Long-Term, Non-Nightly Administration of Zolpidem in the Treatment of Patients With Primary Insomnia

Michael L. Perlis, Ph.D.; W. Vaughn McCall, M.D.; Andrew D. Krystal, M.D., M.S.; and James K. Walsh, Ph.D.

Received Feb. 3, 2004; accepted June 1, 2004. *From the Sleep and Neurophysiology Laboratory, Department of Psychiatry, University of Rochester, and the University of Rochester Medical Center, Neurosciences Program, Rochester, N.Y. (Dr. Perlis); the Department of Psychiatry and Behavioral Medicine, Wake Forest University School of Medicine, Winston-Salem, N.C. (Dr. McCall); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C. (Dr. Krystal); and the Sleep Medicine and Research Center, St. John's/St. Luke's Hospitals and the Department of Psychology, Saint Louis University, St. Louis, Mo. (Dr. Walsh).*

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Financial disclosure and a list of study investigators appear at the end of this article.

Corresponding author and reprints: Michael L. Perlis, Ph.D., Sleep and Neurophysiology Laboratory, Department of Psychiatry, University of Rochester, and the University of Rochester Medical Center, Neurosciences Program, 300 Crittenden Blvd., Rochester, NY 14642 (e-mail: Michael_Perlis@URMC.Rochester.edu).

Introduction: While it is common practice that hypnotics are used on a non-nightly basis, few investigations have been undertaken to evaluate the efficacy of the intermittent dosing strategy. The present study was designed to further evaluate this issue within a large scale, double-blind, placebo-controlled, long-term trial.

Method: Patients who met DSM-IV criteria for primary insomnia participated in the study from January 2000 through October 2001. Patients were randomly assigned to 1 of 2 treatment groups (zolpidem 10 mg or placebo) for a period of 12 weeks. Ten pills were provided in foil packs on an every-other-week basis, and patients were instructed to take no fewer than 3 and no more than 5 pills per week. Sleep was evaluated daily with sleep diaries. Pill use was recorded in the sleep diaries.

Results: 199 patients (mean ± SD age = 41.0 ± 12.8 years; 71% female) were randomly assigned to treatment. On mean, patients receiving zolpidem exhibited (vs. baseline) a 42% decrease in sleep latency, a 52% reduction in number of awakenings, a 55% decrease in wake time after sleep onset, and a 27% increase in total sleep time. These positive clinical gains did not diminish with time and were not associated with dose escalation. There was also no evidence of rebound insomnia.

Conclusions: Over a period of 12 weeks of intermittent treatment with zolpidem, sleep continuity was significantly improved, the clinical gains were sustained, and there was no evidence of subjective rebound insomnia between doses or increases in the amount of medication used during the study interval.

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For patients with chronic insomnia, less-than-nightly usage of hypnotic medication is often recommended.[1–4] The practice of using hypnotics on an intermittent basis also appears to be a strategy that is adopted by patients when using hypnotics ad libitum. Despite the fact that the intermittent dosing approach may be both the recommended and preferred standard of practice, only a small number of studies[5–10] have been conducted to evaluate the efficacy and safety of non-nightly use of hypnotics.

In the first investigation,[6] intermittent dosing was compared with nightly medication use in a multicenter outpatient study. One hundred sixty adult patients (mean age = 45 years) with chronic insomnia took part in the investigation. The patients were treated for 2 weeks with zolpidem (10 mg), either continuously or intermittently (5 nights zolpidem and 2 consecutive nights placebo per week). At the end of the 2-week treatment, patients in the nightly use condition estimated their mean ± SD nightly total sleep time as 6.96 ± 1.19 hours (vs. 6.07 ± 1.25 hours at baseline). Patients in the intermittent dosing group estimated their mean ± SD nightly total sleep time as 6.94 ± 1.30 hours (vs. 5.72 ± 1.46 hours). These results suggest that the effects of zolpidem (10 mg) are comparable whether the drug is administered every night or intermittently. While this study is the first of its kind, its limitations include the use of retrospective estimates, the

use of a fixed and frequent intermittent dosing scheme, and the absence of a placebo control group.

In a second study,[10] the longest investigation to date, intermittent use of zolpidem was compared with placebo for an 8-week trial interval. The study design was a parallel, randomized, double-blind, placebo-controlled clinical trial conducted across 6 sleep research sites. One hundred sixty-three patients (115 women, 48 men; mean ± SE age = 44.1 ± 0.9 years) with DSM-IV–defined primary insomnia participated in the study. The patients were treated with placebo or zolpidem, 10 mg, with instructions to take the study drug 3 to 5 nights per week. Sleep was assessed with both global assessments (patient and investigator ratings) and with daily sleep/wake diaries. On the nights that pills were taken, patients in the intermittent use condition exhibited approximately a 50% reduction in sleep latency (75 vs. 36 min) and approximately a 30% increase in total sleep time (320 vs. 415 min). Patients in the placebo condition exhibited approximately a 25% reduction in sleep latency (67 vs. 50 min.) and approximately a 14% increase in total sleep time (320 vs. 363 min).

The medication effects were stable across the 8-week treatment period, and there was no evidence of discontinuation effects or an increased frequency of pill taking. While the data from this study are compelling, the limitations of the investigation include (1) an analysis of less than the full complement of the standard sleep continuity variables* (i.e., data were presented for sleep latency, number of awakenings and total sleep time but not for wake after sleep onset time) and (2) an analytic strategy that did not allow for the clear resolution of group-by-time effects.

The present placebo-controlled investigation was undertaken to confirm and extend the previous observations with zolpidem. The primary aims were to evaluate efficacy and safety of the intermittent dosing strategy over a 12-week time period and to assess whether intermittent zolpidem dosing is associated with dose escalation or any occurrence of rebound insomnia on drug-free nights.

METHOD

General Summary

This study was a parallel-groups, randomized, double-blind, placebo-controlled clinical trial conducted at 9 centers. The study design was developed jointly by one of the authors (J.K.W.) and Lorex Pharmaceuticals (a member of the Sanofi-Synthelabo Group, New York, N.Y.). The protocol was approved by an institutional review board for each of the study sites, and all patients provided written informed consent prior to being enrolled.

Randomization schedules and the packing of clinical supplies were accomplished by a clinical supply manufacturing group (Covance Inc.; Princeton, N.J.). Except in the event of a medical emergency, the randomization code was not available to any study personnel while the trial was active (including Lorex personnel directly involved with the conduct of the study). Eligible patients were randomly assigned to 1 of 2 treatment conditions (zolpidem 10 mg or placebo) for a period of 12 weeks. Patients were instructed to use medication between 3 and 5 nights per week. All patients completed sleep diaries on a daily basis. Pill use was also recorded in the sleep diaries, and unused medication and study drug packaging were returned to the study site at each visit for verification. Data management and the initial statistical analyses were performed by Medifacts International (Medifacts International; Rockville, Md.). As part of the preparation of this article, a second independent analysis of the treatment outcome data was conducted by the first author (M.L.P.).

Patient Selection and Screening

Patients aged 18 to 64 years were eligible for the study provided they met the DSM-IV criteria for primary insomnia and were deemed to be in good mental and physical health as ascertained by a medical history, physical examination, and standard clinical laboratory tests obtained within 2 weeks of study start.

Exclusion criteria included presence of any significant psychiatric disorder; use of any over-the-counter or prescription sleep medication within 7 days or any investigational drug within 30 days before study start; positive urine screen for medication that could interfere with the assessment of study medication; history of drug addiction, alcoholism, or drug abuse; and history of or current symptoms compatible with sleep apnea or periodic leg movements during sleep. Additionally, female patients were ineligible if they were breastfeeding, pregnant, or not using double-barrier contraceptive methods.

Following the initial screening interview, patients completed a sleep diary for 6 to 14 days to further assess the severity and frequency of their sleep complaints. The information from the sleep diaries was used to establish that the patients reported (on at least 3 of 7 consecutive nights) (1) sleep latency of ≥ 45 minutes or a total sleep time of ≤ 6 hours as estimated each morning and (2) impaired daytime functioning related to their insomnia. This aspect of screening confirmed the patients' characterization of their sleep complaints at intake, familiarized patients with keeping daily sleep diaries, and allowed for an assessment of whether patients would comply with study requirements.

*The term *sleep continuity* is used to represent 1 of the 2 major classes of sleep variables (sleep continuity vs. sleep architecture measures) and denotes the set of variables that are associated with sleep initiation and maintenance (sleep latency, number of awakenings, wake after sleep onset, and total sleep time).

Once enrolled in the study, patients were required to abstain from the use of psychotropic medications or medications with known effects on sleep (e.g., sedating antihistamines, β-blockers). Patients were also asked not to consume large meals within 2 hours of bedtime or to drink alcohol or use CNS-active medications within several hours of going to bed. When using concomitant medication, regardless of type, patients were instructed to record each use in their sleep diaries.

Table 1. Sleep Continuity Variables Obtained From Nightly Sleep Diaries of Patients Taking Zolpidem or Placebo

Variable	Definition
Sleep latency	Amount of time taken to fall asleep—first sleep onset (min)
Number of awakenings	Number of awakenings following initial sleep onset
Wake after sleep onset	Amount of time spent awake during the night—not including sleep latency (min)
Total sleep time	Amount of sleep acquired during the night (min)

Study Medication

Zolpidem is a nonbenzodiazepine hypnotic of the imidazopyridine class and is available in 5-mg and 10-mg tablets for oral administration. Zolpidem has a mean time to peak plasma concentration of about 1.6 hours and a mean elimination half-life of about 2.5 hours. Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

Study medications were provided in blister cards containing 2 one-week supplies of 5 capsules each. Patients were instructed to "take the medication when you think your need it, at bedtime, for a total of between 3 and 5 capsules per week." They were also told to take only 1 pill per night and not to use the study medication to treat early awakenings. Information was provided about a possible next-day carryover effect, and patients were cautioned to use care while doing anything that required complete alertness, such as driving a car, operating machinery, or piloting an aircraft, until they knew how the study medication affected them.

Procedures

Once randomly assigned to treatment, patients estimated and recorded their sleep daily with sleep diaries and were evaluated during biweekly study visits in the clinic.

The sleep diary contained 2 sections. The first section was completed prior to bedtime and was composed of 2 questions: 1 pertaining to date and time, and 1 regarding daytime impairment within the last 24 hours. The second section was completed upon awakening and was composed of 14 questions to assess sleep continuity including sleep latency, number of awakenings, wake after sleep onset, and total sleep time.

Biweekly study visits included the return of the past 2 weeks' study materials, a clinical interview, completion of questionnaires related to clinical effects (sleep and adverse events), and provision of the study drug for the next 2 weeks. The clinical interview included an evaluation by the investigator in which the patient was interviewed and rated on a scale of 1 to 7 referred to as the Investigator's Global Rating (IGR) scale. The IGR scale included a rating of the study drug's global therapeutic effect on sleep (from 1 = marked worsening to 7 = marked improvement). The IGR variable mimics the routine clinical situation in which a physician makes a general assessment of therapeutic benefit on the basis of the patient's in-office retrospective report.

Data Analysis

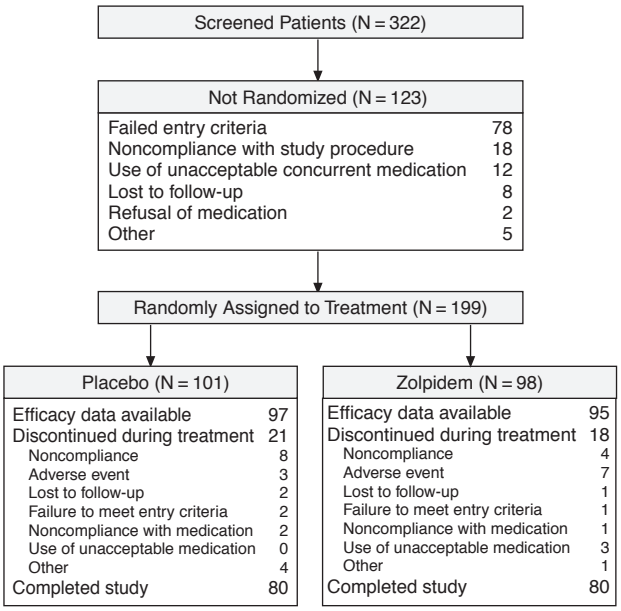
To assure the accuracy and consistency of data, each study site was periodically monitored by a clinical research associate from Lorex who reviewed all case report forms for completeness. The computer database was prepared using double entry of the case report form data. Double entry allows keypunch errors to be identified. The values in the database were, in turn, spot-checked by having a quality assurance auditor visit select study sites and compare the data in the study charts with those in the central database.

The data analysis for this investigation was conducted in 2 parts. The initial and main analyses were conducted by an independent firm on behalf of Lorex (Medifacts International, Rockville, Md.). The secondary set of analyses was conducted post hoc by the first author (M.L.P.). The initial analyses were undertaken using 3-way analyses of variance (ANOVAs), with follow-up analyses comparing each time point to baseline for each of the outcome measures across each of the 3 conditions. The factors for the 3-way ANOVAs were site-by-group-by-time. The post hoc analysis used 2-way ANOVAs in order to more simply and directly evaluate the group-by-time interactions. All of the sleep continuity data presented in this report are from the secondary analyses.

Differences between the zolpidem group and the placebo group were assessed for the 4 primary sleep continuity variables, across 3 conditions, and for frequency of medication use. The 4 primary sleep continuity variables were sleep latency, number of awakenings, wake time after sleep onset, and total sleep time. Definitions of these variables are contained in Table 1.

The values for each group were biweekly average values for nights on which patients took a pill (+ Pill), nights on which patients did not take a pill (– Pill), and for all nights (All). The + Pill condition allowed for the assessment of the direct effects of treatment and the extent to which these improvements were stable with time. The – Pill condition allowed for the characterization of sleep continuity on nights when treatment was not utilized and there was no expectation that sleep would be

Figure 1. Progress of Patients With Primary Insomnia Through the Study



improved. This condition also allowed for the detection of insomnia rebound effects. The All condition allowed for the overall determination of whether patients using zolpidem on an intermittent basis (as compared with placebo) exhibited improved sleep continuity and the extent to which the effects were stable.

The treatment efficacy–related analyses were conducted as serial ANOVAs where 4 mixed-model 2 × 7 ANOVAs were run for each condition. The independent variables for each ANOVA were group (2: zolpidem vs. placebo) and time (7: baseline and 6 biweekly time increments). Baseline values were included in this analysis so the group-by-time effects could be detected, particularly for the initial response to medication use in weeks 1 and 2.

Follow-up analyses for group differences (point-to-point) were accomplished using Duncan t tests. Follow-up analyses to determine the stability of effects for the zolpidem group were accomplished using 1-way ANOVAs (1 × 6) for each of the 3 conditions. Baseline data were eliminated from these analyses so that the issue of effect stability could be assessed.

Analysis of medication use was conducted using a 2 × 6 ANOVA where point-to-point between-group comparisons were accomplished with Duncan t tests.

Finally, the IGR scale scores for each study visit were compared between the 2 groups with the Cochran-Mantel-Haenszel test for categorical variables.

The value set for statistical significance was $p < .05$. The value set for nonsignificance (NS) was $p > .11$. All analyses were conducted using 2-sided tests and intent-to-treat methods. Regarding the latter, in the event of missing data or right-censored data, the last observation was carried forward.

Table 2. Baseline Measures of Patients With Primary Insomnia

Variable	Placebo	Zolpidem	
Demographic			
Age, mean ± SD, y	40.4 ± 12.3	41.3 ± 13.2	NS
Female, %	81	61	.002
Euro-American, %	70	69	NS
Sleep			
Sleep latency	62.2 ± 48.6	66.5 ± 51.1	NS
Number of awakenings	2.23 ±	2.15 ±	NS
Wake after sleep onset	69.3 ± 51.2	71.5 ± 55.9	NS
Total sleep time	330.4 ± 64.3	329.5 ± 67.3	NS

Abbreviation: NS = nonsignificant = $p > .10$.

RESULTS

Patients

Of 322 patients screened for the study, 199 met eligibility criteria and were randomly assigned to treatment. Of the 123 patients not eligible for study, 78% failed to meet entry criteria or were noncompliant with the study procedures during the 6- to 14-day screening period.

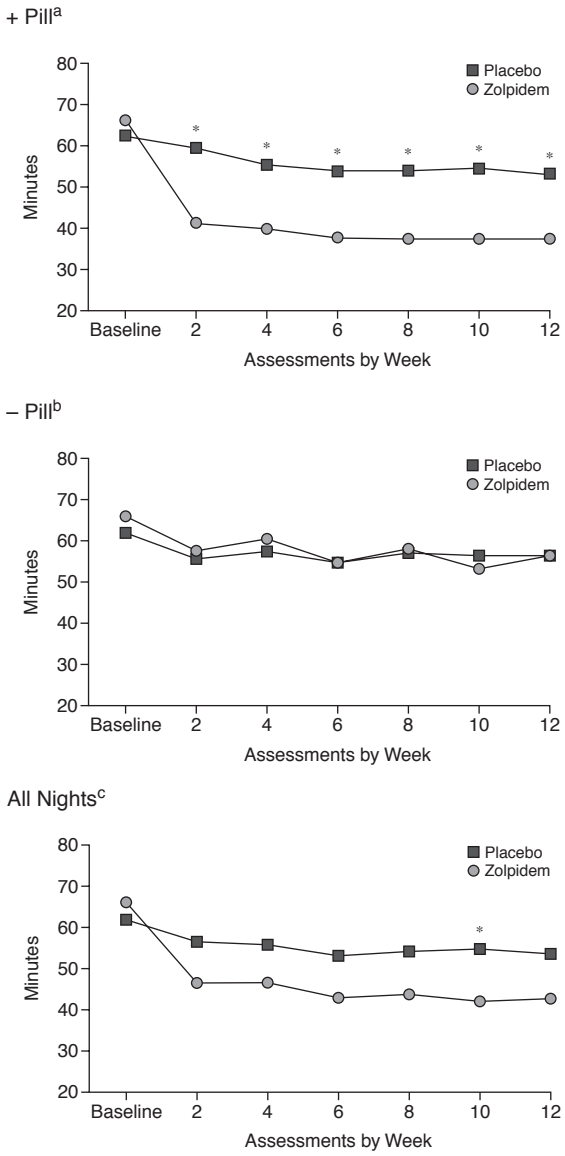
Of the remaining 199 patients, efficacy data were available on 192 patients. The mean ± SD age of the patients randomly assigned to treatment was 41.0 ± 12.8 years (range, 18–64), 71% of the sample was female, and about 70% of the patients were Euro-American.

Figure 1 shows a more complete characterization of the sample acquisition and attrition, and Table 2 presents a sleep-continuity profile for each of the 2 treatment groups at baseline. The groups did not significantly differ at baseline for sleep latency, wake after sleep onset, number of awakenings, or total sleep time.

Treatment Efficacy

Sleep latency (Figure 2). The 2 × 7 ANOVA for the + Pill condition detected significant effects for both main effects (group and time) and for the interaction. The main effect for group corresponds to the overall difference between the 2 group means. Not including the baseline (as these values are captured by the interaction term), the mean (SD) sleep latency for the zolpidem group was 38.4 (33.1) minutes, and the mean (SD) sleep latency for the placebo group was 55.1 (52.3) minutes. The main effect for time corresponds to the small linear trend, which is evident in both groups, for sleep latency to become shorter over the course of the study. Not including the change from baseline to weeks 1 and 2, this corresponds to approximately a 5-minute decrement from the beginning to the end of the study. The significant interaction for group-by-time suggests that the zolpidem group exhibited

Figure 2. Sleep Latency With Non-Nightly Administration of Zolpidem or Placebo for Primary Insomnia



[a]Group effect = 0.0204; time effect = 0.0001; group-by-time interaction = 0.0001.
[b]Group effect = NS; time effect = 0.0008; group-by-time interaction = NS.
[c]Group effect = 0.1451; time effect = 0.0018; group-by-time interaction = 0.0001.
*p ≤ .05 for placebo vs. zolpidem.
Abbreviation: NS = nonsignificant.

a significantly larger change from baseline to the first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for sleep latency at all time points except baseline.

The 2 × 7 ANOVA for the – Pill condition revealed only a significant effect for time. Including the change from baseline to weeks 1 and 2 (given the lack of an interaction), this corresponds to approximately a 9-minute decrement from the beginning to the end of the study. The follow-up serial Duncan t tests revealed that the groups did not significantly differ for sleep latency at any time across the study interval.

The 2 × 7 ANOVA for the All condition revealed significant effects for time and the group-by-time interaction. A modest trend for the group effect was also evident. As with the prior analyses, the main effect for time corresponds to the small linear trend for sleep latency to become shorter over the course of the study, and the group-by-time suggests that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. Duncan t tests revealed that the groups significantly differed for sleep latency only for weeks 9 and 10.

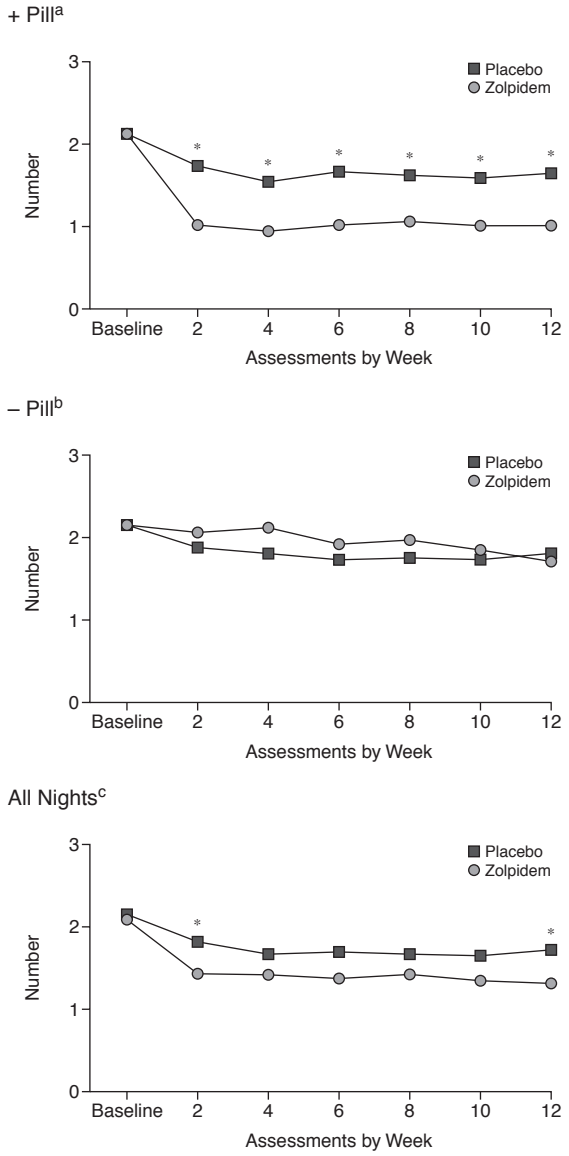
The 3 one-way ANOVAs for the zolpidem conditions (+ Pill, – Pill, All) indicated (as would be expected from the prior analyses) that the clinical gains were not reduced with time but instead showed a tendency for sleep latency to decrease over the study. This was significant for the – Pill and All conditions and tended to be significant for the + Pill condition.

Number of awakenings (Figure 3). The 2 × 7 ANOVA for the + Pill condition detected significant effects for both main effects (group and time) and for the interaction. Not including the baseline, the mean (SD) number of awakenings for the zolpidem group was 1.03 (0.92), and the mean (SD) number of awakenings for the placebo group was 1.64 (1.33). The main effect for time corresponds to a small linear trend for number of awakenings to diminish over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for number of awakenings at all time points except baseline.

The 2 × 7 ANOVA for the – Pill condition detected a significant effect only for time. As with the prior analysis, the main effect for time corresponds to a small linear trend for number of awakenings to diminish over the course of the study. As might be expected, the follow-up serial Duncan t tests did not show the treatment groups to be significantly different at any time point.

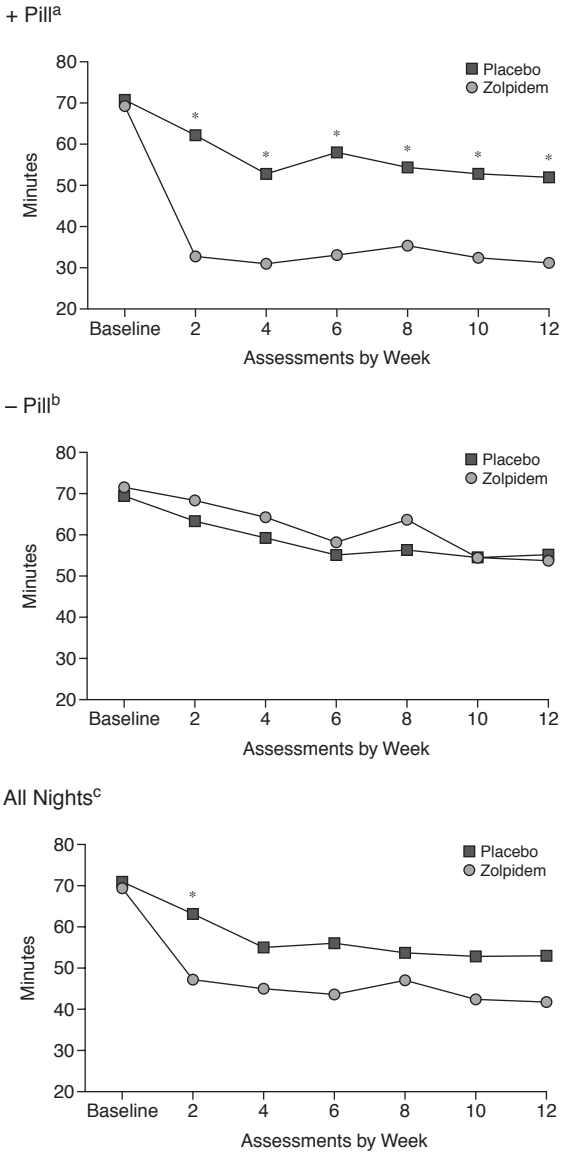
The 2 × 7 ANOVA for the All condition revealed significant effects for time and the group-by-time interaction. A trend for the group effect was also evident. Not including the baseline, the mean (SD) number of awakenings for the zolpidem group was 1.38 (1.00) and the mean (SD) number of awakenings for the placebo group was 1.69 (1.28). The main effect for time corresponds to a slight linear trend for number of awakenings to diminish over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group exhibited a significantly larger change from baseline to the

Figure 3. Number of Awakenings With Non-Nightly Administration of Zolpidem or Placebo for Primary Insomnia



[a]Group effect = 0.0015; time effect = 0.0001; group-by-time interaction = 0.001.
[b]Group effect = NS; time effect = 0.0003; group-by-time interaction = NS.
[c]Group effect = 0.1041; time effect = 0.0001; group-by-time interaction = 0.0126.
*p ≤ .05 for placebo vs. zolpidem.
Abbreviation: NS = nonsignificant.

Figure 4. Wake After Sleep Onset With Non-Nightly Administration of Zolpidem or Placebo for Primary Insomnia



[a]Group effect = 0.0034; time effect = 0.0001; group-by-time interaction = 0.0001.
[b]Group effect = NS; time effect = 0.0001; group-by-time interaction = NS.
[c]Group effect = 0.1481; time effect = 0.0001; group-by-time interaction = 0.009.
*p ≤ .05 for placebo vs. zolpidem.
Abbreviation: NS = nonsignificant.

first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for number of awakenings at weeks 1 and 2 and weeks 11 and 12.

The 3 one-way ANOVAs for the zolpidem conditions (+ Pill, – Pill, All) indicated that the clinical gains with respect to number of awakenings were stable from weeks 1 and 2 to weeks 11 and 12. Number of awakenings did not significantly increase or decrease for either the + Pill or the All conditions. Interestingly, the – Pill group did exhibit a tendency for number of awakenings to decrease over the study.

Wake after sleep onset (Figure 4). The 2 × 7 ANOVA for the + Pill condition detected significant effects for both main effects (group and time) and for the interaction. Not including the baseline, the mean (SD) wake after

sleep onset for the zolpidem group was 32.6 (43.5) minutes, and the mean (SD) wake after sleep onset for the placebo group was 55.4 (56.1) minutes. The main effect for time corresponds to the linear trend that, although evident in both groups, appeared primarily in the placebo group. In general, wake after sleep onset was reduced over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for wake after sleep onset at all time points except baseline.

The 2 × 7 ANOVA for the – Pill condition revealed only a significant effect for time. Including the change from baseline to weeks 1 and 2 (given the lack of an interaction), this corresponds to approximately a 15-minute decrement from the beginning to the end of the study. The follow-up serial Duncan t tests revealed that the groups did not significantly differ for wake after sleep onset at any time across the study interval.

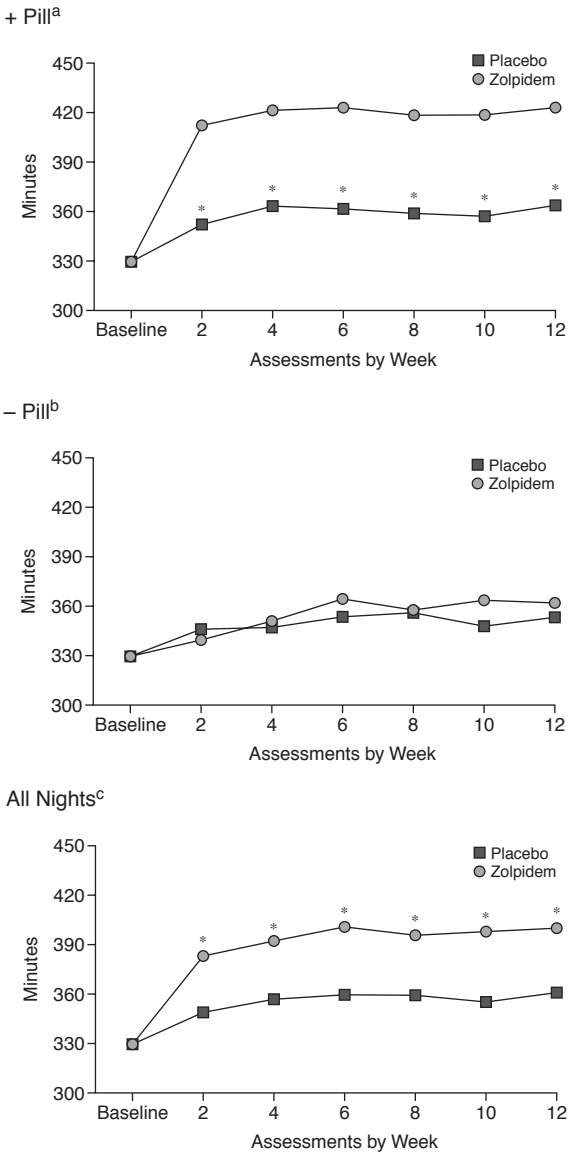
The 2 × 7 ANOVA for the All condition revealed significant effects for time and the group-by-time interaction. A trend for the group effect was also evident. As with the prior analyses, the main effect for time corresponds to a small linear trend for wake after sleep onset to become shorter over the course of the study, and the group-by-time suggests that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. Duncan t tests revealed that the groups significantly differed for wake after sleep onset only for weeks 1 and 2.

The 3 one-way ANOVAs for the zolpidem conditions (+ Pill, – Pill, All) indicated that the clinical gains with respect to wake after sleep onset were stable from weeks 1 and 2 to weeks 11 and 12. Neither + Pill nor All significantly increased or decreased over the study interval. Interestingly, the – Pill group did exhibit a tendency for wake after sleep onset to decrease over the study, and this temporal trend was significant.

Total sleep time (Figure 5). The 2 × 7 ANOVA for the + Pill condition detected significant effects for both main effects (group and time) and for the interaction. Not including the baseline, the mean (SD) total sleep time for the zolpidem group was 417 (64.4) minutes, and the mean (SD) total sleep time for the placebo group was 359.8 (77.1) minutes. The main effect for time corresponds to the linear trend, equally evident in both groups, which showed that total sleep time was increased over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for total sleep time at all time points except baseline.

The 2 × 7 ANOVA for the – Pill condition revealed a significant effect for time and a trend for group-by-time. The main effect for time corresponds to the small linear trend, equally evident in both groups, which showed that total sleep time was increased over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group tended to exhibit more change from baseline through weeks 3 and 4. The follow-up serial Duncan t tests did not show that the groups differed at any time point in particular.

Figure 5. Total Sleep Time With Non-Nightly Administration of Zolpidem or Placebo for Primary Insomnia



[a]Group effect = 0.0001; time effect = 0.0001; group-by-time interaction = 0.0001.
[b]Group effect = NS; time effect = 0.0001; group-by-time interaction = 0.0964.
[c]Group effect = 0.0001; time effect = 0.0001; group-by-time interaction = 0.0001.
*p ≤ .05 for placebo vs. zolpidem.
Abbreviation: NS = nonsignificant.

The 2 × 7 ANOVA for the All condition detected a significant effect for both main effects (group and time) and for the interaction. Not including the baseline, the mean (SD) total sleep time for the zolpidem group was 394.1 (60.1) minutes, and the mean (SD) total sleep time for the placebo group was 355.6 (69.6) minutes. The main effect for time corresponds to the linear trend, equally evident in both groups, which showed that total sleep time was increased over the course of the study. The significant interaction for group-by-time indicates that the zolpidem group exhibited a significantly larger change from baseline to the first 2 weeks of treatment. The follow-up serial Duncan t tests revealed that the groups significantly differed for total sleep time at all time points except baseline.

The 3 one-way ANOVAs for the zolpidem conditions (+ Pill, – Pill, All) indicated that the clinical gains were not reduced with time but instead showed a tendency for total sleep time to increase over the study. This effect was significant for the – Pill and the All conditions and tended to be true for the + Pill condition ($p < .07$).

Global Outcome Measures

Ratings of overall therapeutic effect from the IGR scale differed between groups at each study visit and for the endpoint analysis ($p < .001$ for all comparisons). For example, the mean (SE) IGR scale score at endpoint for the zolpidem group was 6.0 (0.12) versus 4.5 (0.14) for the placebo group.

Medication Use

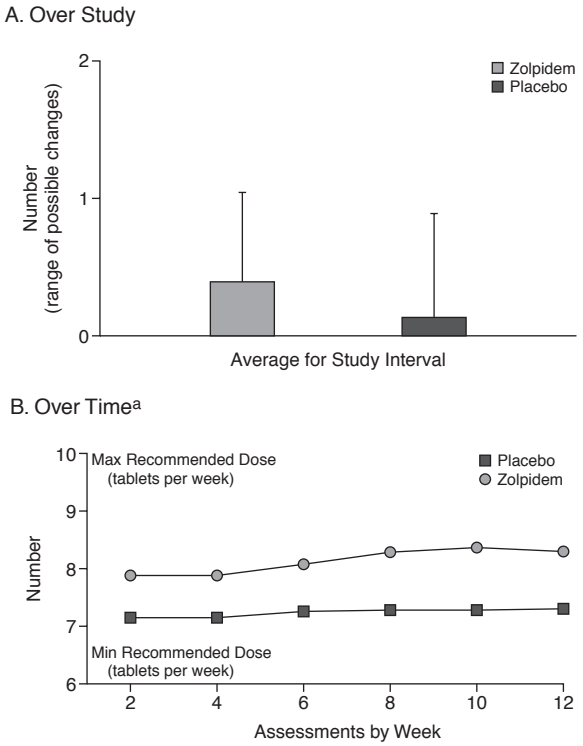
The mean number of doses and the number of doses used per 2-week increment across the 12-week study are represented in Figure 6.

The 2 × 6 ANOVA revealed main effects for group and time. The interaction term was not significant, nor was a trend evident. The main effect for group indicates that placebo group used, on average, less medication for the entire study period (about 1 pill fewer per 2-week interval). The main effect for time suggests that both groups exhibited a trend toward dose escalation. The failure to resolve group-by-time interaction suggests that the tendency to increase dose with time did not occur more for one group as opposed to the other. To ensure that the lack of finding was not due to the stabilizing effects of data carried forward (the last-observation-carried forward procedure), the analysis was rerun for only the subjects who completed the entire protocol. The interaction remained nonsignificant.

Safety Profile

Ten patients discontinued treatment due to adverse events: 7 in the zolpidem group (excessive sleepiness; headache, drowsiness, and dizziness; mood alteration and anxiousness; grogginess; hallucinations; headache; hallucinations) and 3 in the placebo group (cold symptoms, bad dreams, body rash). None of these adverse events was rated as severe. All 7 of these zolpidem patients discontinued within the first 4 weeks of treatment.

Figure 6. Mean Change in Dose With Non-Nightly Administration of Zolpidem or Placebo for Primary Insomnia



[a]Group effect = 0.0005; time effect = 0.0319; group-by-time interaction = NS.
Abbreviation: NS = nonsignificant.

DISCUSSION

This study evaluated efficacy and safety of zolpidem 10 mg in patients with primary insomnia over a 3-month period of intermittent dosing. It was found that zolpidem was significantly better than placebo in improving sleep latency, number of awakenings, wake time after sleep onset, and total sleep time. On average, patients receiving zolpidem (+ Pill) exhibited a 42% decrease in sleep latency, a 51% decrease in the number of awakenings, a 55% decrease in wake time after sleep onset, and a 27% increase in total sleep time. The IGR scale scores were consistent with the sleep continuity measures from the daily sleep diaries and indicated that the investigators judged zolpidem to be effective in improving the patients' sleep from a global perspective. Finally, the observed clinical gains obtained with zolpidem did not diminish over the course of the study and were not associated with escalation of pill taking frequency. There was also no evidence of rebound insomnia between nights of zolpidem intake and no-pill nights.

How Does Zolpidem Compare With Placebo Over a 3-Month Interval of Intermittent Dosing?

In agreement with the Walsh et al. study,[10] the present investigation confirmed that the intermittent use of zolpidem produced better sleep continuity profiles than placebo in patients with primary insomnia and that this effect was "stable" with time. The maintenance of clinical gains over 3 months suggests, in the absence of dose escalation, that habituation and tolerance do not occur with the chronic intermittent use of zolpidem. Whether this is ascribable to the intermittent dosing strategy remains an open question.

Does Long-Term (3 months) Use of Hypnotics Lead to Increased Pill Taking in Patients With Insomnia?

Within the constraints of the study design, there was no evidence that patients taking zolpidem increased the frequency of medication use as compared with patients taking placebo. This said, both groups exhibited a slight, but significant, tendency toward increased pill use over time. These results suggest that a central issue for the present study is not so much whether long-term use of hypnotics leads to increased pill taking, but rather what factors account for the conservative dosing strategy adopted by subjects in this study. That is, what factors account for the observation that subjects in this study voluntarily started the study using less medication than was allowed and voluntarily limited how much medication was used over the study interval? Specifically, patients were free to use up to 10 pills per 2-week interval; instead they chose to initiate treatment at a lower rate (e.g., the zolpidem group took an average of 8 pills during the first 2-week period). This "set point," in turn, means that the patients were free to increase their biweekly use by up to 2 pills; instead, they chose to increase their use by only a fraction of the amount allowed (e.g., the zolpidem group increased the number of pills taken by only 0.4 pills). Put differently, the patients in the zolpidem group voluntarily limited themselves to 80% of the available medication, and their increase in medication use represented only 20% of the possible increase.

Thus, the question is why initial frequency was low and why the frequency escalation was so limited in scope. One possibility is that the study design itself functioned as the rate limiter. That is, patients were not taking medication ad libitum, nor were they told to use medication completely "as needed." Instead they were given the instruction to take at least 3 and no more than 5 pills per week. Thus, it can be argued that the instructions themselves conferred the message to use the medication conservatively. This, in combination with regular monitoring, discouraged patients from "maxing out" initially and resulted in a pattern of use distinct from that which may occur with simple p.r.n. use. Given this perspective, an important topic for further research will be to determine what pill-taking strategies patients deploy when using hypnotics "as needed" in the long-term. Is there evidence of increased pill taking in this context? If so, is it comparable to that observed in the present study?

Finally, the conservative use pattern exhibited in the present study suggests that if non-nightly use is desired during long-term hypnotic therapy, a predictable pattern of use might result from modeling after the instructions of the present protocol. That is, the instruction to use at least 3 and no more than 5 pills per week may also produce, in regular practice, conservative self-medication patterns and the kind of sustained efficacy observed in this clinical trial.

Do Patients With Insomnia Experience Rebound Insomnia Between Nights of Zolpidem Intake Compared With Nights With No Pill Intake?

The data clearly indicate that patients do not experience a worsening of their insomnia symptoms on the nights that medication is not used. In fact, the average values for all the biweekly time points for the "– Pill" condition are below the initial measures of illness severity (baseline values). A very specific evaluation of potential rebound insomnia undertaken in a prior non–nightly-use study of zolpidem[10] also showed no evidence of undesirable discontinuation effects.

This finding may also be useful clinically. Patients may be encouraged to engage in intermittent dosing schedules given the knowledge that on nights that they do not take medication, their sleep is not likely to be worse than before the initiation of intermittent hypnotic treatment. Moreover, patients may be encouraged to know that their average sleep profiles (7 nights a week) are likely to show improvement while using this particular regimen.

Both findings, however, should be considered strictly within the limits of the present study. That is, the present study design was executed with the recommended non-elderly adult dose of zolpidem 10 mg. Whether the same results will occur with lower or higher doses,[11] in elderly subjects, or in patients with more complicated medical and psychiatric profiles remains to be determined.

Is the Relative Absence of Significant Effects for the "All" Condition a Reason for Concern?

No. The main finding for the present study is that the sleep profiles do not differ between the groups on the no-pill nights. This strongly supports the proposition that on no-pill nights, patients using zolpidem do not exhibit a "rebound insomnia." This said, the patients taking zolpidem did, as one would expect, sleep better when using the medication. As a result, the biweekly averages are reduced when the pill and no pill data are considered together. These reductions diminished the overall size and significance of the effects for sleep latency, wake after

sleep onset, and number of awakenings. Interestingly, the changes for total sleep time remained significant. This suggests that the overall gains remain even when one takes into account the data from nights when medication is not used.

FUTURE DIRECTIONS

The data from the present study suggest several questions for future research.

First, given the clear indication that intermittent dosing is associated with long-term efficacy, does the intermittent dosing strategy (as compared with a q.h.s. schedule) extend the efficacy half-life of zolpidem or like compounds?

Second, when allowed to use medication ad libitum, what dosing schedules do patients with insomnia most frequently use, and is the strategy conservative or liberal?

Third, is it possible that long-term, non-nightly therapy can yield sustained results after medication is discontinued?

Drug name: zolpidem (Ambien).

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