
Nervous system	4 (11)	1 (3)	6 (16)
Confusion			1 (3)
Dizziness			1 (3)
Hypoesthesia	1 (3)	1 (3)	1 (3)
Nervousness	1 (3)		
Somnolence	2 (5)		3 (8)
Vertigo			1 (3)
Respiratory system	2 (5)		2 (5)
Skin and appendages	2 (5)	2 (6)	
Urogenital system	1 (3)		

[a]Data are presented as number (%). Body system totals may not be the sum of individual events because a patient may have reported more than 1 event in the same body system.

Table 2—Concomitant Medications Taken by at Least 5% of Patients in at Least 1 Group

Medication Category	Placebo (n = 37)	Zaleplon (n = 36)	Zolpidem (n = 37)
Aminoalkyl ethers	2 (5)	2 (6)	2 (5)
Anilides	5 (14)	4 (11)	3 (8)
Ascorbic acid (vitamin C, plain)	2 (5)	2 (6)	2 (5)
Calcium-channel blockers	3 (8)	3 (8)	3 (8)
Estrogens	2 (5)	2 (6)	2 (5)
HMG coA reductase inhibitors	2 (5)	2 (6)	2 (5)
Multivitamins, other combinations	2 (5)	2 (6)	2 (5)
Other plain vitamin preparations	3 (8)	3 (8)	3 (8)
Progestogens and estrogens, fixed combinations	5 (14)	5 (14)	5 (14)
Propionic acid derivatives	6 (16)	4 (11)	5 (14)
Proton pump inhibitors	2 (5)	2 (6)	2 (5)
Salicylic acid derivatives	4 (11)	6 (17)	4 (11)
Thyroid hormones	2 (5)	2 (6)	2 (5)
All other therapeutic products	3 (8)	3 (8)	3 (8)

Data are presented as number (%).

DISCUSSION

The results of this study indicate that zaleplon 10 mg and zolpidem 10 mg both reduce the time to fall asleep relative to placebo when administered after experimental nighttime awakenings to individuals with maintenance insomnia. This is one of a small number of studies to evaluate middle-of-the-night dosing in individuals with sleep-maintenance insomnia. Although forced and experimentally prolonged awakenings are not an exact correlate to naturally occurring middle-of-the-night awakenings that might prompt PRN drug use, the feasibility of PSG studies of spontaneous middle-of-the night awakenings and PRN use is limited, given the time and expense of waiting for naturally occurring awakenings and the choice to use medication. This study design therefore provides insight into the potential efficacy and next-day sedative effects associated with the middle-of-the-night dosing rather than a direct test of PRN use. The application of the experimental model used here is supported by other studies that have examined next-day sedation following experimenter-induced awakenings and middle-of-the-night dosing of hypnotics.[28]

PRN middle-of-the-night dosing is a novel and potentially important strategy that represents a departure from traditional prophylactic treatment models in which patients are advised to take medication at bedtime, prior to the occurrence of symptoms. The PRN strategy enables patients to take hypnotic medication when needed, in response to symptoms. One benefit of this strategy is that the timing of hypnotic dosing and maximum drug concentrations (t_{max}) coincides with symptom occurrence, providing a temporally targeted and possibly more effective treatment. Using this strategy, individuals who do not experience maintenance insomnia on a nightly basis may consume fewer doses of hypnotic medication over time, as medication is used only when symptoms occur rather than nightly in anticipation of insomnia. This may have both significant clinical and significant economic advantages.[22,25]A potential drawback to the PRN approach to treatment is that the individual must experience insomnia prior to dosing, whereas prophylactic models may prevent symptoms before they occur. Another potential drawback is that nightly dosing may have therapeutic effects on the morbidities associated with chronic insomnia[29] that may not be addressed with intermittent or PRN treatments.

Zaleplon 10 mg was found to be no different from placebo on objective measures of sleep latency obtained 4 to 7 hours after dosing, indicating the absence of residual sedation the morning following middle-of-the-night dosing. Neither were any significant differences found between zaleplon 10 mg and placebo on the measures of functioning upon morning awakening (including self-report measures of alertness and ability to concentrate, memory, and psychomotor performance testing), except for a significant improvement in psychomotor skills 7 hours after treatment, which may have been observed by chance. In contrast, significant differences were observed between zolpidem 10 mg and placebo on objective measures of sleep latency and most measures of functioning upon morning awakening. The differences between active drug and placebo observed here are consistent with the pharmacokinetic and pharmacodynamic profiles of the zaleplon and zolpidem. The absence of differences between zaleplon and placebo is not likely to be a matter of low statistical power; the mean values indicate (nonsignificantly) better results for zaleplon on almost all measures.

Overall, the data suggest that both zaleplon 10 mg and zolpidem 10 mg are effective in reducing sleep latency following experimental nighttime awakenings in individuals with maintenance insomnia, without significant AEs or treatment-emergent AEs. However, middle-of-the-night dosing with zaleplon 10 mg is not associated with residual sedation, as measured by self-report instruments, or performance impairment on the Digit Symbol Substitution Test, whereas similar use of zolpidem 10 mg is associated with residual sedation and performance impairment. This study is important because it demonstrates that a sleep medication can safely reduce LPS and increase TST when it is used during a middle-of-the-night awakening.

ACKNOWLEDGEMENTS

The authors' primary roles in this study: Dr. Mangano was involved in study planning, protocol design, and data analysis; Drs. Zammit, Corser, Doghramji, Fry, and Krystal were principal investigators (PIs) responsible for execution of the study and manuscript preparation; Dr. James provided assistance with manuscript preparation. Dr. Mark Mahowald served as a PI for this study but declined to co-author the manuscript. The authors gratefully acknowledge the contributions of the following persons to this work: Mark A. DiPhillipo, BA, RPSGT; Ruth Elling, RPSGT; Jeffrey A. Kramer, PharmD; Stephen Lund, MD; David W. Mayleben, PhD; Kathleen Rice, PhD; Adam Roth, BA; and Sharon Schutte, MD. The authors also would like to thank Ms. Bridget Banas for her assistance in preparation of the manuscript.

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