ORIGINAL ARTICLE

Eszopiclone Coadministered With Escitalopram in Patients With Insomnia and Comorbid Generalized Anxiety Disorder

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Context: Insomnia and generalized anxiety disorder (GAD) are prevalent disorders that may coexist.

Objective: To determine the efficacy of eszopiclone combined with escitalopram oxalate in treating insomnia comorbid with GAD.

Design: Double-blind, randomized, placebo-controlled, parallel-group, add-on therapy 10-week study.

Setting: Multicenter outpatient study from July 2005 to April 2006.

Patients: Adults aged 18 to 64 years meeting *DSM-IV-TR* criteria for GAD and insomnia.

Interventions: Patients received 10 mg of escitalopram oxolate for 10 weeks and were randomized to also receive either 3 mg of eszopiclone (n=294) or placebo (n=301) nightly for 8 weeks. For the last 2 weeks, eszopiclone was replaced with a single-blind placebo.

Main Outcome Measures: Sleep, daytime functioning, psychiatric measures, and adverse events.

Results: Compared with treatment with placebo and escitalopram, treatment with eszopiclone and escitalopram resulted in significantly improved sleep and daytime functioning ($P<.05$), with no evidence of tolerance. Patients taking eszopiclone and escitalopram had greater improvements in total Hamilton Anxiety Scale (HAM-A) scores at each week ($P<.05$) and at weeks 4 through 10 with the insomnia item removed. Clinical Global Impressions (CGI) of Improvement scores were improved with eszopiclone and escitalopram at every point ($P<.02$), while CGI of Severity of Illness scores were not significantly different after week 1. The HAM-A response (63% vs 49%, respectively, $P=.001$) and remission (42% vs 36%, respectively, $P=.09$) rates at week 8 were higher in patients treated with eszopiclone and escitalopram than those treated with placebo and escitalopram, and median time to onset of anxiolytic response was significantly reduced ($P\leq.05$). After eszopiclone discontinuation, there was no evidence of rebound insomnia, and while treatment differences in anxiety measures were maintained, differences in sleep outcomes were not. Overall adverse event rates were 77.6% with cotherapy and 67.9% with monotherapy. The most common adverse events with cotherapy were unpleasant taste, headache, dry mouth, and somnolence.

Conclusions: Coadministration of eszopiclone and escitalopram was well tolerated and associated with significantly improved sleep, daytime functioning, anxiety, and mood in patients with insomnia and GAD.

Trial Registration: clinicaltrials.gov Identifier: NCT00235508

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INSOMNIA AND GENERALIZED ANXIety disorder (GAD) are highly prevalent conditions with significant associated distress and morbid consequences.[1,2] These conditions commonly coexist and have considerable symptomatic overlap. At least two-thirds of patients with GAD have at least 1 form of comorbid sleep disturbance.[3,4] This is not surprising given that sleep disturbances are included in the *DSM-IV* diagnostic criteria for GAD ("difficulty falling or staying asleep, or restless unsatisfying sleep").[5] Conversely, GAD is one of the most common psychiatric comorbidities occurring in individuals with insomnia.[6,7] Sleep disturbance is a key feature among older adults with GAD and is also common among those with subsyndromal levels of anxiety.[8] Worrying has been found to be negatively related to sleep duration among college students and young adults.[9,10]

Individuals with significant insomnia are more likely to feel anxious, tense, and worried at bedtime than those without a sleep disturbance[11]; they also experience elevated rates of physiological symptoms of anxiety, including tachycardia, trembling, sweating, dizziness, and gastrointestinal distress.[5] Additionally, the symptomatic overlap between insomnia and anxiety includes agitation, irritability, loss of appetite, muscle tension, and poor concentration. Polysomnography in patients

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with GAD has revealed increased sleep latency; initial, middle, and early morning insomnia; decreased total sleep time, sleep continuity, sleep efficiency, and quality measures; and variable degrees of reported abnormalities in rapid eye movement sleep and sleep architecture.[4,5,12-18] Insomnia may predispose individuals to develop anxiety disorders[19] or insomnia may develop subsequent to the onset of anxiety,[7,20] though it is unknown whether targeted treatment of insomnia may affect the course of GAD.

Although some clinical guidelines have recommended antidepressant monotherapy for the treatment of insomnia associated with major depression,[21,22] inadequate treatment of insomnia in patients with depression receiving antidepressants is associated with poor clinical outcomes. Sedating antidepressants (eg, amitriptyline, trazodone, and mirtazapine) are sometimes administered at bedtime to treat insomnia that is coexistent with a mood or anxiety disorder. Although sometimes successful, the use of these agents may be associated with attendant adverse effects, including anticholinergic effects, daytime sedation, or weight gain. As discussed in the National Institutes of Health State of the Science Conference Statement on the Manifestations and Management of Chronic Insomnia in Adults,[23] there are relatively few systematic data addressing this strategy and none comparing it with hypnotic augmentation.

Augmentation of antidepressant therapy with a hypnotic drug is believed to effectively treat insomnia associated with depression.[24] In one study, zolpidem augmentation improved sleep in depressed patients with persistent insomnia treated with selective serotonin reuptake inhibitors (SSRIs), though there was no additional improvement in depressive symptoms, and rebound insomnia was evident on discontinuation.[25] In another study, eszopiclone cotherapy with fluoxetine appeared to improve sleep and accelerate and increase the magnitude of the antidepressant effect compared with antidepressant treatment alone, with the sleep improvements maintained after eszopiclone was discontinued.[26] There are no clear databased consensus guidelines for the treatment of comorbid insomnia and GAD. However, given the frequency of the cooccurrence of these conditions and their morbid effects, examination of the role of targeted insomnia treatment for individuals receiving pharmacotherapy for GAD is warranted.

Eszopiclone is a nonbenzodiazepine γ-aminobutyric acid receptor agonist indicated for the treatment of sleep onset and maintenance insomnia, with demonstrated sustained efficacy and safety.[27-29] Its efficacy for both onset and maintenance insomnia and its decreased potential to induce tolerance make it a good candidate to test in combination with an SSRI in patients with insomnia and comorbid GAD. The aims of this study were to examine (1) the hypnotic efficacy and safety of eszopiclone coadministered with the SSRI escitalopram compared with escitalopram and placebo for patients with insomnia and GAD and (2) whether coadministration of eszopiclone would increase the magnitude and/or accelerate the anxiolytic response compared with the antidepressant alone.

METHODS

This was a randomized, double-blind, placebo-controlled, parallel-group, add-on therapy trial consisting of patients with insomnia comorbid with GAD who were treated with 10 mg of open-label escitalopram oxalate at bedtime every day and were randomized to also receive either 3 mg of eszopiclone or placebo nightly for 8 weeks. This multicenter study was conducted at 69 sites. Sites were required to have a psychiatrist as the principal investigator or subinvestigator and were selected only if they had experience conducting studies in patients with GAD. All patients gave written informed consent; the institutional review board for each study site approved the protocol; and the study was carried out in accordance with the Declaration of Helsinki (1989).

The trial consisted of a maximum 10-day, single-blind, double-placebo (placebo for both agents), run-in period; 8 weeks of double-blind treatment; and a 2-week, single-blind run-out period, during which time patients continued to receive 10 mg of escitalopram oxalate along with a placebo. Patients visited the clinic 8 times during the study period, spending a total of approximately 12 weeks in the study.

PATIENTS

Male and female patients aged 18 to 64 years (inclusive) meeting *DSM-IV-TR* criteria for GAD and insomnia related to GAD (confirmed by the Mini-International Neuropsychiatric Interview[30] if one had not been completed within 2 weeks of the visit) who reported sleep latency of 30 minutes or longer and a total sleep time of 6.5 hours or less at least 3 times a week, each week, throughout the previous month were screened. There was no requirement for a particular temporal relationship between the onset of GAD and insomnia. To qualify, patients must have had a score of 10 or greater on the self-administered anxiety subscale of the Hospital Anxiety and Depression Scale[31]; a score of 4 or greater on the Clinical Global Impressions of Severity Scale (CGI-S); and a score of 20 or greater on the clinician-administered Hamilton Anxiety Scale (HAM-A),[32] with a score of at least a 2 on items 1 and 2 (anxious mood and tension) at screening (visit 1). Patients could also have depression (but with GAD as the primary disorder) as long as it was no more than mild to moderate in severity, as operationalized by a score of less than 20 on the clinician-administered Montgomery Asberg Depression Rating Scale,[33] and there was no evidence of acute suicidality, as operationalized by a score of less than 3 on item 10 of the Montgomery Asberg Depression Rating Scale. Other exclusion criteria were any unstable medical condition; any other primary sleep disorder or condition known to interfere with sleep; any history of drug or alcohol abuse or refractory GAD (ie, previously unresponsive to ≥ 2 adequate courses of SSRI, selective noradrenergic reuptake inhibitor, benzodiazepine, or nonbenzodiazepine treatment for GAD); and prior use of eszopiclone.

STUDY PROCEDURES

At visit 1, participants were screened for entry criteria, and eligible patients were trained on the use of an electronic diary to complete daily assessments of sleep (including sleep onset, maintenance, duration, and quality) and daytime insomnia symptoms (alertness, ability to concentrate, ability to function, and sense of well-being). Patients were instructed to complete the sleep diary daily between 6 and 10 AM. All patients received single-blind matched placebo with instructions to take both pills at night immediately before going to bed and to return to the clinic within 7 to 10 days. The purpose of this run-in was to establish baseline values for sleep and daytime functioning and

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to ensure compliance with the dosing regimen and completion of the diary. Patients who completed at least 70% of the diary entries and took at least 70% of the required doses of single-blind placebo between visits 1 and 2 were then randomized to receive 3 mg of eszopiclone or matching placebo for 8 weeks and 10 mg of open-label escitalopram oxalate per day, both administered at bedtime. In addition, clinicians completed the HAM-A, Hamilton Depression 17-item Rating Scale (HAM-D),[34] CGI-S, and Clinical Global Impressions of Improvement (CGI-I) scales, and patients completed the Hospital Anxiety and Depression Scale, the Insomnia Severity Index (ISI),[35] the Quality of Life Enjoyment Satisfaction Questionnaire,[36] and the Sheehan Disability Scale.[37] For these end points, visit 2 was used as the baseline. All investigational site staff were trained and certified in the administration of the HAM-A, HAM-D, CGI-I, and CGI-S scales.

After randomization, patients returned to the clinic at weeks 1, 2, 4, 6, 8, and 10. At each visit, the clinician completed the HAM-A, HAM-D, CGI-S, and CGI-I scales, and patients completed the Hospital Anxiety and Depression Scale. The ISI was completed at weeks 1, 4, 8, and 10; the Sheehan Disability Scale was completed at weeks 4, 8, and 10; and the Quality of Life Enjoyment Satisfaction Questionnaire was completed at weeks 8 and 10. At the week 8 visit, patients received single-blind placebo in place of eszopiclone or placebo, and they continued open-label escitalopram treatment for 2 weeks. The purpose of this run-out period was to evaluate rebound and withdrawal effects following abrupt discontinuation.

Safety assessments were made throughout the study by evaluating adverse events, vital signs, clinical laboratory assessments, and brief physical examinations. Urine drug toxicology and serum and urine pregnancy tests were performed at screening, with positive findings resulting in exclusion from the study. Adverse events were monitored by reviewing a medical event calendar at each visit, which was used by patients throughout the study to record changes in their health status and medications.

STUDY END POINTS

The primary end point was the change from baseline in sleep latency averaged across the double-blind period. Key secondary end points were (1) the change from baseline in total sleep time throughout the double-blind period, (2) change from baseline to week 8 in HAM-A score, (3) change from baseline to week 8 in CGI-S score, (4) 50% response based on total HAM-A score at week 8, and (5) time to onset of anxiolytic response based on CGI-I score (CGI-I score ≤ 2).

Sleep and daytime functioning variables assessed included sleep latency, wake time after sleep onset, total sleep time, number of awakenings, sleep quality, sleep depth, daytime alertness, ability to function, ability to concentrate, physical well-being (the last 6 of these assessments were rated on an 11-point Likert scale [0-10], with higher scores indicating better functioning), and the total ISI score. The ISI is composed of 7 items assessing the severity of sleep onset and sleep-maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. Each item is rated on a scale from 0 to 4 and the total score ranges from 0 to 28 (total scores of 0-7 = not clinically significant insomnia; 8-14 = subthreshold insomnia; 15-21 = moderate insomnia; and 22-28 = severe insomnia). Anxiety and depression end points were change from baseline in total HAM-A score (with and without the sleep item), response ($\geq$50% reduction in total HAM-A score from baseline), and remission (total HAM-A score ≤ 7); CGI-S and CGI-I scores; and total HAM-D score (with and without sleep items), response, and remission; and changes in Hospital Anxiety and Depression Scale scores.

STATISTICAL ANALYSIS

Efficacy and safety analyses of the double-blind, randomized treatment phase of the study included all patients who received at least 1 dose of double-blind study medication. All statistical tests were 2-sided and conducted at the 5% significance level unless otherwise specified. To protect against type II error due to multiple comparisons, a sequential testing approach was used for the prospectively defined primary and key secondary end points, with each considered to be statistically significant only if all preceding tests were significant.

End points were tested in the following order:

1. Primary end point: change from baseline in sleep latency averaged across the double-blind period.
2. Key secondary end points:

Change from baseline in total sleep time averaged across the double-blind period.

Change from baseline in total HAM-A score at week 8.

Change from baseline in CGI-S score at week 8.

Anxiolytic response based on 50% reduction from baseline in HAM-A score at week 8.

Time to onset of anxiolytic response based on CGI-I score (CGI score ≤ 2).

A last-observation-carried-forward method was used for analysis of the double-blind data, except for time to response analyses. All continuous variables (except CGI-I score, which does not have a baseline assessment) were compared across treatment groups, with an analysis of covariance model to assess change from baseline, with treatment and site as fixed effects and baseline score as the covariate. All of those with sleep latency and wake time after sleep onset longer than 540 minutes and a total sleep time longer than 840 minutes were excluded from the analysis, and sleep latency and wake time after sleep-onset end points were log transformed before analyses.

The 50% anxiolytic response in total HAM-A score was summarized for each treatment group and analyzed using the Cochran-Mantel-Haenszel test of general association with no stratification factors. The time to onset of anxiolytic response based on CGI-I score was estimated using the Kaplan-Meier method and compared using the log-rank test. The distributions of time to specific events (50% anxiolytic response, remission, and CGI-I and CGI-S responses) were estimated using the Kaplan-Meier method by treatment group and compared between treatment groups using the log-rank test.

The statistical plan also included a subgroup analysis of response by baseline anxiety (more severe, baseline HAM-A score $\geq$ observed median; less severe, HAM-A score $<$ observed median) using an analysis of covariance with treatment and site as fixed effects and baseline score as the covariate. In addition, post hoc exploratory analyses were performed to examine the relationship of other potential predictors of response to treatment, including age, sex, and presence and severity of depression with anxiety outcome, represented by the change in HAM-A score from baseline to week 8. These analyses were performed using analysis of covariance, with treatment and site as fixed effects and baseline HAM-A score as the covariate. For each of the potential predictors listed, we added terms for the main effect of the predictor and the predictor by treatment interaction. The purpose of these analyses was to assess the significance of the interaction term, eg, was the magnitude of the difference between the combination and monotherapy arms the same in those with more severe anxiety at baseline as for those with less severe anxiety? The same type of analyses were repeated for the 2 main sleep measures: change from baseline in sleep latency and total sleep time. Because the diagnostic results from the Mini-International Neuropsychiatric Interview were not collected across sites for analysis, a score of 16 or

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Table 1. Patient Disposition in a Study of Individuals With Insomnia and Comorbid Generalized Anxiety Disorder

Population by Study Phase	No. (%) of Patients: Treated With Placebo and Escitalopram Oxolate	No. (%) of Patients: Treated With Eszopiclone and Escitalopram
Randomized	301	294
Completed double-blind period	237 (78.7)	235 (79.9)
Single-blind run-out population	235 (78.1)	233 (79.3)
Completed the study[a]	233 (77.4)	229 (77.9)
Discontinued study	68 (22.6)	65 (22.1)
Adverse event	17 (5.6)	16 (5.4)
Protocol violation	12 (4.0)	11 (3.7)
Voluntary withdrawal	15 (5.0)	13 (4.4)
Lost to follow-up	18 (6.0)	17 (5.8)
Insomnia treatment failure	3 (1.0)	2 (0.7)
Other	3 (1.0)	6 (2.0)

[a]Completed the double-blind and single-blind run-out periods.

greater on the HAM-D was considered consistent with a diagnosis of major depression.

RESULTS

DISPOSITION AND BASELINE CHARACTERISTICS OF PATIENTS

A total of 945 patients were screened, 595 were randomized (301 to placebo and escitalopram and 294 to eszopiclone and escitalopram), and 462 (77.6%) completed the study (**Table 1**). The most common reasons for screen failure included not meeting diagnostic or severity entry criteria (n=94) and use of excluded medications (n=12). The mean age was 40 years, most patients were female (66%), and most patients were Caucasian (70%). There were no differences between treatment groups for any demographic, sleep history, anxiety, or other efficacy parameter at baseline (**Table 2** and **Table 3**). Approximately 75% of patients in each treatment group had moderate or severe insomnia (total ISI score ≥14), while 4% of patients taking placebo and escitalopram and 3% of patients taking eszopiclone and escitalopram had no clinically meaningful insomnia based on an ISI score of 7 or less. The mean (SD) duration of GAD based on patients' medical history at screening was 87.9 months (118.0 [range, 0.03-695.3] months), ie, 7.3 years. Forty-three percent (n=253) of participants had an HAM-D score of 16 or greater at baseline, which is consistent with the diagnosis of major depression, with no significant differences between treatment arms (patients taking placebo and escitalopram, 45%; patients taking eszopiclone and escitalopram, 41%; $P=.37$).

Approximately 78% of patients in each group completed the study. Discontinuation rates were similar between the treatment groups (Table 1). Overall discontinuations due to adverse events were greater during the first 2 weeks in the group assigned to received placebo and escitalopram, while these rates were fairly stable in the group assigned to received eszopiclone and escitalopram during the study period. Discontinuation rates due to insomnia treatment failure were similar in both groups (1%).

PRIMARY AND KEY SECONDARY END POINTS

Relative to treatment with placebo and escitalopram, treatment with eszopiclone and escitalopram resulted in significantly reduced sleep latency averaged across the double-blind period (−25 vs −11 minutes; $P<.001$) (**Table 4**). There were significant improvements from baseline with eszopiclone and escitalopram relative to placebo and escitalopram in the key secondary end points of total sleep time averaged across the double-blind period (increase of 61 vs 35 minutes, respectively; $P<.001$) and HAM-A score at week 8 (−11.96 vs −10.80, respectively; $P=.007$). The mean change from baseline CGI-S score at week 8 was not significantly different between treatment groups ($P=.12$). There were improvements in patients receiving eszopiclone and escitalopram compared with patients receiving placebo and escitalopram in response rate (50% reduction in HAM-A score) at week 8 (63% vs 49%, respectively; $P=.001$) and the time to onset of response based on a CGI-I score of 2 or less (18 vs 28 days, respectively; $P=.052$); however, owing to the hierarchical testing approach, these differences are not considered statistically significant.

SUPPORTIVE SLEEP END POINTS

There were significant improvements from baseline in all nighttime insomnia and daytime functioning end points except physical well-being (not significantly different at weeks 6 and 8) in the eszopiclone and escitalopram group compared with the placebo and escitalopram group at each point during double-blind treatment (**Figure 1** and Table 2), with no evidence of tolerance observed during the study period. Total ISI scores were significantly different at weeks 1, 4, and 8. At week 8, significantly more patients receiving eszopiclone and escitalopram had no clinically meaningful insomnia based on an ISI score of 7 or less compared with the placebo and escitalopram group (47% vs 33%, respectively; $P<.001$).

SUPPORTIVE ANXIETY AND DEPRESSION MEASURES

In participants in the eszopiclone and escitalopram group, significant improvements from baseline ($P<.05$) were observed in total HAM-A scores each week (including week 8, the key secondary end point) and at weeks 4 through 10, when the insomnia item was excluded (Table 3 and **Figure 2**). Individual HAM-A items of tension, insomnia, and somatic complaints (both muscular and sensory) were improved from baseline in the eszopiclone and escitalopram group relative to the placebo and escitalopram group at week 8 ($P<.05$; data not shown). In the eszopiclone and escitalopram group, there were also significant improvements from baseline at week 8 in both the Psychic and Somatic Anxiety subscales of the HAM-A (Table 3). Clinical Global Impressions of Improvement scores were significantly improved with eszopiclone and escitalopram

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Table 2. Sleep and Daytime Functioning in Patients With Insomnia and Comorbid Generalized Anxiety Disorder

Assessment Time	Treatment		Change From Baseline by Treatment		*P* Value[a]
	Placebo and Escitalopram Oxolate	Eszopiclone and Escitalopram	Placebo and Escitalopram	Eszopiclone and Escitalopram	
Median Sleep Latency, min					
Baseline	66.4	63.3			
Week 1	51.3	33.6	−9.0	−22.0	<.001
Week 2	45.5	33.5	−13.9	−25.6	<.001
Week 4	48.8	33.7	−15.1	−27.1	<.001
Week 6	43.7	30.0	−15.3	−28.3	.001
Week 8	42.0	30.2	−16.8	−27.1	<.001
Week 10	46.1	39.8	−15.1	−18.7	.41
Double-blind average	48.8	36.9	−11.5	−25.0	<.001
Median Total Sleep Time, min					
Baseline	338.1	337.4			
Week 1	363.7	400.4	20.0	53.6	<.001
Week 2	384.4	407.8	34.3	55.7	<.001
Week 4	380.5	416.9	33.3	64.8	<.001
Week 6	391.9	420.0	44.3	72.2	<.001
Week 8	398.6	421.2	41.1	68.7	<.001
Week 10	390.0	405.6	41.7	55.7	.19
Double-blind average	384.1	412.6	35.1	60.6	<.001
Median Wake Time After Sleep Onset, min					
Baseline	43.4	43.8			
Week 1	39.5	20.0	−4.0	−13.7	<.001
Week 2	29.9	17.1	−10.9	−16.4	<.001
Week 4	25.7	18.1	−12.9	−16.5	<.001
Week 6	22.3	14.5	−15.0	−20.3	.004
Week 8	18.9	13.0	−18.1	−22.5	.006
Week 10	17.8	17.3	−18.3	−17.2	.98
Double-blind average	28.2	18.3	−10.2	−17.4	<.001
Median No. of Awakenings/Night					
Baseline	1.6	1.6			
Week 1	1.4	1.0	−0.3	−0.5	<.001
Week 2	1.1	1.0	−0.4	−0.5	.007
Week 4	1.0	0.9	−0.5	−0.6	.002
Week 6	0.9	0.8	−0.6	−0.7	.03
Week 8	0.8	0.7	−0.6	−0.8	.04
Week 10	0.8	0.9	−0.6	−0.7	.86
Double-blind average	1.1	0.9	−0.5	−0.6	<.001
Median Daytime Alertness Score[b]					
Baseline	4.9	5.0			
Week 1	5.0	5.7	0.2	0.6	<.001
Week 2	5.4	6.0	0.6	0.9	<.001
Week 4	5.8	6.3	0.8	1.1	.002
Week 6	6.0	6.4	0.9	1.3	.009
Week 8	6.2	6.6	1.1	1.3	.02
Week 10	6.0	6.4	1.1	1.0	.51
Double-blind average	5.7	6.2	0.8	1.0	<.001
Median Ability to Function Score[b]					
Baseline	5.1	5.4			
Week 1	5.3	5.8	0.1	0.5	<.001
Week 2	5.8	6.2	0.5	0.8	.007
Week 4	6.0	6.5	0.8	1.0	.001
Week 6	6.4	6.6	0.9	1.1	.04
Week 8	6.4	6.8	1.0	1.2	.02
Week 10	6.3	6.7	0.9	0.9	.68
Double-blind average	5.9	6.4	0.7	0.9	.002
Median Ability to Concentrate Score[b]					
Baseline	4.9	5.1			
Week 1	5.1	5.7	0.2	0.5	<.001
Week 2	5.7	6.2	0.6	0.9	.002
Week 4	5.9	6.4	0.8	1.0	<.001
Week 6	6.1	6.6	0.9	1.1	.02
Week 8	6.2	6.7	1.0	1.2	.02
Week 10	6.3	6.5	1.1	1.1	.54
Double-blind average	5.8	6.3	0.7	0.9	<.001
Median Physical Well-being Score[b]					
Baseline	5.0	5.2			
Week 1	5.3	5.8	0.3	0.5	.002
Week 2	5.7	6.2	0.6	0.9	.007
Week 4	5.9	6.4	0.9	1.1	.01
Week 6	6.3	6.6	1.0	1.2	.11
Week 8	6.3	6.7	1.0	1.3	.054
Week 10	6.3	6.5	1.0	1.2	.59
Double-blind average	5.9	6.3	0.8	1.0	.007

[a] Change from baseline in the eszopiclone and escitalopram group vs the placebo and escitalopram group (analysis of covariance).
[b] Rated on an 11-point Likert scale (0-10), with higher scores indicating better functioning.

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Table 3. Anxiety and Depression in Patients With Insomnia and Comorbid Generalized Anxiety Disorder

Assessment Time	Treatment		Change From Baseline by Treatment		*P* Value[a]
	Placebo and Escitalopram Oxolate	Eszopiclone and Escitalopram	Placebo and Escitalopram	Eszopiclone and Escitalopram	
Total HAM-A Score, Mean (SD)					
Baseline	22.4 (6.0)	21.8 (6.3)			
Week 1	17.7 (7.1)	16.3 (7.2)	−4.6 (5.8)	−5.5 (5.6)	.01
Week 2	14.4 (7.1)	13.0 (7.0)	−7.9 (6.3)	−8.8 (6.1)	.03
Week 4	13.1 (7.3)	11.4 (6.6)	−9.2 (6.9)	−10.4 (6.3)	.004
Week 6	12.1 (7.7)	10.4 (6.7)	−10.3 (7.2)	−11.4 (6.6)	.006
Week 8	11.5 (7.8)	9.8 (6.6)	−10.8 (7.6)	−12.0 (6.6)	.007
Week 10	11.4 (8.1)	10.0 (6.7)	−11.0 (7.7)	−11.8 (7.1)	.03
HAM-A Score Excluding Insomnia Item, Mean (SD)					
Baseline	19.4 (5.7)	18.9 (6.0)			
Week 1	15.3 (6.5)	14.4 (6.6)	−4.1 (5.3)	−4.5 (5.1)	.13
Week 2	12.5 (6.5)	11.5 (6.4)	−7.0 (5.8)	−7.4 (5.6)	.12
Week 4	11.4 (6.6)	10.1 (6.1)	−8.0 (6.4)	−8.9 (5.9)	.02
Week 6	10.5 (7.0)	9.3 (6.2)	−8.9 (6.7)	−9.7 (6.0)	.03
Week 8	9.9 (7.1)	8.7 (6.1)	−9.5 (7.0)	−10.3 (6.1)	.03
Week 10	9.8 (7.4)	8.5 (6.2)	−9.6 (7.0)	−10.5 (6.5)	.03
HAM-A Psychic Anxiety Subscale Score, Mean (SD)					
Baseline	14.0 (3.1)	13.6 (3.4)			
Week 1	11.3 (4.1)	10.1 (4.3)	−2.7 (3.5)	−3.5 (3.5)	<.001
Week 2	9.2 (4.4)	8.3 (4.2)	−4.8 (4.0)	−5.4 (3.8)	.03
Week 4	8.5 (4.4)	7.1 (4.0)	−5.5 (4.1)	−6.5 (3.9)	<.001
Week 6	7.6 (4.7)	6.5 (4.1)	−6.4 (4.4)	−7.1 (4.2)	.004
Week 8	7.3 (4.8)	6.2 (4.0)	−6.6 (4.7)	−7.4 (4.0)	.005
Week 10	7.3 (5.0)	6.5 (4.1)	−6.7 (4.8)	−7.1 (4.4)	.08
HAM-A Somatic Anxiety Subscale Score, Mean (SD)					
Baseline	8.4 (4.0)	8.1 (4.0)			
Week 1	6.5 (3.9)	6.1 (3.9)	−1.9 (3.2)	−2.1 (3.0)	.42
Week 2	5.2 (3.7)	4.8 (3.6)	−3.1 (3.4)	−3.4 (3.4)	.11
Week 4	4.7 (3.6)	4.3 (3.4)	−3.7 (3.8)	−3.9 (3.6)	.22
Week 6	4.5 (3.6)	3.9 (3.4)	−3.9 (3.9)	−4.3 (3.6)	.05
Week 8	4.2 (3.7)	3.6 (3.3)	−4.2 (4.0)	−4.6 (3.8)	.05
Week 10	4.1 (3.8)	3.4 (3.3)	−4.3 (3.9)	−4.8 (3.9)	.02
50% Anxiolytic Response Based on HAM-A Score, % of Patients					
Baseline					
Week 1	14	18			.15
Week 2	30	37			.04
Week 4	39	47			.05
Week 6	46	56			.02
Week 8	49	63			.001
Week 10	51	60			.04
Clinical Global Impressions Severity of Illness Score, Mean (SD)					
Baseline	4.4 (0.7)	4.3 (0.7)			
Week 1	3.9 (1.0)	3.7 (0.9)	−0.5 (0.7)	−0.6 (0.8)	.03
Week 2	3.4 (1.0)	3.3 (1.0)	−1.0 (0.9)	−1.0 (1.0)	.22
Week 4	3.2 (1.1)	3.0 (1.1)	−1.2 (1.0)	−1.3 (1.0)	.23
Week 6	2.9 (1.2)	2.8 (1.1)	−1.5 (1.1)	−1.5 (1.1)	.23
Week 8	2.8 (1.2)	2.6 (1.1)	−1.6 (1.2)	−1.7 (1.1)	.12
Week 10	2.7 (1.3)	2.7 (1.1)	−1.6 (1.2)	−1.6 (1.1)	.95
Clinical Global Impressions of Improvement Score, Mean (SD)					
Week 1	3.2 (0.9)	3.0 (0.9)			<.001
Week 2	2.8 (1.0)	2.5 (0.9)			.004
Week 4	2.5 (1.0)	2.3 (1.0)			.02
Week 6	2.4 (1.1)	2.1 (1.0)			.005
Week 8	2.3 (1.1)	2.1 (1.0)			.008
Week 10	2.2 (1.1)	2.2 (1.2)			.93
Total HAM-D Score, Mean (SD)					
Baseline	14.8 (4.2)	14.5 (4.7)			
Week 1	13.0 (5.5)	11.7 (5.3)	−1.8 (4.3)	−2.8 (4.3)	.001
Week 2	11.0 (5.5)	9.7 (5.4)	−3.8 (4.7)	−4.8 (4.8)	.004
Week 4	10.5 (5.7)	8.7 (5.2)	−4.3 (5.1)	−5.8 (4.9)	<.001
Week 6	9.6 (6.0)	7.9 (5.6)	−5.2 (5.3)	−6.6 (5.2)	<.001
Week 8	9.4 (6.0)	7.8 (5.8)	−5.4 (5.6)	−6.7 (5.4)	.002
Week 10	9.1 (6.1)	8.3 (5.7)	−5.7 (5.8)	−6.2 (5.5)	.09
HAM-D Score, Excluding Sleep Items, Mean (SD)					
Baseline	10.4 (3.7)	10.2 (4.1)			
Week 1	9.4 (4.5)	8.9 (4.4)	−1.0 (3.5)	−1.2 (3.5)	.19
Week 2	8.2 (4.4)	7.5 (4.4)	−2.3 (3.7)	−2.6 (3.9)	.14
Week 4	7.8 (4.6)	6.8 (4.2)	−2.6 (4.1)	−3.3 (4.1)	.01
Week 6	7.1 (4.7)	6.2 (4.5)	−3.3 (4.4)	−3.9 (4.3)	.02
Week 8	7.0 (4.8)	6.1 (4.8)	−3.4 (4.7)	−4.0 (4.4)	.03
Week 10	6.7 (4.8)	6.1 (4.7)	−3.7 (4.6)	−4.0 (4.4)	.13

Abbreviations: HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression 17-item Scale.
[a] Change from baseline in the eszopiclone and escitalopram group vs the placebo and escitalopram group (analysis of covariance).

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Table 4. Analysis of Primary and Key Secondary End Points in a Study of Eszopiclone Coadministered With Escitalopram

End Point	Treatment: Placebo and Escitalopram Oxolate	Treatment: Eszopiclone and Escitalopram	*P* Value
Primary, change from baseline sleep latency			
Median double-blind average, min	−11.45	−24.99	<.001
Mean (SD) double-blind average, min	−27.65 (86.75)	−41.83 (69.77)	
Key secondary			
Change from baseline total sleep time			
Median double-blind average, min	35.05	60.59	<.001
Mean (SD) double-blind average, min	41.33 (79.49)	71.35 (66.23)	
Mean (SD) change in HAM-A score from baseline to week 8	−10.80 (7.63)	−11.96 (6.60)	.007
Mean (SD) change in CGI-S score from baseline to week 8	−1.56 (1.17)	−1.65 (1.07)	.12
Week 8 50% response in HAM-A, %	49	63	.001
Median time to onset of response (CGI-I score ≤2), d	28	18	.052

Abbreviations: CGI-I, Clinical Global Impressions of Improvement Scale; CGI-S, Clinical Global Impressions of Severity Scale; HAM-A, Hamilton Anxiety Scale.

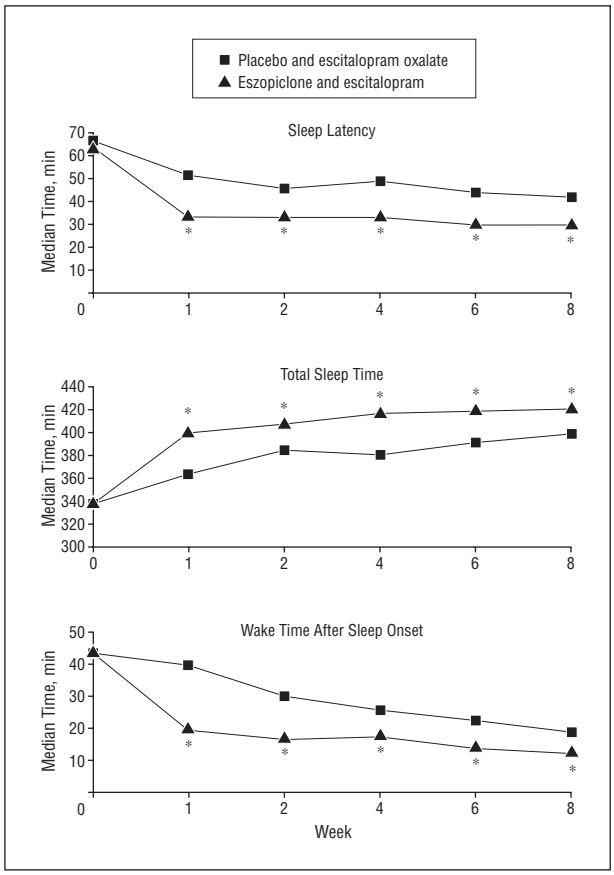

Figure 1. Sleep outcomes in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. * Indicates $P<.001$ compared with placebo (analysis of covariance).

treatment at every point in the double-blind period relative to treatment with placebo and escitalopram ($P<.02$), while CGI-S scores were not significantly different after week 1 (Table 3). Median time to onset of anxiolytic response was reduced in the eszopiclone and escitalopram group compared with the placebo and escitalopram group based on a 50% reduction in HAM-A scores from baseline (29 vs 32 days, respectively; $P=.02$). Furthermore, there was a higher proportion of patients achieving HAM-A remission criteria (42% vs 36%; $P=.09$) by week 8 in the eszopiclone and escitalopram group (**Figure 3**). Total HAM-D scores (including and excluding insomnia items) were significantly improved from baseline in the eszopiclone and escitalopram group relative to the placebo and escitalopram group at weeks 4, 6, and 8 ($P<.05$) (Table 3 and **Figure 4**).

OTHER SUPPORTIVE MEASURES

There were no treatment differences observed in the total Quality of Life Enjoyment Satisfaction Questionnaire or total Sheehan Disability Scale scores (except for the Quality of Life Enjoyment Satisfaction Questionnaire's medication satisfaction item) at any point during the double-blind period ($P>.05$ for all; data not shown).

POTENTIAL PREDICTORS OF TREATMENT RESPONSE

In patients with more severe anxiety at baseline (HAM-A score ≥ the median score of 22), there were significant improvements in mean HAM-A scores with eszopiclone and escitalopram relative to placebo and escitalopram at week 8 (−14.3 vs −12.5, respectively; $P=.01$), whereas in patients with less severe anxiety at baseline (HAM-A score <22), there were no significant differences between treatment groups at week 8 (−9.0 vs −8.5, respectively; $P=.21$). When patients were analyzed by baseline HAM-D score, significant differences in the change in mean HAM-A scores were noted in both strata at week 8 when the eszopiclone and escitalopram group was compared with the placebo and escitalopram group (HAM-D score <16: −11.7 vs −10.8, respectively [$P<.05$]; HAM-D score ≥16: −12.4 vs −10.9, respectively [$P<.01$]). When patients were stratified by age (≤50 years or >50 years), there were no significant differences in HAM-A score by treatment arm in either age category (≤50 years: −11.8 vs −10.9, respectively [$P=.08$]; >50 years: −12.6 vs −10.5, respectively [$P=.1$]). There was some evidence of a treatment × sex interaction, with men in the eszopiclone and escitalopram group displaying significant improvement on HAM-A scores relative to men in the placebo and escitalopram group at week 8 (−12.0 vs −9.6, respectively; $P=.01$) compared

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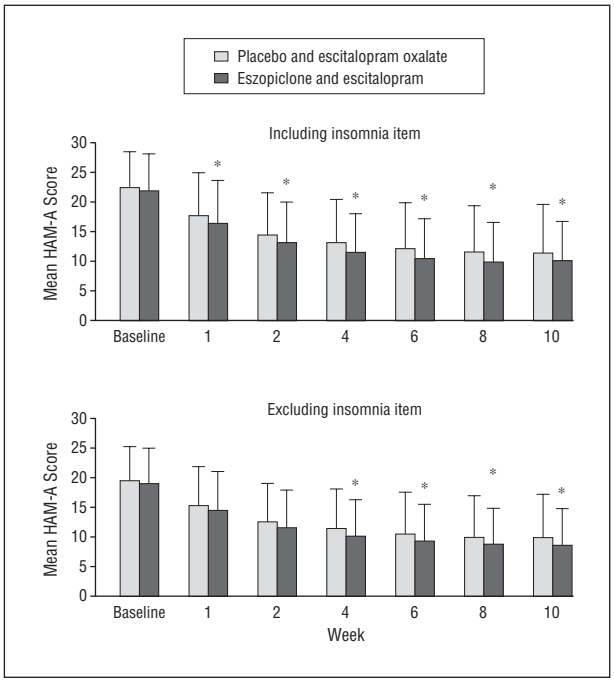

Figure 2. Hamilton Anxiety Scale (HAM-A) scores, including and excluding the insomnia sleep item, in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. Error bars represent SDs. Week 10 was the end of the single-blind run-out period. * Indicates change from baseline $P<.05$ compared with placebo (analysis of covariance).

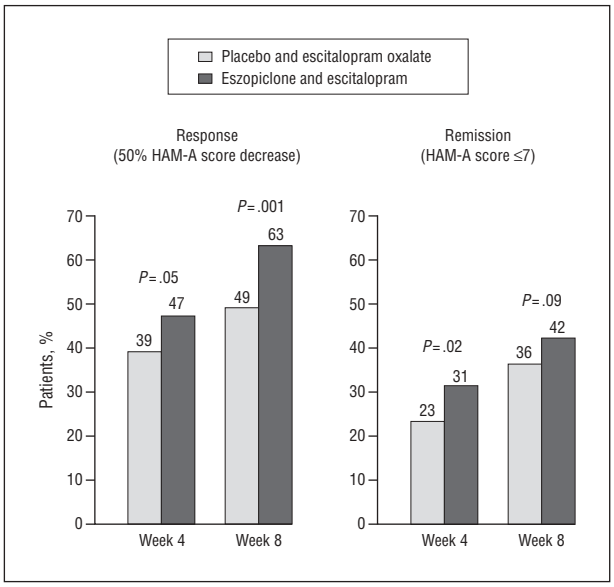

Figure 3. Hamilton Anxiety Scale (HAM-A) response and remission in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. Response based on 50% improvement in HAM-A score from baseline. Remission based on an HAM-A score of 7 or less. *P* values reflect change from baseline using analysis of covariance.

with women (−11.8 for women in the eszopiclone and escitalopram group vs −11.2 for women in the placebo and escitalopram group; $P=.33$). However, neither age, sex, baseline anxiety, nor baseline depression were significant predictors of sleep-related outcomes.

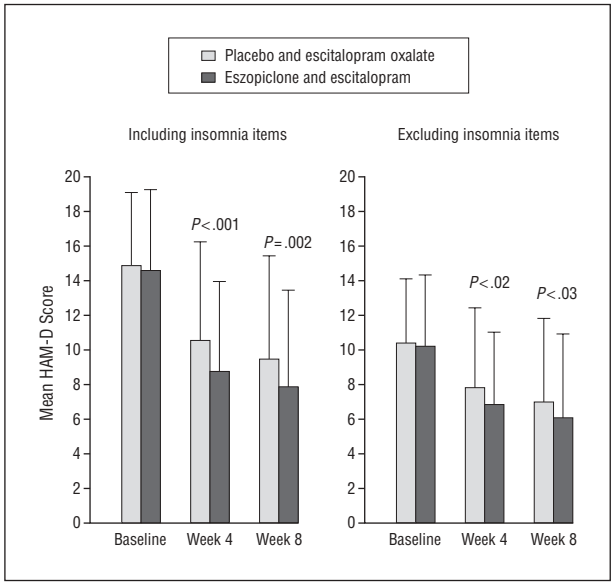

Figure 4. Hamilton Depression 17-item Scale (HAM-D) scores, including and excluding insomnia items, in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. Error bars represent SDs. *P* values reflect change from baseline using analysis of covariance.

DISCONTINUATION PERIOD

Following discontinuation of eszopiclone, there was no evidence of rebound insomnia (defined as a worsening in sleep parameters following discontinuation of treatment compared with baseline) (**Figure 5**), but there were no longer significant treatment differences from those achieved with SSRI monotherapy. In contrast, significant differences between groups on measures of anxiety, including change from baseline HAM-A score (−11.8 in the eszopiclone and escitalopram group vs −11.0 in the placebo and escitalopram group; $P<.05$) and HAM-A responder status (60% vs 51%, respectively; $P<.05$), were maintained at week 10 (Table 3).

TREATMENT SAFETY

There were no systematic treatment group differences in any laboratory test or physical examination finding during the double-blind period. The overall rates of treatment-emergent adverse events were 77.6% in the cotherapy group and 67.9% in the monotherapy group, with unpleasant taste, headache, dry mouth, and somnolence reported more frequently with eszopiclone and escitalopram (**Table 5**). Most adverse events were mild to moderate in both treatment groups, with severe events occurring in 13% of patients randomized to receive eszopiclone and escitalopram and 10% of patients randomized to receive placebo and escitalopram. There were 8 serious adverse events during the study: 5 in the placebo and escitalopram group (ovarian cancer, headache and hypertension, fall with joint dislocation and alcohol withdrawal, cholelithiasis and cholecystitis, and overdose and somnolence) and 3 in the eszopiclone and escitalopram group (asthma, cholelithiasis, and concussion with multiple fractures and loss of consciousness). The investigator considered all of the se-

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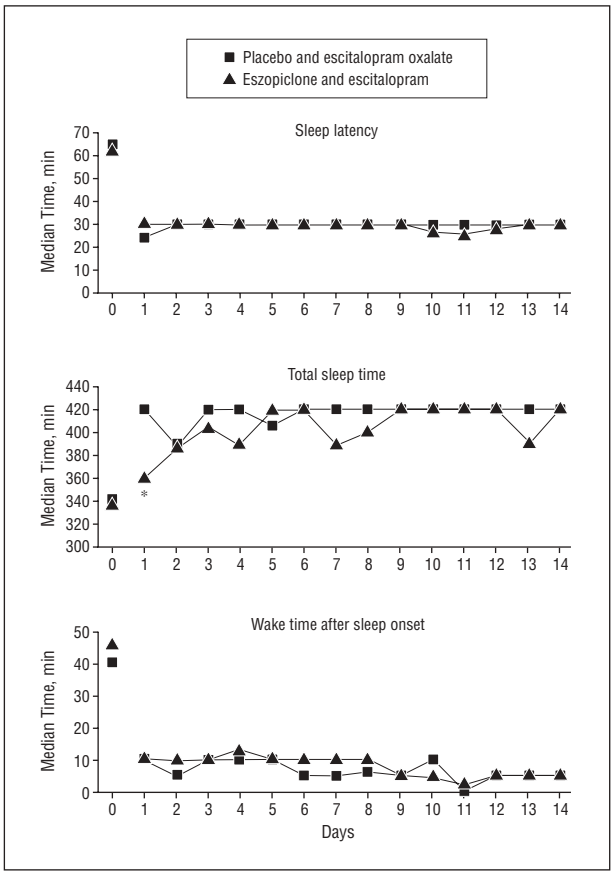

Figure 5. Sleep outcomes during single-blind run-out period in patients with insomnia and comorbid generalized anxiety disorder treated with placebo and escitalopram or eszopiclone and escitalopram. * Indicates change from baseline $P < .05$ vs placebo (analysis of covariance).

rious adverse events in the placebo and escitalopram group to be unrelated to the study drug, except for the overdose and somnolence, and all serious adverse events in the eszopiclone and escitalopram group to be possibly related to the study drug. The patient who experienced a concussion, fractures, and loss of consciousness slipped on a wet floor coming out of the shower in the late afternoon/early evening. The patient was treated in the emergency department, but the event resolved the same day without hospital admission. The patient was 12 days into double-blind eszopiclone and escitalopram treatment when the serious adverse event occurred. There were identical rates of adverse events that led to discontinuation in both groups (5.4%), with no events of unpleasant taste leading to discontinuation and no specific treatment-related pattern of adverse events. Adverse events that led to discontinuation in more than 1 patient included headache (2 patients in the eszopiclone and escitalopram group), somnolence (2 patients in the placebo and escitalopram group), disturbance in attention (2 patients in the placebo and escitalopram group), and anxiety (5 patients in the placebo and escitalopram group). Rates of severe central nervous system adverse events were 4.4% in the eszopiclone and escitalopram group and 3.0% in the placebo and escitalopram group during the double-blind period; rates of all central nervous system adverse events were 3.0% and 3.4%, respectively, during the single-blind run-out period.

Table 5. Adverse Events During the Double-blind Study Period[a]

Adverse Event	Adverse Event Rate, %: Patients Treated With Placebo and Escitalopram Oxolate (n=299)	Adverse Event Rate, %: Patients Treated With Eszopiclone and Escitalopram (n=294)
Overall	67.9	77.6
Unpleasant taste	3.7	24.1
Headache	15.1	19.4
Dry mouth	9.4	15.6
Somnolence	7.4	10.5
Nausea	14.7	10.2
Nasopharyngitis	9.7	9.5
Diarrhea	6.4	7.5
Fatigue	4.0	6.8
Upper respiratory infection	4.0	6.5
Dizziness	4.7	6.5
Decreased libido	2.7	5.4
Upper abdominal pain	5.7	2.4

[a] Adverse event rate of at least 5% in either treatment group.

Table 6. Adverse Events During the Single-blind Run-Out Study Period[a]

Adverse Event	Adverse Event Rate, %: Patients Treated With Placebo and Escitalopram Oxolate (n=235)	Adverse Event Rate, %: Patients Treated With Eszopiclone and Escitalopram (n=233)
Overall	15.7	15.5
Back pain	0.4	2.1
Nasopharyngitis	1.7	1.7
Headache	1.3	1.3
Pharyngolaryngeal pain	0	1.3

[a] Adverse event rate of at least 1% in either treatment group.

Overall adverse events during the single-blind run-out period were similar between groups (15.7% after placebo and escitalopram run-out vs 15.5% after eszopiclone and escitalopram run-out). No single adverse event occurred in either group at a rate greater than 3% (**Table 6**).

COMMENT

To our knowledge, this study represents the first large, double-blind, randomized, clinical trial examining the use of an indicated, targeted treatment for insomnia in conjunction with an SSRI for insomnia comorbid with GAD. The coadministration of eszopiclone and escitalopram was associated with rapid improvement in insomnia by week 1, demonstrated by changes in sleep onset, maintenance, and duration as well as improvements in daytime functioning. Consistent with data from trials with eszopiclone in patients with primary insomnia[27-29] and a study of eszopiclone in insomnia comorbid with major depressive disorder,[26] there was no evidence for the develop-

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ment of tolerance during treatment in this trial nor withdrawal symptomatology during the discontinuation period. Measures of sleep remained improved from baseline following discontinuation of eszopiclone, though they were no longer significantly different from those achieved with SSRI monotherapy. The clinical significance of the improvement in sleep measures is reflected in the significantly greater proportion of patients treated with eszopiclone and escitalopram having no clinically meaningful insomnia (47%) as assessed by the ISI at the end of the double-blind treatment period compared with patients treated with placebo and escitalopram (33%; $P<.001$).

Escitalopram and eszopiclone cotherapy resulted in a greater magnitude and apparent acceleration of anxiolytic effects, demonstrated by reductions in HAM-A and CGI-I scores as early as the first week of treatment, persisting through the 8 weeks of treatment and even after eszopiclone treatment was discontinued. This cotherapy also resulted in increased response rates at weeks 4 and 8 and remission rates at week 4. The time to onset of anxiolytic response was reduced in the eszopiclone and escitalopram group relative to the placebo and escitalopram group based on HAM-A score reduction ($P=.02$; medians of 29 and 32 days, respectively) and CGI-I score ($P=.052$; medians of 18 and 28 days, respectively). These results suggest that targeted treatment of insomnia with eszopiclone along with escitalopram may not only have resulted in improvement in sleep associated with GAD but may also have affected overall anxiolytic response. However, taking into account the sequential testing approach used to guard against multiple comparisons, the finding of faster onset with cotherapy should be viewed as supportive.

Some antidepressants, including clomipramine and SSRIs such as fluoxetine, disturb sleep early in treatment. However, these effects are generally short lived and there are very few significant differences between the drugs after a few weeks of treatment.[38] Patient-reported sleep typically improves after 3 to 4 weeks of antidepressant treatment. For example, in the study of cotherapy for insomnia in individuals with depression by Fava et al,[26] fluoxetine and placebo resulted in improvements in sleep latency, total sleep time, and wake time after sleep onset. Similarly, in the present study in patients with GAD, escitalopram improved sleep. However, there are relatively few systematic studies of the relative effects of different antidepressants on objective sleep parameters, particularly in patients with mood and anxiety disorders, and thus further study is necessary to determine the generalizability of our findings across the different antidepressants.

Our findings relative to GAD end points in the placebo and escitalopram group are consistent with those observed in a previously published 8-week study of escitalopram therapy in patients with GAD.[39] In the current study, the number of patients needed to treat (NNT) to get 1 more individual to achieve responder status with the addition of eszopiclone relative to placebo was 7 and the NNT for remission was 17.

Insomnia is a relatively common treatment-emergent adverse effect in patients with GAD taking an SSRI and may contribute to a reduction in the magnitude of improvement in somatic anxiety scores.[40] In the current study, eszopiclone cotherapy significantly reduced both psychic and somatic anxiety at weeks 6 and 8, improvements that were still present at week 10 after eszopiclone discontinuation. The greater improvement in anxiety, as reflected by reduction in HAM-A scores, persisted even after removal of the insomnia item and achieved significance at week 4, suggesting that targeted insomnia treatment may have contributed to greater overall anxiolysis, perhaps beyond that attributable to both GAD-related and antidepressant-induced sleep disturbance. This finding is consistent with evidence from smaller studies with racemic zopiclone monotherapy in patients with severe insomnia associated with GAD, indicating that the hypnotic drug not only improved all sleep parameters but also had a mild anxiolytic effect that was significantly greater than with 0.5 mg of triazolam[41] or 5.0 mg of nitrazepam.[42] However, the present study evaluated eszopiclone as cotherapy with escitalopram in patients with insomnia comorbid with GAD. The effects of eszopiclone monotherapy in patients with GAD are unknown.

The improvement in sleep, daytime functioning, anxiety, and depression observed in the eszopiclone and escitalopram group was not associated with markedly increased rates of adverse events or any related treatment-discontinuation adverse effects. The rates of adverse events observed in this study are consistent with previous reports of eszopiclone in patients with primary insomnia.[27] We found no evidence of significant withdrawal symptomatology during the period following eszopiclone discontinuation, which parallels reports of eszopiclone use in primary insomnia[28] and insomnia comorbid with major depressive disorder[26] or perimenopause.[43]

In a series of post hoc exploratory analyses to examine potential predictors of response, we did not find evidence of significant interactions with treatment by age, baseline anxiety, or baseline depression. The degree of improvement for patients with lower levels of baseline anxiety were not significantly different between treatment groups, which may reflect a floor effect. We did, however, find a quantitative interaction between treatment and sex, whereby the improvement in anxiety scores for those treated with eszopiclone and escitalopram relative to those treated with placebo and escitalopram was greater in men than in women, though we did not find that sex had a significant effect on sleep outcomes. The significance of the sex interaction is unclear. One of the few studies looking at the relationship of sex and GAD found no sex by treatment interaction on improvement in anxiety as assessed by HAM-A and CGI-I. However, the authors did note that women had an earlier age at onset and more somatic anxiety symptoms compared with men.[44] In contrast, in the open phase of another treatment study in patients with GAD, women had a significantly poorer overall response to fluoxetine than men,[45] though sex alone was no longer a significant predictor of response after adjusting for age at onset of GAD. However, in the present study, we did not systematically obtain data on age at onset of GAD or other factors, such as hormonal status, that may be relevant to understanding our results.[46] Furthermore, the relationship of sleep with anxiety may be different in men and women and influence the nature of the findings observed here. Attention to these issues in the design of future studies would be valuable to examine these relationships in more detail.

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Though it is possible that unblinding may have occurred in some individuals owing to the differential occurrence of unpleasant taste in the eszopiclone and escitalopram group (24.1% vs 3.7% with placebo and escitalopram), most patients did not experience this adverse effect, and the sleep and anxiety results for patients not experiencing this were consistent with the results of the entire patient population (data not shown). Our study did not include objective measures of sleep, such as polysomnography. However, patient-reported sleep is generally used for diagnosis and outcome assessment in clinical practice and may arguably be more relevant for practitioners.

The results of this study are consistent with the findings of Fava et al,[26] which demonstrated rapid improvement in insomnia and a quicker and greater magnitude of antidepressant response in patients with depression and insomnia receiving cotherapy of eszopiclone and fluoxetine compared with an SSRI and placebo. However, there were some notable differences between our study and theirs. In our study, the improvement in sleep with eszopiclone occurred early and was then maintained, whereas in their patients with major depressive disorder, improvements in sleep occurred early and continued to gradually increase during the 8-week, double-blind period. Additionally, the therapeutic advantage of eszopiclone cotherapy over SSRI monotherapy in treating sleep found during the double-blind period was maintained during the single-blind run-out period in the depression study,[24] but not in our study. The reasons for these differences are unclear. Evidence suggests that insomnia has a different relationship to GAD than it does to major depressive disorder when it occurs comorbidly.[7,19,20] However, it appears that, at least in the short-term, maintaining the additional sleep benefit of eszopiclone cotherapy may require continued coadministration in patients with GAD but not necessarily in patients with depression.

Residual insomnia is associated with increased rates of relapse in major depression,[47] though this relationship has not been specifically tested in GAD. It is not known whether the effect of eszopiclone cotherapy on depressive and anxiety end points in the comorbid depression study[26] and the current study is specific to eszopiclone or whether it may occur with other hypnotic drugs as well. However, a recently reported study of GAD treated with extended-release zolpidem and escitalopram did not find differences between treatment groups for improvement in anxiety symptoms.[48] Whether or not targeted treatment of insomnia may decrease rates of relapse for patients with GAD responding to anxiolytic therapy warrants further investigation.

In summary, we found that eszopiclone cotherapy significantly improved sleep with no evidence of tolerance in patients with comorbid insomnia and GAD compared with escitalopram monotherapy. In addition, the improvements in sleep noted in the cotherapy group occurred in conjunction with significantly greater improvements in measures of anxiety and mood. Abrupt withdrawal of eszopiclone did not result in rebound insomnia nor other withdrawal effects, though the additional benefits on sleep were not maintained during the run-out period. Lastly, 8 weeks of nightly eszopiclone treatment administered with escitalopram was generally well tolerated.

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