Sleep Latency Is Shortened During 4 Weeks of Treatment With Zaleplon, a Novel Nonbenzodiazepine Hypnotic

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Background: Zaleplon is a short-acting pyrazolopyrimidine hypnotic with a rapid onset of action. This multicenter study compared the efficacy and safety of 3 doses of zaleplon with those of placebo in outpatients with DSM-III-R insomnia. Zolpidem, 10 mg, was used as an active comparator.

Method: After a 7-night placebo (baseline) period, 615 adult patients were randomly assigned to receive, in double-blind fashion, 1 of 5 treatments (zaleplon, 5, 10, or 20 mg; zolpidem, 10 mg; or placebo) for 28 nights, followed by placebo treatment for 3 nights. Sleep latency, sleep maintenance, and sleep quality were determined from sleep questionnaires that patients completed each morning. The occurrence of rebound insomnia and withdrawal effects on discontinuation of treatment was also assessed. All levels of significance were $p \leq .05$.

Results: Median sleep latency was significantly lower with zaleplon, 10 and 20 mg, than with placebo during all 4 weeks of treatment and with zaleplon, 5 mg, for the first 3 weeks. Zaleplon, 20 mg, also significantly increased sleep duration compared with placebo in all but week 3 of the study. There was no evidence of rebound insomnia or withdrawal symptoms after discontinuation of 4 weeks of zaleplon treatment. Zolpidem, 10 mg, significantly decreased sleep latency, increased sleep duration, and improved sleep quality at most timepoints compared with placebo; however, after discontinuation of zolpidem treatment, the incidence of withdrawal symptoms was significantly greater than that with placebo and there was an indication of significant rebound insomnia for some patients in the zolpidem group compared with those in the placebo group. The frequency of adverse events in the active treatment groups did not differ significantly from that in the placebo group.

Conclusion: Zaleplon is effective in the treatment of insomnia. In addition, zaleplon appears to provide a favorable safety profile, as indicated by the absence of rebound insomnia and withdrawal symptoms once treatment was discontinued.

(J Clin Psychiatry 1999;60:536–544)

Received Jan. 12, 1999; accepted June 21, 1999. From the Centre de Recherche F. Seguin, Montréal, Québec, Canada (Dr. Elie); the Psychiatrische Universitätsklinik Göttingen, Göttingen, Germany (Dr. Rüther); the American-Cyanamid Co., Madrid, Spain (Dr. Farr, who is now with Rhône-Poulenc Rorer, SA, Madrid, Spain); and Wyeth-Ayerst, Paris, France (Drs. Emilien and Salinas).

A complete list of the members of the Zaleplon Clinical Study Group appears at the end of this article.

Supported by Wyeth-Ayerst Research, Radnor, Pa.

These data have been presented in part at the 14th Congress of the European Sleep Research Society, Madrid, Spain, Sept. 8–12, 1998, and the 11th Congress of the European College of Neuropsychopharmacology, Paris, France, Oct. 31–Nov. 4, 1998.

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Surveys of industrialized Western countries indicate that insomnia is a significant public health problem, affecting 16% to 40% of the general population.[1–5] Of those people who report difficulties in initiating or maintaining sleep, 9% to 25% indicate that insomnia is a chronic problem.[3,4] Chronic insomnia is often associated with difficulties in concentration, memory, and the ability to cope with minor irritations.[4] In addition, people with insomnia are known to be at increased risk for other health problems[1,5,6] and fatigue-related automobile accidents.[4,7] The total annual cost of insomnia has conservatively been estimated to be between 92.5 and 107.5 billion U.S. dollars.[5]

For the past 4 decades, treatment of insomnia has shifted away from the use of barbiturates and other central nervous system (CNS) depressants toward hypnotics of the benzodiazepine class. Although the clinical efficacy of the benzodiazepines as hypnotics has been well established,[3,4,8] the use of many of these compounds is associated with a number of side effects, such as rebound insomnia, withdrawal effects, and residual sedation.[2,3,8] In the past decade, there has been a trend toward the development of nonbenzodiazepine hypnotics that share some pharmacologic characteristics with benzodiazepines, but have improved safety profiles.

Zaleplon is a new pyrazolopyrimidine hypnotic with a rapid onset of action and a short terminal half-life of about 1 hour.[9] Although not a benzodiazepine in structure, zaleplon binds differentially to the benzodiazepine type 1

site on the γ-aminobutyric acid subtype A ($GABA_A$)/chloride-ion channel complex.[10] Pharmacologically, zaleplon shows sedative, anxiolytic, muscle relaxant, and anticonvulsive effects.[10,11] Recent studies in humans have shown that single doses of zaleplon up to 30 mg are well tolerated,[9] and 10-mg doses do not result in psychomotor or memory impairment or next-day residual effects.[9,12,13]

Zolpidem is currently the single most commonly prescribed hypnotic in the United States.[14] It is an imidazopyridine hypnotic that has been generally shown to be a safe and effective hypnotic.[15,16] Like zaleplon, zolpidem shows selective binding for the benzodiazepine type 1 site,[4,17,18] and thus was chosen as an active comparator for this study.

This multicenter study was designed to compare the efficacy and safety of zaleplon, 5, 10, or 20 mg, with those of placebo during 28 days of administration to outpatients with insomnia. The possible occurrence of withdrawal symptoms or rebound insomnia on discontinuation of treatment was also investigated.

METHOD

Patients

Patients were included in the study if they met the criteria for primary insomnia or insomnia associated with mild nonpsychotic psychiatric disorders based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R).[19] All investigators were trained in the use of DSM-III-R before the start of the study to ensure consistency in applying inclusion criteria for insomnia. Patients (age range, 18 to 65 years) were of any race and included men, nonpregnant women who were using a medically acceptable method of contraception, or postmenopausal women. During the month preceding study enrollment, patients must have experienced the following symptoms: a typical sleep latency of ≥ 30 minutes, daytime impairment due to sleep disturbance, and either a mean total sleep duration per night of ≤ 6.5 hours or prolonged (≥ 30 minutes) or frequent (3 or more per night) nocturnal awakenings with difficulty returning to sleep. Patients were excluded from the study if they experienced transient insomnia, situational insomnia, or insomnia associated with sleep-wake schedules (e.g., shift-work) or the use of alcohol or drugs. Also excluded were patients with a history or current manifestations of sleep apnea, restless legs syndrome, or a major psychiatric disorder and patients whose raw score on either the Zung Self-Rating Anxiety Scale[20] or the Zung Self-Rating Depression Scale[21] was > 49.

All patients provided written consent to participate in the study after the procedures and potential side effects had been explained to them. The protocol was approved by the ethics committee (Europe) or research ethics board (Canada) at each site, and the study was conducted according to the provisions of the Declaration of Helsinki and its amendments.

Study Design and Procedures

This was a randomized, double-blind, placebo-controlled, parallel-group, outpatient study that was conducted at 39 centers in Canada and Europe. The study was divided into 4 phases: a prestudy washout period (1 to 3 weeks), a single-blind placebo run-in period (7 nights), a double-blind treatment period (28 nights), and a single-blind placebo run-out period (3 nights).

Before entering the 7-night placebo run-in period, eligible patients discontinued use of all CNS-active medications and completed a prestudy washout period of 1 to 3 weeks, depending on the half-life of the medication. Patients who had not taken any CNS-active medication within 1 to 3 weeks of initial screening directly entered the placebo run-in period.

The aim of the 7-night placebo run-in phase was to confirm patient eligibility and obtain baseline data. Each night, patients received 2 placebo capsules in a single-blind fashion to be taken orally before bedtime. Patients were instructed to continue their usual intake of caffeine-containing beverages (at or below the protocol-specified limit of 5 drinks per day, none of which were to be consumed within 3 hours of dose administration) and to not eat heavy meals within 3 hours of dose administration. During this period, patients completed sleep questionnaires before taking study medication at night and in the morning after awakening.

Eligible patients were randomly assigned in a double-blind fashion to receive 1 of 5 treatment groups after completion of the placebo run-in period. According to group assignment, either zaleplon (5, 10, or 20 mg), zolpidem (10 mg), or placebo was provided weekly to be taken orally before bedtime for 28 nights. Following the same procedures as those described above, patients completed the presleep and postsleep questionnaires on each day of the double-blind treatment period. Patients returned to the trial site each week to receive study medication and to return their questionnaires; patient treatment diaries and postsleep questionnaires were checked weekly to ensure treatment compliance and accurate completion of the questionnaires.

During the posttreatment phase, patients took single-blind placebo for 3 nights (nights +1, +2, +3) and continued to complete the sleep questionnaires. This placebo run-out period was followed by 4 to 7 days of no treatment, after which patients returned to the center for final assessments.

Efficacy Assessments

Sleep variables obtained from daily postsleep questionnaires were averaged for each week of the double-blind treatment period. Subjective measurement of sleep

variables using postsleep questionnaires is necessary in a large multicenter study, and subjectively measured variables have a good overall correlation with objectively measured variables.[16,22] The mean baseline value for each sleep variable was calculated from data collected during the placebo run-in period. The primary efficacy variable was the patient's assessment of sleep latency. Secondary efficacy variables included the patient's assessment of sleep duration, number of awakenings, and sleep quality. Sleep quality was rated subjectively on an ordinal scale from 1 (excellent) to 7 (extremely poor).

Assessment of Rebound Insomnia and Withdrawal Effects

Rebound insomnia is defined as a temporary worsening from baseline values of symptoms of insomnia once treatment is discontinued. The possible occurrence of rebound insomnia, a discontinuation phenomenon associated with hypnotics, was assessed from sleep variable data derived from postsleep questionnaires completed after each night of the placebo run-out phase.

Withdrawal effects were evaluated using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ),[23] a listing of 20 symptoms that are commonly reported on abrupt discontinuation of short-acting benzodiazepines. This scale identifies withdrawal symptoms and quantifies the severity of the withdrawal syndrome associated with benzodiazepine use.[23] Each item on the checklist was scored as 0 = not present, 1 = present to a moderate degree, and 2 = present to a severe degree. The BWSQ was completed by patients the morning after the last night of the placebo run-in period (baseline), after 2 and 4 weeks of double-blind treatment, and after nights +1, +2, and +3 of the placebo run-out period. A patient was considered to have experienced a withdrawal effect if at least 3 new symptoms were checked on the BWSQ. A symptom reported during the placebo run-out period was considered new if it had not been reported during either the single-blind placebo run-in or the double-blind treatment periods.

Safety Assessments

Safety assessments were based on reports of adverse events and the results of physical examinations, laboratory determinations, vital signs, electrocardiograms (ECGs), and neurologic impairment assessments. Treatment-emergent adverse events were defined as events that either started after administration of double-blind treatment or worsened during treatment.

Statistical Analysis Methods

Efficacy analyses were based on sleep questionnaire information obtained during each week of double-blind treatment. Patients who had received at least one dose of double-blind medication and for whom sleep questionnaires during the placebo run-in and double-blind treatment periods were available for at least 1 night were included in the efficacy analyses. Patients for whom source documentation was lost or missing were excluded from the efficacy analyses.

Data from centers that enrolled a small number of patients were pooled according to geographic considerations before the blind was broken. For each sleep variable, values for each patient were averaged for each treatment week. Treatment effects were evaluated using an analysis of covariance (ANCOVA) with treatment and center grouping as factors and the mean baseline value as the covariate. Because data for sleep latency, sleep duration, and number of awakenings generally did not meet assumptions underlying the ANCOVA model (e.g., normal distribution, homogeneity of variance), the ANCOVA was performed after rank transformation of the data.

Comparisons between each dose of zaleplon and placebo were primary and were performed by using the Dunnett t distribution, which adjusts for the number of comparisons. The Jonckheere-Terpstra test was used to assess the presence of a trend with increasing zaleplon doses, both with and without placebo as the 0-mg dose. All other pairwise comparisons were performed by using F tests, which did not adjust for the number of comparisons.

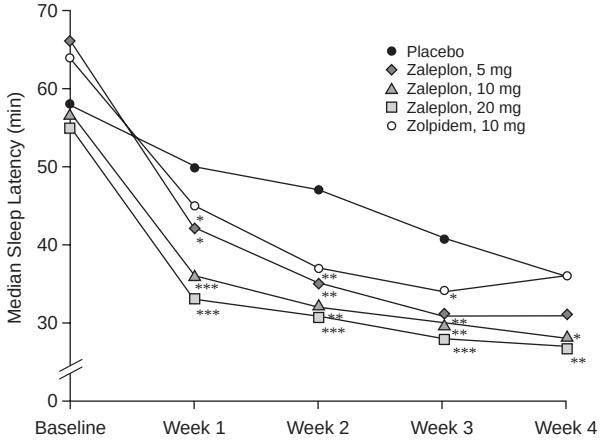
To further examine significant treatment differences on sleep quality scores, an additional analysis was performed to compare the numbers of patients that showed improvement in sleep quality. Improvement in sleep quality was determined for each patient by subtracting the median value for each week of treatment from the median baseline value. Because lower scale ratings indicated better sleep quality, a difference score > 0 categorized patients who showed improvement during therapy, and a difference score ≤ 0 indicated no improvement or a worsened sleep quality. An odds ratio and respective 95% confidence intervals compared the number of patients who showed improved sleep quality in each treatment group with the number who showed improvement in the placebo group. Odds ratio values that were greater than 1.0 signified an advantage of active treatment over placebo. Dose effects on improved sleep quality were assessed with a chi-square analysis.

Sleep latency, sleep duration, and number of awakenings were analyzed by ANCOVA on run-out nights as for the on-treatment nights. To further examine treatment differences for rebound insomnia, a secondary analysis was performed. Patients were categorized as showing rebound insomnia if sleep values during the placebo run-out period exceeded the worst symptoms at baseline (i.e., the maximum baseline value for sleep latency and number of awakenings and the minimum baseline value for sleep duration). For each efficacy variable, the number of patients who showed rebound insomnia on discontinuation of treatment in each active treatment group was compared

Table 1. Demographic Characteristics of Patients Included in the Efficacy Analyses

Characteristic	Placebo (N = 118)	Zaleplon 5 mg (N = 113)	Zaleplon 10 mg (N = 112)	Zaleplon 20 mg (N = 116)	Zolpidem 10 mg (N = 115)
Age, y, mean ± SD	42.1 ± 12.0	42.5 ± 12.9	42.6 ± 12.5	42.6 ± 12.2	44.3 ± 12.5
Sex, N (%)					
Female	74 (63)	66 (58)	72 (64)	81 (70)	77 (67)
Male	44 (37)	47 (42)	40 (36)	35 (30)	38 (33)
Ethnic origin, N (%)					
Black	1 (1)	…	…	…	…
Asian	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
White	116 (98)	112 (99)	111 (99)	115 (99)	114 (99)
Weight, kg, mean ± SD	68.3 ± 15.9	68.1 ± 14.3	67.4 ± 14.5	67.7 ± 11.4	68.7 ± 13.1
Zung self-rating scales					
Anxiety score, mean ± SD	36.4 ± 6.4	36.3 ± 6.7	36.6 ± 6.3	36.2 ± 6.7	36.1 ± 6.2
Depression score, mean ± SD	38.3 ± 6.2	38.7 ± 6.6	37.8 ± 7.0	38.2 ± 8.7	37.4 ± 6.5

Figure 1. Treatment Effects on Sleep Latency[a]



[a]Median sleep latency was significantly reduced during weeks 1 through 4 with zaleplon, 10 mg, and zaleplon, 20 mg, compared with placebo. Sleep latency was significantly reduced during weeks 1 through 3 with zaleplon, 5 mg, and zolpidem, 10 mg.
*p ≤ .05. **p ≤ .01. ***p ≤ .001. Zaleplon vs. placebo: Dunnett test; zolpidem vs. placebo: F test.

with the number in the placebo group. The incidence of rebound insomnia and withdrawal effects in each of the active treatment groups during the placebo run-out period was compared with that of the placebo group by using the Fisher exact probability test.

The Pearson chi-square test was used for between-group comparisons of the percentage of patients who withdrew from the study. The percentage of patients having common treatment-emergent adverse events was compared among treatment groups by using the Fisher exact probability test. Laboratory data and vital signs were analyzed by using an ANCOVA, with treatment as a factor and the baseline value as the covariate.

All tests were 2-tailed, and statistical significance for all analyses was determined by a probability level of ≤ .05.

RESULTS

Study Population

A total of 615 patients were randomly assigned to receive either zaleplon, 5 mg (N = 122); zaleplon, 10 mg (N = 121); zaleplon, 20 mg (N = 124); zolpidem, 10 mg (N = 122); or placebo (N = 126) under double-blind conditions; 1 patient each in the zaleplon 5- and 10-mg groups never took the medication. The remaining 613 patients were included in the safety analyses. Efficacy data from the 39 study centers were pooled into 26 groups that included 12 to 41 patients (mean = 24 patients). Thirty-nine patients were excluded from the efficacy analyses because of inadequate source documentation. Demographic characteristics of the 574 patients included in the efficacy analyses are presented in Table 1.

Efficacy Results

Figure 1 shows that median sleep latency was significantly reduced during week 1 with zaleplon, 5 mg (p ≤ .02); zaleplon, 10 mg (p ≤ .001); zaleplon, 20 mg (p ≤ .001); and zolpidem, 10 mg (p ≤ .05), compared with placebo. The Jonckheere-Terpstra test showed a significant dose-response trend with increasing doses of zaleplon for all 4 weeks in calculations with (p ≤ .01) or without (p ≤ .05) placebo as the 0-mg dose. Patients receiving zaleplon during week 1 experienced median sleep latencies that were 21 to 24 minutes shorter than at baseline, whereas the median sleep latency for patients receiving placebo was 8 minutes shorter than at baseline. The significant decrease in sleep latency observed during week 1 persisted through week 4 with zaleplon, 10 and 20 mg, and through week 3 with zaleplon, 5 mg, despite a progressive decrease in sleep latency observed with placebo during the study. Similar to the 5-mg dose of zaleplon, zolpidem, 10 mg, significantly reduced sleep latency during weeks 1 through 3.

Sleep maintenance was evaluated using patients' subjective assessments of sleep duration and number of awakenings (Table 2). Compared with placebo, zaleplon, 20 mg, significantly (p ≤ .05) increased sleep duration during all but week 3 of double-blind treatment. During week 1, patients in the zaleplon 20-mg group experienced a median sleep duration of 370 minutes compared with 351 minutes in the placebo group. By week 4, the median sleep duration had increased to 385 minutes for patients

Table 2. Sleep Maintenance and Sleep Quality

	Total Time Slept (min)		Number of Awakenings		Sleep Quality[a]	
Therapy by Week	N	Median	N	Median	N	Mean
Baseline						
Placebo	118	334	118	2	118	4.5
Zaleplon, 5 mg	113	313	112	2	113	4.6
Zaleplon, 10 mg	112	331	111	2	112	4.5
Zaleplon, 20 mg	116	328	114	2	116	4.5
Zolpidem, 10 mg	115	330	114	2	115	4.4
Week 1						
Placebo	118	351	112	2	118	4.1
Zaleplon, 5 mg	113	351	104	2	113	4.1
Zaleplon, 10 mg	112	370	101	2	112	3.9*
Zaleplon, 20 mg	116	370*	103	2	116	3.8**
Zolpidem, 10 mg	115	379###	100	2	115	3.7###
Week 2						
Placebo	115	359	113	2	115	3.9
Zaleplon, 5 mg	110	359	100	2	110	4.0
Zaleplon, 10 mg	109	368	100	2	110	3.9
Zaleplon, 20 mg	113	369*	101	2	113	3.8
Zolpidem, 10 mg	110	387###	99	2	110	3.6###
Week 3						
Placebo	113	365	103	2	113	3.9
Zaleplon, 5 mg	102	384	91	2	102	3.8
Zaleplon, 10 mg	103	371	95	2	104	3.8
Zaleplon, 20 mg	108	374	92	1	108	3.6
Zolpidem, 10 mg	105	385###	95	2	105	3.6#
Week 4						
Placebo	107	377	96	2	107	3.8
Zaleplon, 5 mg	102	372	87	2	102	3.8
Zaleplon, 10 mg	99	384	82	2	100	3.7
Zaleplon, 20 mg	103	385*	86	1	103	3.6
Zolpidem, 10 mg	100	400###	84	2	100	3.4##

[a]Scale: 1 = excellent, 2 = very good, 3 = good, 4 = fair, 5 = poor, 6 = very poor, 7 = extremely poor.
*p ≤ .05. **p ≤ .001. Different from placebo using Dunnett test.
#p ≤ .05. ##p ≤ .01. ###p ≤ .001. Different from placebo using F test.

taking zaleplon, 20 mg, compared with 377 minutes for patients taking placebo. Zaleplon, 10 mg, produced an increase in sleep duration (370 minutes during week 1 and 384 minutes during week 4) similar to that observed with zaleplon, 20 mg, although the comparison with placebo did not reach statistical significance. Zolpidem, 10 mg, significantly ($p \leq .001$) increased the median sleep duration during all weeks of double-blind treatment (379 minutes during week 1, 400 minutes during week 4). No significant differences in sleep duration were found between zaleplon, 5 mg, and placebo. No significant differences were observed in number of awakenings between the placebo and active treatment groups during the double-blind treatment period.

Mean scores for sleep quality were significantly better than with placebo during week 1 with zaleplon, 10 and 20 mg, and for all weeks with zolpidem, 10 mg (see Table 2). The number of patients reporting improved sleep quality relative to baseline was significantly greater in the zolpidem 10-mg group during weeks 1 and 4 (Table 3). There were no significant differences in numbers of patients with improved sleep quality with zaleplon compared with placebo.

Table 3. Patients Showing Improvement in Sleep Quality

	Patients[a]		p Value	Odds Ratio
Therapy by Week	N/Total	%	(χ^2)	(95% Confidence Interval)
Week 1				
Placebo	53/116	45.7		
Zaleplon, 5 mg	58/112	51.8	.357	1.28 (0.76 to 2.15)
Zaleplon, 10 mg	55/112	49.1	.605	1.15 (0.68 to 1.93)
Zaleplon, 20 mg	60/115	52.2	.324	1.30 (0.77 to 2.17)
Zolpidem, 10 mg	70/114	61.4	.017	1.89 (1.12 to 3.20)
Week 2				
Placebo	56/113	49.6		
Zaleplon, 5 mg	64/109	58.7	.171	1.45 (0.85 to 2.46)
Zaleplon, 10 mg	58/110	52.7	.636	1.14 (0.67 to 1.92)
Zaleplon, 20 mg	58/112	51.8	.738	1.09 (0.65 to 1.84)
Zolpidem, 10 mg	68/109	62.4	.054	1.69 (0.99 to 2.88)
Week 3				
Placebo	63/111	56.8		
Zaleplon, 5 mg	65/101	64.4	.259	1.38 (0.79 to 2.39)
Zaleplon, 10 mg	58/104	55.8	.884	0.96 (0.56 to 1.65)
Zaleplon, 20 mg	59/107	55.1	.810	0.94 (0.55 to 1.60)
Zolpidem, 10 mg	63/104	60.6	.570	1.17 (0.68 to 2.02)
Week 4				
Placebo	55/105	52.4		
Zaleplon, 5 mg	66/101	65.3	.059	1.71 (0.98 to 3.00)
Zaleplon, 10 mg	59/100	59.0	.340	1.31 (0.75 to 2.27)
Zaleplon, 20 mg	64/102	62.7	.132	1.53 (0.88 to 2.67)
Zolpidem, 10 mg	66/99	66.7	.038	1.82 (1.03 to 3.20)

[a]The number of patients in the sleep quality analysis in this table is not necessarily the same as that in Table 2 because both baseline and treatment week data for each patient were required to determine improvement in sleep quality.

Rebound Insomnia and Withdrawal Effects

Table 4 shows that values for sleep latency, sleep duration, and number of awakenings on the first night after discontinuation of 4 weeks of treatment were significantly different from placebo with zolpidem, 10 mg, but not with any dose of zaleplon. Group means and standard deviations are presented in the table in addition to the medians to better illustrate the treatment differences that were detected with the ANCOVA. The mean values with zolpidem on night +1 for sleep latency and number of awakenings were higher than at baseline; however, the mean value for sleep duration on that night was not lower than at baseline, which would suggest that the significant difference from placebo was due to the increased sleep duration with placebo over the duration of the study. There were no significant differences in values on nights +2 or +3 with any active treatment compared with placebo, with the exception that the number of awakenings on night +2 was significantly greater than with placebo (mean = 1.8) with 5 mg of zaleplon (mean = 2.5, $p \leq .03$) and 10 mg of zolpidem (mean = 2.4, $p \leq .03$).

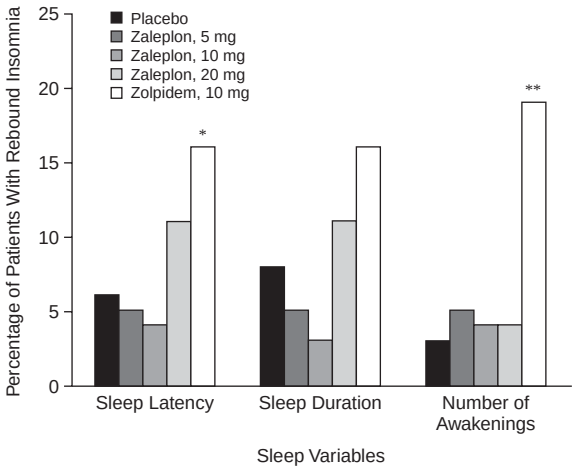
The results of the secondary analysis for rebound effects (Figure 2) revealed that the number of zaleplon-treated patients showing rebound insomnia for any of the 3 variables was not significantly different from that for placebo-treated patients on night +1. On night +2, there were significantly more patients ($p \leq .05$) showing rebound insomnia for the number of awakenings with

Table 4. Sleep Latency, Sleep Duration, and Number of Awakenings for Night +1

Characteristic	Placebo	Zaleplon 5 mg	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg
Sleep latency (min)					
Baseline	118	113	112	116	115
Mean ± SD	72.0 ± 47.0	78.0 ± 45.4	78.8 ± 55.1	71.28 ± 46.7	73.0 ± 39.0
Median	58	66	57	55	64
Night +1	102	99	94	97	92
Mean ± SD	49.6 ± 58.4	51.7 ± 56.57	57.6 ± 79.1	50.4 ± 77.7	91.6 ± 100.4
Median	30	30	30	30	55***
Sleep duration (min)					
Baseline	118	113	112	116	115
Mean ± SD	316.3 ± 75.1	305.4 ± 83.4	311.5 ± 86.8	308.5 ± 85.3	319.2 ± 70.2
Median	334	313	331	328	330
Night +1	104	99	95	99	94
Mean ± SD	353.0 ± 105.0	344.3 ± 100.3	349.6 ± 93.9	339.2 ± 120.9	324.7 ± 133.0
Median	360	360	360	360	360*
Number of awakenings					
Baseline	118	112	111	114	114
Mean ± SD	2.5 ± 1.4	2.6 ± 1.5	2.5 ± 2.0	2.4 ± 1.7	2.5 ± 1.3
Median	2	2	2	2	2
Night +1	70	61	57	67	63
Mean ± SD	1.8 ± 1.0	2.3 ± 1.5	2.0 ± 1.4	1.8 ± 1.1	2.6 ± 1.7
Median	1	2	2	1	2**

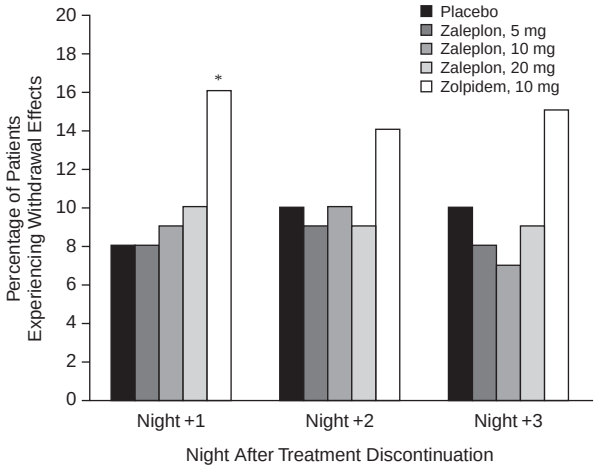
*p ≤ .05. **p ≤ .01. ***p ≤ .001. Different from placebo using F test.

Figure 2. Incidence of Rebound Insomnia on Night +1[a]



[a]The number of patients showing increased sleep latency and number of awakenings relative to their baseline results on run-out night +1 was significantly greater for the zolpidem 10-mg group than for the placebo group. The incidence of rebound insomnia with any dose of zaleplon was not significantly different from placebo for any variable. *p ≤ .05. **p ≤ .01. Fisher exact probability test.

Figure 3. Incidence of 3 or More New Withdrawal Symptoms After Discontinuation of Treatment[a]



[a]On the first night after treatment was discontinued, the incidence of withdrawal effects (defined as 3 or more new symptoms) was significantly higher in the zolpidem 10-mg group than in the placebo group. No significant differences in the incidence of withdrawal symptoms were detected between the zaleplon dose groups and the placebo group on any night of the placebo run-out period. *p ≤ .05. Fisher exact probability test.

zaleplon, 10 and 20 mg, than with placebo, and on night +3, there were significantly fewer patients (p ≤ .05) showing rebound for the number of awakenings with zaleplon, 20 mg. There was no significant difference from placebo in the incidence of rebound insomnia observed for sleep duration with zolpidem, 10 mg, on night +1. In contrast, on the first night after treatment was discontinued, significantly more patients who had received zolpidem, 10 mg, (16%) experienced longer sleep latencies relative to baseline than those who had received placebo (6%) and significantly more patients in the zolpidem 10-mg group (19%) experienced an increase from baseline in the number of awakenings compared with those in the placebo group (3%).

Significant withdrawal effects were also noted on discontinuation of treatment with 10 mg of zolpidem. As displayed in Figure 3, significantly more patients in the zol-

Table 5. Common[a] Treatment-Emergent Adverse Events Reported in Any Active Treatment Group at Twice the Rate or More of That Reported in the Placebo Group

			Zaleplon						Zolpidem	
	Placebo (N = 126)		5 mg (N = 121)		10 mg (N = 120)		20 mg (N = 124)		10 mg (N = 122)	
Body System	N	%	N	%	N	%	N	%	N	%
Body as a whole										
Abdominal pain	4	3	1	< 1	11	9	7	6	7	6
Asthenia	4	3	6	5	10	8	6	5	6	5
Nervous system										
Amnesia	3	2	1	< 1	5	4	5	4	6	5
Paresthesia	3	2	1	< 1	9	8	6	5	4	3
Somnolence	1	< 1	3	2	6	5	3	2	6	5
Respiratory system										
Pharyngitis	4	3	5	4	2	2	2	2	9	7
Special senses										
Taste perversion	4	3	3	2	7	6	5	4	1	< 1

[a]Reported by ≥ 5% of the patients in any treatment group.

pidem 10-mg group reported withdrawal effects (3 or more new symptoms) on the first night after treatment was discontinued than those in the placebo group. Among the most common withdrawal symptoms seen on discontinuation of zolpidem were depressed mood, pain in muscles, peculiar taste, loss of memory, and olfactory sensitivity. Although there was a similar incidence of withdrawal effects with zolpidem on nights +2 and +3, comparisons with the placebo group were not statistically significant after night +1. No significant differences were detected in the incidence of withdrawal symptoms between the zaleplon dose groups and the placebo group on any night of the placebo run-out period.

Safety Results

Treatment-emergent adverse events were reported by 80 patients (63%) in the placebo group, 71 (59%) in the zaleplon 5-mg treatment group, 87 patients (73%) in the zaleplon 10-mg treatment group, 76 (61%) in the zaleplon 20-mg group, and 78 patients (64%) in the zolpidem 10-mg group. Table 5 shows the incidence of the most common treatment-emergent adverse events (at least 5% in any group) that were reported in at least one of the active treatment groups at twice the rate of the placebo group. The most common treatment-emergent adverse event was headache, which was reported by 23% of patients in the placebo group, 15% in the zaleplon 5-mg group, 18% in the zaleplon 10-mg group, 31% in the zaleplon 20-mg group, and 25% in the zolpidem 10-mg group. There were no significant differences in the frequency of treatment-emergent adverse events between any of the active treatment groups and the placebo group. Central nervous system–related treatment-emergent adverse events that have been associated with hypnotics, when present, were brief and resolved without sequelae.

Adverse events were cause for discontinuation for 2 patients (2%) in the placebo group, 2 patients (2%) in the zaleplon 5-mg group, 7 patients (6%) in the zaleplon 10-mg group, 2 patients (2%) in the zaleplon 20-mg group, and 7 patients (6%) in the zolpidem 10-mg group.

There were no clinically important differences between the active treatment groups and placebo in the mean change from baseline for laboratory values or vital signs. Three patients experienced clinically important changes from baseline in ECGs; however, no dose-related trends were observed.

DISCUSSION

Zaleplon offers a new therapeutic approach in the treatment of insomnia. The results of this outpatient study demonstrated that zaleplon, 10 and 20 mg, effectively reduced sleep latency for 4 weeks of treatment. The 5-mg dose of zaleplon significantly decreased sleep latency for the first 3 weeks. There were indications of better sleep quality with zaleplon, 10 and 20 mg, and better sleep duration with zaleplon, 20 mg, when compared with placebo. The incidence of treatment-emergent adverse events was not significantly different with zaleplon than with placebo, and discontinuation of zaleplon treatment was not associated with significant indications of rebound insomnia or withdrawal symptoms.

In recent years, there has been a trend away from development of long-acting benzodiazepines, which are likely to produce hangover and other next-day residual effects,[2,3,8] toward short-acting benzodiazepines. There has also been a trend toward development of nonbenzodiazepine hypnotics that bind selectively to $GABA_A$/benzodiazepine receptor subtypes[24,25] in an effort to discover effective hypnotics that do not have side effects such as rebound insomnia and withdrawal effects, which are more commonly associated with short-acting hypnotics.[2,3,8] The nonbenzodiazepine hypnotics zaleplon and zolpidem are both rapidly absorbed and have short onsets of action. Zaleplon has a time to peak plasma concentration and an apparent terminal-phase elimination half-life of approximately 1 hour.[9] Zolpidem exhibits a somewhat longer time to peak concentration (approximately 2 hours) and a slower terminal-phase elimination half-life (1.5 to 3.2 hours).[17] Even differences as small as these may result in different efficacy and safety profiles.

In the present study, both zaleplon and zolpidem significantly decreased sleep latency compared with placebo, which is consistent with their rapid onsets of action. Sleep duration was significantly lengthened with zolpidem, 10 mg, consistent with its longer half-life. Nevertheless, total time slept with zaleplon, 10 and 20 mg, was at least 6 hours for all 4 weeks of treatment, indicating that the short half-life of zaleplon did not result in early morning awakening.

Rebound insomnia and withdrawal effects generally occur more often after abrupt discontinuation of short- to

intermediate-acting hypnotics.[26] Rebound insomnia refers to the worsening of the symptoms of insomnia beyond baseline levels, and it has been reported after relatively short treatment periods.[26,27] The withdrawal symptoms measured in this study are those that are typically observed after discontinuation of long-term treatment with benzodiazepines, such as dizziness, muscle pain, and sensitivity to noise.[23] Abrupt discontinuation after 4 weeks of zaleplon treatment did not result in significant evidence of rebound insomnia or withdrawal phenomena compared with placebo, except variably for number of awakenings on nights +2 or +3. It is unlikely that rebound effects on nights +2 or +3 that were not seen on night +1 have any clinical significance for a compound with a 1-hour half-life.

There were significant differences between the zolpidem 10-mg group and the placebo group for all 3 efficacy variables on the first night after treatment discontinuation, although sleep duration on that night was not shorter than at baseline. Significantly more patients in the zolpidem group than those in the placebo group reported longer sleep latencies and more awakenings relative to baseline after discontinuation of treatment, which suggests that rebound effects may present problems for some patients. There was also a significantly higher incidence of withdrawal effects for patients in the zolpidem group on the first night after treatment discontinuation. However, the evidence of rebound insomnia and withdrawal effects on the first night after treatment discontinuation would probably constitute only a minor difficulty for the patients that experience those effects.

There was no evidence of pharmacologic tolerance to the hypnotic effects of any of the active treatments in this study, as shown by the maintenance of shorter sleep latencies and longer sleep durations relative to baseline throughout 4 weeks of treatment.

In summary, zaleplon's rapid hypnotic action is well suited for people who have trouble falling asleep. Its favorable safety profile includes a lack of pharmacologic tolerance during 4 weeks of treatment and no withdrawal effects or rebound insomnia after discontinuation of treatment.

Drug names: zaleplon (Sonata), zolpidem (Ambien).

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