Zolpidem for Persistent Insomnia in SSRI-Treated Depressed Patients

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Background: Depressed individuals effectively treated with selective serotonin reuptake inhibitors (SSRIs) often report persistent insomnia and require adjunctive sleep-promoting therapy.

Method: Men (N = 40) and women (N = 150) with a mean age of 41.6 years who had persistent insomnia in the presence of effective and stable treatment (at least 2 weeks) with fluoxetine (≤ 40 mg/day), sertraline (≤ 100 mg/day), or paroxetine (≤ 40 mg/day) for DSM-IV major depressive disorder, dysthymic disorder, or minor depressive disorder of mild-to-moderate severity (and score of ≤ 2 on item 3 of the Hamilton Rating Scale for Depression [HAM-D]) participated in this randomized, double-blind, parallel-group study. At study entry, patients were required to score ≤ 12 on the HAM-D. During a 1-week single-blind placebo period, patients had to report on at least 3 nights a latency of ≥ 30 minutes or a sleep time of < 6.5 hours and clinically significant daytime impairment. Patients received either placebo (N = 96) or zolpidem, 10 mg (N = 94) nightly, for 4 weeks and single-blind placebo for 1 week thereafter. Sleep was measured with daily questionnaires and during weekly physician visits.

Results: Compared with placebo, zolpidem was associated with improved sleep: longer sleep times (weeks 1 through 4, $p < .05$), greater sleep quality (weeks 1 through 4, $p < .01$), and reduced number of awakenings (weeks 1, 2, and 4; $p < .05$), together with feeling significantly more refreshed, less sleepy, and more able to concentrate. After placebo substitution, the zolpidem group showed significant worsening relative to pretreatment sleep on the first posttreatment night in total sleep time and sleep quality, reverted to pretreatment insomnia levels on the other hypnotic efficacy measures, or maintained improvement (fewer number of awakenings). There was no evidence of dependence or withdrawal from zolpidem (DSM-IV criteria). Incidence rates of adverse events were similar in both treatment groups (74% and 83% for placebo and zolpidem, respectively), but 7 zolpidem patients discontinued compared with 2 placebo patients.

Conclusion: In this defined patient population, zolpidem, 10 mg, was effectively and safely coadministered with an SSRI, resulting in improved self-rated sleep, daytime functioning, and well-being.

(J Clin Psychiatry 1999;60:668–676)

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Supported in part by Lorex Pharmaceuticals, Skokie, Ill.

Participation in the conduct of this study by the following sites is gratefully acknowledged: Jose DeLaGandara, M.D., Memory Disorder Center, Pompano Beach, Fla.; Maurizio Fava, M.D., Clinical Psychopharmacology Unit-Massachusetts General Hospital, Boston, Mass.; Harvey Moldofsky, M.D., The Toronto Hospital, Western Division, Toronto, Ontario, Canada; G. Vernon Pegram, Ph.D., Clinical Research Office, Birmingham, Ala.; Ward T. Smith, M.D., Portland, Ore.; and J. Catesby Ware, Ph.D., Sleep Disorders Center, Eastern Virginia Medical School, Sentara Norfolk General Hospital, Norfolk, Va.

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Sleep disturbances are common among patients with depressive disorders and can contribute to the physiologic, psychological, social, emotional, and vocational impairment of the patient.[1] For many depressed patients, insomnia remits or improves on resolution of other depressive symptoms.[2] For others, sleep disturbance persists despite otherwise successful treatment of the depressive symptomatology.[3]

The selective serotonin reuptake inhibitors (SSRIs), currently the most widely used class of antidepressants,[4] have been characterized as "activating" antidepressants.[5,6] Sleep disturbances that are different from those typical of depression and that persist after resolution of depressive symptoms have been considered a reflection of these activating effects.[1] Persistent insomnia in depression could reflect a treatment-resistant symptom or an inadequate antidepressant response, but there is evidence in SSRI-treated patients that persistent insomnia may be induced by the SSRI itself.[5–9] Sedating medications such as triazolam,[10] H_1 antihistamines,[11–13] and trazodone[14] have been coadministered with SSRIs to provide symptomatic relief of insomnia.

Zolpidem, the most commonly used hypnotic, has not been studied to date for this clinical situation. Based on

demonstrated efficacy[15–18] and the relative lack of residual sedation with zolpidem,[19] as well as minimal interactions between zolpidem and SSRI metabolism via cytochrome P450 (CYP450),[20–22] some advantages for combined SSRI-zolpidem therapy may exist compared with other sedating drugs. The effective doses for symptomatic treatment of insomnia are unknown for H_1 antihistamines. Orthostatic hypotension and priapism are potential serious side effects with trazodone.[23]

The present study was designed to evaluate the hypnotic efficacy, impact on daytime function and quality of life, and safety of zolpidem, 10 mg, in the management of persistent insomnia in depressed patients treated with fluoxetine, sertraline, or paroxetine.

METHOD

This randomized, parallel-group, 6-week study was conducted at 14 sites in the United States and Canada. The study consisted of a 1-week, single-blind placebo screening/baseline week; 4 weeks of double-blind treatment with zolpidem, 10 mg, or placebo at bedtime; and a 1-week, single-blind placebo follow-up. Throughout the study, each patient was maintained on a constant therapeutic SSRI regimen. The study was carried out in accordance with the tenets of the Declaration of Helsinki.

Patients and Screening

Men and women, 18 to 66 years of age, experiencing insomnia and currently treated for a depressive disorder with fluoxetine, ≤ 40 mg/day; sertraline, ≤ 100 mg/day; or paroxetine, ≤ 40 mg/day, were recruited through psychiatric practices and through media advertisements. Preliminary screening was conducted by telephone interview. Those individuals appearing appropriate for enrollment were scheduled for a screening office visit, which included obtaining written informed consent; medical, sleep, and psychiatric histories; physical examination; clinical laboratory assessments; urine drug screen; serum pregnancy test; and completion of the Hamilton Rating Scale for Depression (HAM-D).

All patients were required to meet DSM-IV criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder based on their psychiatrist's diagnosis or the interview with a study psychiatrist. For each diagnosis, symptoms must have been of mild or moderate severity, according to DSM-IV, and been present a minimum of 4 consecutive weeks. Patients with a HAM-D score of > 12, a history of suicide attempt or contemplation, or psychotropic medication treatment other than the SSRI or who were pregnant, lactating, or sexually active without approved contraception were also excluded. Provided there was a clinical response to the SSRI and the patient had been treated for at least 2 weeks with a stable dose of SSRI, patients were also required to report persistent insomnia as characterized by a typical sleep latency of > 30 minutes, a typical nightly total sleep time of < 6.5 hours, or > 2 awakenings on a typical night and clinically significant daytime impairment. Patients with histories suggestive of insomnia secondary to any condition other than the depressive disorder or SSRI therapy (e.g., shift work, substance abuse, anxiety disorder), with histories consistent with a diagnosis of restless legs or periodic limb movement syndromes, or with a medical condition likely to influence sleep were excluded. Thereafter, patients participated in a 1-week single-blind, nighttime placebo screening and baseline period, during which time they completed evening and morning questionnaires[17] to ensure insomnia eligibility criteria. Patients with complaints of insomnia causing clinically significant distress and a reported total sleep time of less than 6.5 hours or reported sleep latency of at least 30 minutes for at least 3 of the previous 7 nights/days were randomly assigned to either zolpidem, 10 mg, or placebo.

A total of 273 patients underwent in-office screening, and 194 were randomly assigned. Of those, 192 received either the study drug or placebo, and 190 provided some data for analysis. Thirty-seven patients discontinued during double-blind treatment (16 placebo, 21 zolpidem). The most common reasons were protocol violations (5 placebo, 6 zolpidem), adverse events (2 placebo, 7 zolpidem), lack of effect (3 placebo, 2 zolpidem), and lost to follow-up (4 each group). During the single-blind placebo follow-up week, 3 patients (all placebo group) discontinued. Thus, 154 completed the study. Adverse events leading to premature discontinuation included one placebo patient who attempted suicide and another placebo patient who fractured a rib. The adverse events leading to premature discontinuation are presented in Table 1.

Table 1. Adverse Events Leading to Premature Discontinuation[a]

	Placebo (N = 97)		Zolpidem (N = 95)	
Adverse Event	N	%	N	%
Influenza-like symptoms	0	0.0	1	1.1
Dizziness	0	0.0	2	2.1
Headache	0	0.0	1	1.1
Somnolence	0	0.0	2	2.1
Bone disorder	1	1.0	0	0.0
Agitation	0	0.0	1	1.1
Anorexia	0	0.0	1	1.1
Impaired concentration	0	0.0	2	2.1
Depression	0	0.0	1	1.1
Depression aggravated	0	0.0	1	1.1
Manic reaction	0	0.0	1	1.1
Suicide attempt	1	1.0	0	0.0

[a]Two placebo-treated (2.1%) and 7 zolpidem-treated patients (7.4%) discontinued prematurely because of adverse events.

Procedures

Four weeks of double-blind treatment with either placebo or zolpidem, 10 mg, followed random assignment.

One week of single-blind placebo administration followed for both groups. Evening and morning sleep questionnaires were completed daily throughout this 5-week period (as well as during the screening/baseline week). The following subjective sleep variables were derived from the morning questionnaire: sleep latency, ease of falling asleep, total sleep time, number of awakenings, wake time after sleep onset, and quality of sleep. Patients also rated ability to concentrate (1 = excellent, 2 = good, 3 = fair, 4 = poor), morning sleepiness (Visual Analog Scale [VAS] 0 mm = very sleepy, 100 mm = not at all sleepy), and refreshed feeling (VAS 0 mm = very refreshed, 100 mm = not at all refreshed). On the nighttime questionnaire, patients rated their difficulty doing activities during the prior 24 hours due to sleep problems: 1 = not at all, 2 = a little bit, 3 = some, 4 = quite a bit, 5 = could not do daily work.

A HAM-D was administered at each visit. Total score, an insomnia score (the mean of the 3 insomnia items), and a non-insomnia score (total score – insomnia score) were calculated. Patients were seen each week at the study site to complete a Global Impression of Therapy form, a series of VAS (ratings of daytime alertness, ability to function, mood, ability to concentrate, and creative thinking), and sleep-related Quality-of-Life Questionnaire.[24] At each visit, the investigator completed a Clinical Global Impressions (CGI) form evaluating both insomnia and depression. Severity of illness (severity of symptoms: 1 = not at all, 2 = very mild, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, 7 = extremely severe) and therapeutic effect (1 = marked worsening, 2 = moderate worsening, 3 = minimal worsening, 4 = unchanged, 5 = minimal improvement, 6 = moderate improvement, 7 = marked improvement) were scored by the investigator. Overall quality of life was evaluated by the Medical Outcome Study Short Form (SF-36),[25] which was administered at the beginning of week 1 and week 4 of double-blind treatment.

Throughout the study, adverse events were evaluated by the investigator in terms of incidence, duration, severity, and possible relationship to the study drug.

Data Analysis

Categorical baseline characteristics were compared between treatment groups with the Pearson chi-square test (except when more than 20% of expected cell counts were 5 or less, in which case the Fisher exact test was used.) For continuous variables, a 1-way analysis of variance (ANOVA) utilizing treatment group as its only term was used.

Change scores (from baseline) were derived for sleep quantity and quality measures for all patients from their daily questionnaires. Weekly means were calculated, except during the single-blind posttreatment period, where the initial 3 posttreatment nights and days were also evaluated individually. Continuous variables were analyzed with ANOVA, with terms for treatment, investigator, and their interaction. Because not all patients contributed data for all study weeks, an ANOVA was performed for each week rather than rely upon deduced data. Ordinal categorical variables from the sleep-related Quality-of-Life Questionnaire and the patient and investigator CGI forms (with the exception of "medication strength") were treated as continuous and analyzed using the Wilcoxon rank sum test. Categorical, nonordinal outcome variables were analyzed using the Cochran-Mantel-Haenszel test controlling for the investigator.

Based on the diagnostic criteria for sedative, hypnotic, or anxiolytic withdrawal (DSM-IV, 292.0), all adverse events that occurred during the posttreatment, single-blind placebo substitution week were reviewed. Any patient who had 1 or 2 of the symptoms listed in criterion B ([1] autonomic hyperactivity (e.g., sweating or pulse rate greater than 100); [2] increased hand tremor; [3] insomnia; [4] nausea or vomiting; [5] transient visual, tactile, or auditory hallucinations or illusions; [6] psychomotor agitation; [7] anxiety; [8] grand mal seizures[26(p266)]), not including insomnia, was then evaluated for rebound insomnia by comparing hypnotic measures at baseline with posttreatment values.

Table 2. Patient Demographic Characteristics at Study Entry

Characteristic	Placebo (N = 96)	Zolpidem (N = 94)	p Value
Sex, N (%)			.705
Female	75 (78.1)	75 (79.8)	
Male	21 (21.9)	19 (20.2)	
Race, N (%)			.891
White	86 (89.6)	84 (89.4)	
Other	10 (10.4)	10 (10.6)	
Age, y			.959
Mean (SE)	41.6 (1.0)	41.6 (1.2)	
Range	21–64	18–66	
Weight, kg			.738
Mean (SE)	79.9 (2.0)	79.4 (2.0)	
Range	49–173	50–134	
SSRI treatment, N (%)			.772
Fluoxetine	35 (36.5)	39 (41.5)	
Paroxetine	26 (27.1)	24 (25.5)	
Sertraline	35 (36.5)	31 (33.0)	
SSRI therapy duration, d			.441
Median	204	176	
Mean (SE)	434 (53)	362 (44)	
Range	19–2602	22–1962	

RESULTS

A total of 273 patients were enrolled, 194 of whom were randomized. Only 190 actually provided some data following randomization. Therefore, all results are for 190 patients, 96 in the placebo group and 94 in the zolpidem group. Demographic characteristics and baseline severity of insomnia of the patient sample appear in Tables 2 and 3, respectively. No statistical differences were found in demographic or insomnia-related characteristics between the 2 treatment groups.

Table 3. Severity of Insomnia at Baseline Based on Morning Questionnaire and Hamilton Rating Scale for Depression (HAM-D) Scores[a]

	Placebo (N = 96)		Zolpidem (N = 94)		
Outcome	Mean	SEM	Mean	SEM	p Value
Sleep measure					
Sleep latency, min	63.0	5.2	61.3	4.8	.708
Total sleep time, min	377.0	7.3	376.5	7.0	.824
No. of awakenings	2.09	0.10	2.36	0.16	.313
WASO, min	53.3	4.4	65.4	6.1	.500
Sleep quality[b]	2.77	0.05	2.83	0.06	.569
HAM-D					
HAM-D total	8.09	0.29	8.19	0.31	.832
HAM-D sleep items	3.72	0.12	3.66	0.11	.539
Next-morning measures					
Ability to concentrate	2.65	0.05	2.67	0.06	.851
Morning sleepiness[c]	41.3	1.5	40.9	1.8	.885
Refreshed feeling[d]	56.8	1.5	58.2	1.8	.582

[a]Abbreviation: WASO = Wake time after sleep onset.
[b]1 = excellent, 2 = good, 3 = fair, 4 = poor.
[c]0 = very sleepy, 100 = not at all sleepy.
[d]0 = very refreshed, 100 = not at all refreshed.

Table 4. Effect of Zolpidem on Subjective Sleep Latency (mean ± SEM, minutes) During Double-Blind Treatment

	Placebo			Zolpidem			
Time	N	Mean	SEM	N	Mean	SEM	p Value
Baseline	96	63.0	5.2	94	61.3	4.8	.708
Week 1	96	48.1	3.7	94	40.7	5.4	.049
Week 2	86	43.5	3.7	84	39.2	5.2	.110
Week 3	84	39.6	3.9	80	38.4	4.2	.701
Week 4	80	42.5	3.8	76	34.0	4.2	.079

Daily Questionnaires: Sleep Data

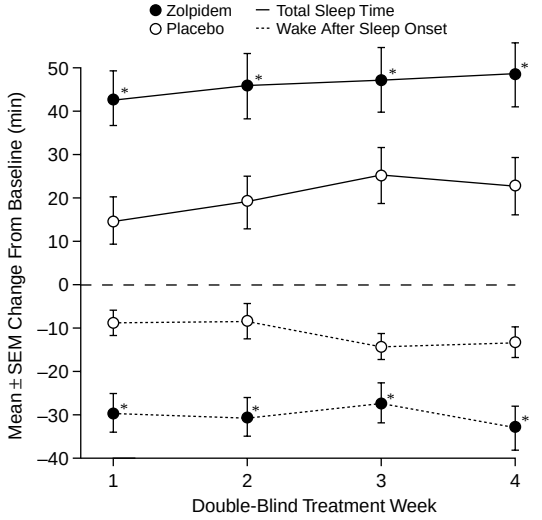
Results of the analyses of subjective sleep latency are summarized in Table 4. Patients in the zolpidem group had a significantly shorter mean sleep latency than did patients in the placebo group during the first treatment week ($p = .049$; zolpidem: mean ± SEM = 40.7 ± 5.4 minutes, placebo: mean ± SEM = 48.1 ± 3.7 minutes). Treatment differences in the last treatment week approached significance ($p = .079$; zolpidem: mean ± SEM = 34.0 ± 4.2 minutes, placebo: mean ± SEM = 42.5 ± 3.8 minutes). Supplementary nonparametric analyses (Wilcoxon rank sum tests) resulted in significant treatment differences at week 1 ($p = .012$), week 2 ($p = .042$), and week 4 ($p = .006$).

The discrepancy between the parametric and nonparametric analyses of latency probably reflects the relative influence in the 2 analyses of 2 zolpidem patients with large latency values: one patient did not fall asleep during 12 different nights scattered throughout the study period (3 baseline nights, 7 double-blind treatment nights, and 2 posttreatment nights); another patient did not fall asleep during any of the nights of week 2 (the patient took naps during the day).

Mean change from baseline values for total sleep time (TST) and wake time after sleep onset (WASO) is illustrated in Figure 1. For TST, there were significant main effects for treatment on all 4 weeks. Increase in TST was significantly greater for the zolpidem group than the placebo group at each week ($p < .05$ for each). On the average, TST was 26 minutes greater for zolpidem than for placebo. Similarly, for WASO, there was a main effect for treatment (all $p < .05$) at all 4 weeks with an average change from baseline of 30 minutes for zolpidem versus 11 minutes with placebo.

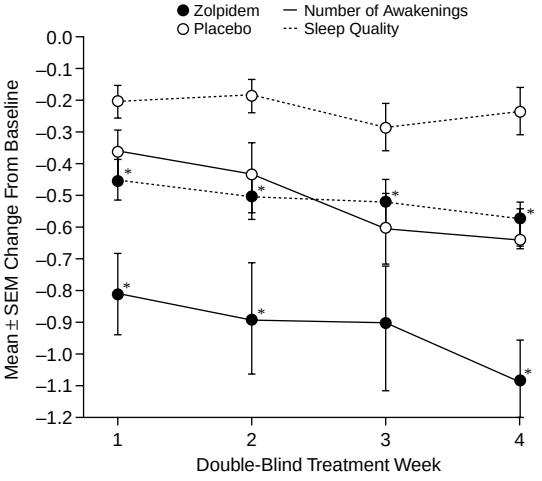
The effects of zolpidem on number of awakenings and sleep quality ratings (1 = excellent, 2 = good, 3 = fair, 4 = poor) are shown in Figure 2. Mean changes from baseline in both parameters were significantly greater in

Figure 1. Effects of Zolpidem on Total Sleep Time and Wake After Sleep Onset During Double-Blind Treatment



*Significantly different from placebo ($p < .05$).

Figure 2. Effects of Zolpidem on Number of Awakenings and Sleep Quality During Double-Blind Treatment[a]

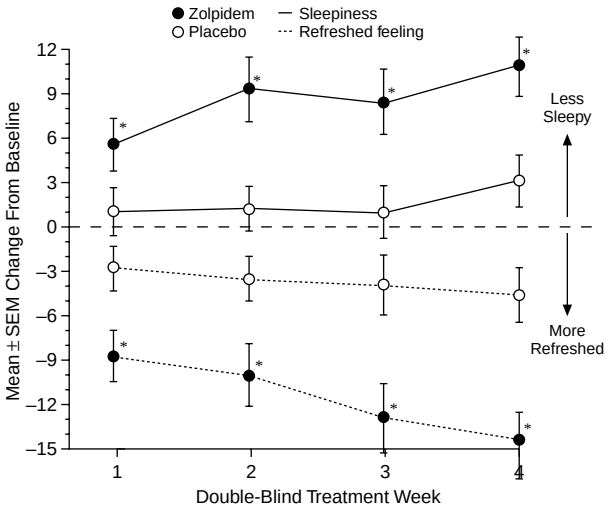


[a]1 = excellent, 2 = good, 3 = fair, 4 = poor.
*Significantly different from placebo ($p < .05$).

Table 5. Effect of Zolpidem on HAM-D Total Score and HAM-D Sleep Items (mean ± SEM change from baseline scores)

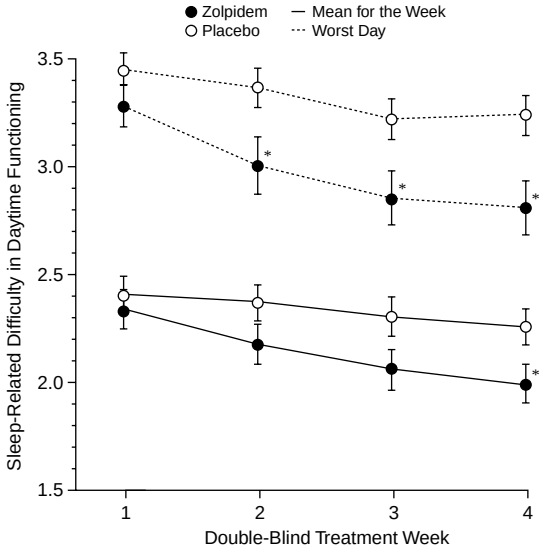
		Placebo		Zolpidem		p
Time	Outcome	Mean	SEM	Mean	SEM	Value
Week 1	Total	–0.99	0.3	–1.01	0.38	.561
	Sleep items	–0.67	0.16	–1.46	0.16	< .001
	Non-insomnia	–0.32	0.24	0.45	0.30	.163
Week 2	Total	–1.25	0.35	–2.05	0.40	.159
	Sleep items	–0.80	0.17	–1.85	0.16	< .001
	Non-insomnia	–0.45	0.27	–0.20	0.34	.593
Week 3	Total	–1.95	0.33	–1.88	0.48	.656
	Sleep items	–1.21	0.18	–1.88	0.19	.003
	Non-insomnia	0.74	0.25	0.00	0.40	.275
Week 4	Total	–1.99	0.35	–2.75	0.41	.075
	Sleep items	–1.33	0.17	–2.13	0.16	< .001
	Non-insomnia	–0.60	0.26	–0.62	0.34	.695

Figure 3. Effect of Zolpidem on Next-Morning Sleepiness (0 mm = very sleepy, 100 mm = not at all sleepy) and Refreshed Feeling (0 mm = very refreshed, 100 mm = not at all refreshed) During Double-Blind Treatment



*Significantly different from placebo (p < .05).

Figure 4. Effect of Zolpidem on Sleep-Related Daytime Functioning[a]



[a]Difficulty doing daily activities during the prior 24 hours due to problems with sleep was assessed daily (1 = not at all, 2 = a little bit, 3 = some, 4 = quite a bit, 5 = could not do daily work). Scores are depicted in terms of the mean during each week of double-blind treatment and as the score on the worst day of each week.
*Significantly different from placebo (p < .05).

the zolpidem-treated patients, with the exception of the 3-week data point for number of awakenings, where the difference did not reach statistical significance (overall, 38% and 18% change from baseline for number of awakenings and sleep quality, respectively, in the zolpidem group compared with 18% and 9% for placebo). Patients receiving zolpidem reported a greater ease of falling asleep (VAS: 0 mm = very easy, 100 mm = not easy) than did placebo-treated patients at weeks 1 and 4 (p < .05).

Both treatment groups had small improvements (22% and 33% for placebo and zolpidem, respectively) in their total HAM-D scores over the 4-week treatment period. However, the change in total HAM-D score was accounted for to a large extent by the reduction in the score of the sleep items (items 4, 5, 6). Ratings on only the sleep items were significantly different for all 4 weeks of treatment. The non-insomnia HAM-D score (total HAM-D score minus the sleep item score) did not differ between the treatment groups during the 4 weeks (Table 5).

Daily Questionnaires: Daytime Data

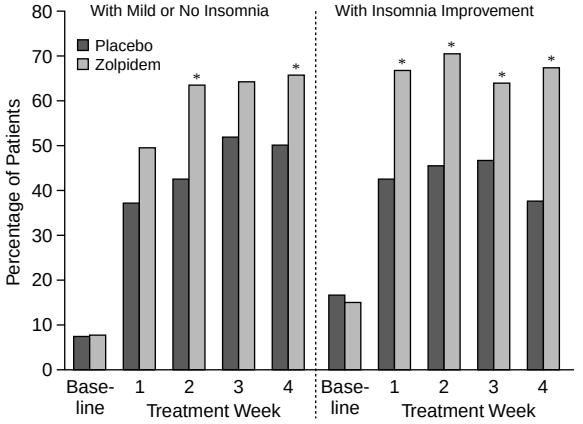
Figure 3 illustrates the effects of zolpidem on morning sleepiness and refreshed feeling. For both parameters, patients treated with zolpidem showed a significantly greater improvement at all timepoints compared with patients treated with placebo, i.e., more refreshed and less sleepy. Patients also rated their ability to concentrate in the morning as significantly more improved in the zolpidem group at weeks 2, 3, and 4 (p < .05).

Finally, each patient rated "how much difficulty they had doing daily activities" during the prior 24 hours due to problems with sleep. When this item was scored as a weekly mean, there was significantly less difficulty in the zolpidem group by week 4; when the score for the difficulty item was selected for the worst day of each week, significant improvement was seen for zolpidem at weeks 2, 3, and 4 (Figure 4).

Weekly and Monthly Measures

The investigator assessed weekly severity and therapeutic effect separately for depression and insomnia. No

Figure 5. Effect of Zolpidem on the Investigator Clinical Global Impressions Scale: Insomnia Severity (left panel) and Insomnia Improvement (right panel)



*p < .05 from placebo.

significant treatment differences were found with respect to the severity of depression or therapeutic effect on depression during the baseline week or during double-blind treatment. On the other hand, improvement in insomnia was reported significantly more frequently with zolpidem than with the placebo at all weeks. Based on the investigator CGI scores and compared with placebo, the fraction of patients with insomnia of mild or less-than-mild severity was significantly higher in the zolpidem group at weeks 2 and 4 (Figure 5, left panel). Similarly, the fraction of patients with insomnia improvement of minimal or more was significantly greater in zolpidem patients at all weeks of treatment (Figure 5, right panel).

On the SF-36, treatment with zolpidem was associated with a significantly more improved score (from baseline to week 4) in the vitality domain compared with placebo (mean ± SEM change from baseline = 12.0 ± 2.1 vs. 2.9 ± 1.5; p = .002). None of the other domains (physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, and mental health) was modified differentially by the 2 treatments.

Posttreatment Single-Blind Placebo Period

As summarized in Table 6, for the zolpidem-treated patients, sleep latency and ratings of ease of falling asleep did not significantly differ from baseline (within-group comparison) on any of the 3 discontinuation nights or for the mean of the posttreatment week. These patients, however, experienced significantly shortened total sleep time on the first night of the posttreatment period than at baseline and also experienced significantly worsened sleep quality on that night compared with baseline. In contrast, zolpidem-treated patients retained significantly fewer awakenings on nights 2 and 3 and over the entire week.

Table 6. Discontinuation Effects on Hypnotic Efficacy Variables: Mean ± SEM Changes From Baseline

Variable and Period	Placebo N	Placebo Mean	Placebo SEM	Zolpidem N	Zolpidem Mean	Zolpidem SEM	p Value
Latency							
Night 1	76	–19.9	6.5*	73	–4.8	6.9	.269
Night 2	76	–25.9	5.8*	74	11.1	11.4	.006
Night 3	77	–26.5	5.7*	74	–8.3	6.5	.183
Entire week	78	–25.3	5.3*	75	–4.7	4.9	.027
Total sleep time							
Night 1	76	29.9	10.4*	74	–26.1	12.1*	.002
Night 2	76	31.9	10.0*	73	10.5	14.4	.361
Night 3	77	46.4	10.2*	74	11.9	11.0	.080
Entire week	78	26.3	7.2*	75	0.6	7.5	.045
Ease of falling asleep[a]							
Night 1	76	–10.5	3.3*	74	4.4	3.7	.007
Night 2	76	–12.8	3.0*	71	–1.2	4.2	.015
Night 3	77	–14.8	3.1*	74	–2.2	3.7	.024
Entire week	78	–13.0	2.5*	75	–3.5	2.7	.013
No. of awakenings							
Night 1	75	–0.79	0.14*	72	–0.04	0.26	.027
Night 2	76	–0.70	0.13*	72	–0.40	0.19*	.174
Night 3	76	–0.63	0.15*	74	–0.45	0.16*	.429
Entire week	78	–0.66	0.11*	75	–0.43	0.10*	.163
WASO							
Night 1	75	–18.1	4.3*	72	0.6	7.2	.026
Night 2	76	–21.4	4.4*	72	–3.1	7.9	.119
Night 3	76	–18.0	4.5*	74	–8.4	7.4	.266
Entire week	78	–16.6	3.2*	75	–9.6	4.9	.161
Sleep quality[b]							
Night 1	76	–0.42	0.09*	73	0.19	0.09*	<.001
Night 2	76	–0.41	0.09*	70	–0.10	0.11	.038
Night 3	76	–0.44	0.09*	72	–0.12	0.09	.026
Entire week	78	–0.37	0.07*	75	–0.07	0.06	.004

*Within-group change from baseline differs significantly (p < .05) from zero.
[a]0 = very easy, 100 = not at all easy.
[b]1 = excellent, 2 = good, 3 = fair, 4 = poor.

The placebo group maintained improved sleep over baseline values (see Table 6), as assessed by all hypnotic parameters during the entire posttreatment period. Significant treatment differences in the change from baseline in latency, ease of falling asleep, and sleep quality favoring placebo were observed on posttreatment night 2 and for the entire posttreatment week. In addition, on night 1, there was a significant difference for total sleep time and number of awakenings; for the weekly score, a significant difference was found for total sleep time.

Tables 7 and 8 summarize the treatment-emergent adverse events that were reported by at least 5% of patients during the double-blind treatment period (Table 7) and those experienced by at least 2% of patients during the posttreatment period (Table 8) in at least 1 of the 2 treatment groups. During both treatment periods, the overall incidence rates were comparable in the 2 groups, 74% and 83% for placebo and zolpidem, respectively, during double-blind treatment and 43% for placebo and 39% for zolpidem during the posttreatment week. In both groups and treatment periods, by far the most frequently reported treatment-emergent adverse event was headache.

Table 7. Treatment-Emergent Adverse Events During Double-Blind Treatment (4 weeks)[a]

	Placebo (N = 97)		Zolpidem (N = 95)	
Adverse Event	N	%	N	%
Headache	24	24.7	32	33.7
Upper respiratory tract infection	12	12.4	9	9.5
Dysmenorrhea	9	9.3	11	11.6
Dyspepsia	9	9.3	9	9.5
Somnolence	8	8.2	9	9.5
Back pain	7	7.2	9	9.5
Influenza-like symptoms	9	9.3	7	7.4
Myalgia	7	7.2	8	8.4
Nausea	7	7.2	7	7.4
Sinusitis	7	7.2	6	6.3
Arthralgia	9	9.3	3	3.2
Mouth dry	4	4.1	6	6.3
Diarrhea	6	6.2	4	4.2
Dizziness	3	3.1	6	6.3
Pharyngitis	4	4.1	5	5.3
Allergy	5	5.2	1	1.1

[a]Treatment-emergent adverse events reported by at least 5% of patients in at least 1 of the 2 treatment groups. Overall, 72 placebo-treated patients (74.2%) and 79 zolpidem-treated patients (83.2%) experienced treatment-emergent adverse events during double-blind treatment.

Table 8. Treatment-Emergent Adverse Events During Posttreatment (1 week)[a]

	Placebo (N = 79)		Zolpidem (N = 75)	
Adverse Event	N	%	N	%
Back pain	3	3.8	1	1.3
Malaise	1	1.3	2	2.7
Headache	7	8.9	10	13.3
Dyspepsia	3	3.8	2	2.7
Abnormal hepatic function	2	2.5	0	0.0
Arthralgia	3	3.8	0	0.0
Myalgia	2	2.5	1	1.3
Paroniria	3	3.8	2	2.7
Dysmenorrhea	3	3.8	3	4.0
Vaginitis	2	2.5	0	0.0
Coughing	1	1.3	2	2.7
Rhinitis	2	2.5	1	1.3
Sinusitis	3	3.8	3	4.0
Upper respiratory infection	2	2.5	0	0.0

[a]Treatment-emergent adverse events reported by at least 2% of patients in at least 1 of the 2 treatment groups. Overall, 34 placebo-treated patients (43.0%) and 29 zolpidem-treated patients (38.7%) experienced treatment-emergent adverse events during posttreatment.

During the analysis of adverse events in terms of a potential withdrawal reaction from zolpidem, no patient in the placebo or the zolpidem group had 2 or more of the 8 symptoms constituting criterion B of a sedative/hypnotic withdrawal syndrome (DSM-IV). In the zolpidem group, 1 patient each reported nausea with vomiting or nausea alone. In the analysis of their respective sleep patterns, the first patient with moderate nausea and mild vomiting felt unrefreshed the first morning posttreatment, but reported sleep parameters that were identical to those of the last zolpidem treatment night. The patient rated the second posttreatment night better than both the first posttreatment night and the last double-blind treatment night. The second patient with mild nausea reported sleep that was identical to her baseline sleep and that she was "feeling great" and "refreshed," i.e., there was no impairment or distress associated with that sleep (criterion C of DSM-IV 292.0). Thus, in neither case was there evidence for a withdrawal reaction from zolpidem.

DISCUSSION

In this study of SSRI-treated outpatients, zolpidem demonstrated significant hypnotic efficacy based on subjective reports of sleep quantity and quality. It is noteworthy that no development of tolerance was apparent during the 4-week treatment period. Furthermore, based on the HAM-D scores or clinical assessments, no evidence of worsening of depression symptoms during the period of zolpidem-SSRI coadministration was found. At the time of randomization, patients had depression scores of minimal severity, i.e., 8.09 and 8.19 in the placebo and zolpidem groups, respectively. In contrast, most patients entering clinical trials for depression have HAM-D scores of at least 18.[27] Thus, generalization of the present data to other depressed patient populations is not possible.

At study entry, the patients' insomnia symptoms were no different from the insomnia symptoms of nondepressed insomniacs,[28] with an average sleep latency of approximately 1 hour, total sleep time of less than 6.5 hours, multiple awakenings during the night, and clinically significant daytime impairment. Thus, irrespective of etiology, the sleep complaints in the present patient population appear comparable to symptoms of insomnia identified in adult patients with chronic (DSM-III-R) or primary insomnia (DSM-IV). It is reasonable, therefore, that zolpidem would be effective in treating insomnia in the present patient population as in other insomnia patients in previous studies.[15–18]

The subjective hypnotic efficacy of zolpidem was accompanied by subjective reports of improved ability to function during waking hours. In addition, based on the overall quality-of-life questionnaire (the SF-36) administered at the end of double-blind treatment, patients treated with zolpidem had a significantly improved score in the vitality domain, but not other domains. Overall, this study is the first to demonstrate that coadministration of a hypnotic, i.e., zolpidem, with an SSRI might improve the patient's perception of daytime functioning.

The insomnia score (mean score of insomnia items) of the HAM-D improved to a significantly larger extent in zolpidem-treated patients, but without a significantly different impact on the total HAM-D score or the non-insomnia score (total score minus insomnia score). These results are important in that they appear to show that coadministration of zolpidem with an SSRI does not affect

the antidepressant activity of the SSRI, that zolpidem itself has no antidepressant activity, and most importantly, that zolpidem did not worsen the depression (despite 1 case of discontinuation in the zolpidem group due to aggravated depression).

Although significantly smaller in extent than in zolpidem-treated patients, some progressive improvement in all parameters of hypnotic efficacy and next-day functioning was seen in the placebo group. This phenomenon has been observed in many studies using subjective outcome measures in chronic insomniacs[29] and is generally attributed to the implicit focus on regularization of sleep habits due to study participation. In the present study, these placebo effects take on particular significance when the active treatment is discontinued and placebo is substituted in a single-blind manner in the zolpidem-treated group while placebo treatment is continued for the fifth week in the placebo group. Based on the definition of rebound insomnia as a sleep disturbance that follows discontinuation of hypnotic drug use and is characterized by greater sleep disturbance than existed before treatment,[30] outcome measures during the substitution week were compared with respective baseline values. The discontinuation effects in the zolpidem group consisted of a worsening of sleep on night 1 (subjective total sleep time and self-rated quality of sleep were significantly different from respective baseline values) followed by a return to baseline conditions during the rest of the placebo substitution week. This is a common phenomenon in subjective sleep studies, since patients rate their sleep relative to the immediately preceding night.

More importantly, none of the patients withdrawn from zolpidem subsequent to 4 weeks of treatment met the criteria for sedative/hypnotic withdrawal (DSM-IV). This observation excludes the possibility that the sleep disturbances recorded during the first posttreatment night were intrinsic to any withdrawal effects of zolpidem and simply reflects the absence of hypnotic medication in the patient's perception of sleep. As one would expect, the improvement achieved in the placebo group during double-blind treatment continued during this last week, thus actually resulting in a between-group difference in favor of placebo in change from baseline.

An interesting and important question remains to be answered, namely, What kind of discontinuation effects would have occurred in both groups upon withdrawal of all treatment, i.e., change to no medication intake, which would resemble the real-life situation? Two clinical investigations have presented evidence that there might actually be some form of rebound insomnia in placebo-treated insomniac patients subsequent to pill discontinuation.[31,32] As has been suggested for other hypnotic drugs, any zolpidem-related sleep disturbances would probably be preventable by tapering to the lower recommended dose of zolpidem (5 mg) for 2 or 3 nights. At present, no data with zolpidem in support of this approach are available. Another approach to the management of possible rebound sleep disturbances could be to combine hypnotic medication with behavioral therapy during the double-blind treatment phase and maintain behavioral modification during the discontinuation phase.

In extrapolating the overall utility of zolpidem in the treatment of insomnia in depressed patients in general, it is important to remember the constraints of the present trial. It was designed to examine the effects of zolpidem in a relatively narrow subpopulation of initially mildly to moderately depressed patients who had responded to SSRI therapy according to the treating clinician, but were complaining of persistent insomnia. The mean HAM-D score at randomization was 8.14 points, of which slightly less than half (3.69 points) was related to the 3 insomnia items (see Table 3). Since patients were required to have evidence of early and middle insomnia, this entry criterion may have led to inclusion of more patients with SSRI treatment-emergent insomnia. The design of the study, however, did not permit definitive differentiation between treatment-resistant, depression-related insomnia and SSRI-related insomnia. Therefore, given the uncertain interrelationship between depression and insomnia,[33] it is impossible to define the etiology of the insomnia in the present patient population.

As anticipated, given previous pharmacokinetic interaction studies between zolpidem and SSRIs, zolpidem, 10 mg, was coadministered safely with the stable SSRI regimen. The incidence of adverse events is higher in this study than in insomnia studies with nondepressed patients of similar treatment duration.[15,28] The higher rates may be a function of the overreporting or actual experience of more side effects by depressed patients. Although the incidence rates of adverse events during double-blind treatment, as well as during the posttreatment period, were similar in the 2 treatment groups, 7 zolpidem-treated patients discontinued during treatment owing to adverse events compared with only 2 placebo patients. Some of the events that led to discontinuation might be indicative of the necessary caution to be taken during coadministration of an SSRI and zolpidem. On the other hand, similar side effects have been reported with zolpidem and other hypnotics in nondepressed patients with insomnia.

At the moment of substitution of placebo for zolpidem, the zolpidem-treated patients reverted to pretreatment insomnia symptoms with some significant subjective rebound sleep disturbances for 1 night, which might be avoidable by tapering the zolpidem dose. Theoretically, the discontinuation problem could be avoided by chronic coadministration of zolpidem with the SSRI. Such a solution might entail an additional therapeutic benefit. The presence of insomnia in remitted depressed patients has been shown to be associated with a risk for relapse of a depressive episode.[34,35] Thus, a partially recovered de-

pressed patient with insomnia might be at risk for a relapse,[36] and therefore, chronic treatment of insomnia might be indicated. On the other hand, chronic coadministration of zolpidem with an SSRI antidepressant might be an uncertain option, since no controlled data are available on the safety and continuous efficacy of zolpidem for periods longer than 3 months.[37] Overall, however, the results of the present study suggest that zolpidem would be safe and effective for the treatment of insomnia in patients successfully treated for depression.

Drug names: fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), triazolam (Halcion), zolpidem (Ambien).

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