Improved Insomnia Symptoms and Sleep-Related Next-Day Functioning in Patients With Comorbid Major Depressive Disorder and Insomnia Following Concomitant Zolpidem Extended-Release 12.5 mg and Escitalopram Treatment: A Randomized Controlled Trial

Maurizio Fava, MD; Gregory M. Asnis, MD; Ram K. Shrivastava, MD; Bruce Lydiard, MD, PhD; Bijan Bastani, MD; David V. Sheehan, MD, MBA; and Thomas Roth, PhD

Objective: This investigation was performed to assess the efficacy and safety of zolpidem extended-release in patients with insomnia associated with major depressive disorder (MDD).

Method: Patients (N = 385) received open-label escitalopram 10 mg/d and were randomized to concomitant zolpidem extended-release 12.5 mg/night or placebo for 8 weeks (phase 1) in a randomized, parallel-group, multicenter trial. Responders (≥ 50% in 17-item Hamilton Depression Rating Scale [$HDRS_{17}$] score) continued 16 weeks of double-blind treatment (phase 2); escitalopram only was given during a 2-week run-out period. The study was conducted between February 2006 and June 2007. The primary efficacy measure was change from baseline in subjective total sleep time. Secondary efficacy measures included subjective sleep-onset latency, number of awakenings, wake time after sleep onset, sleep quality, sleep-related next-day functioning, $HDRS_{17}$, Sleep Impact Scale score, Patient and Clinical Global Impressions of Insomnia Treatment, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Adverse events were recorded throughout the study; sleep measures were also evaluated during the run-out period.

Results: Throughout phase 1, zolpidem extended-release led to significantly greater improvements in total sleep time ($P < .0001$), wake time after sleep onset, sleep onset latency, number of awakenings, and sleep quality ($P \leq .0003$), and some measures of sleep-related next-day functioning but not in depressive symptoms or quality of life. During phase 2, improvements with the zolpidem extended-release/escitalopram group occurred for total sleep time (significant [$P < .05$] at weeks 12 and 16), as well as for a few other secondary efficacy measures but not in depressive symptoms or quality of life. The most common adverse events associated with combination treatment included nausea, somnolence, dry mouth, dizziness, fatigue, and amnesia.

Conclusions: Zolpidem extended-release administered concomitantly with escitalopram for up to 24 weeks was well tolerated and improved insomnia and some sleep-related next-day symptoms and next-day functioning in patients with MDD but did not significantly augment the antidepressant response of escitalopram.

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Corresponding author: *Maurizio Fava, MD, MGH Clinical Trials Network and Institute, Massachusetts General Hospital, 55 Fruit St, Bulfinch 351, Boston, MA (MFava@Partners.org).*

Patients with major depressive disorder (MDD) experience feelings of worthlessness, fatigue, and diminished ability to concentrate and commonly complain of insomnia, including difficulty falling asleep, maintaining sleep, awakening early, and experiencing nonrestorative sleep. Previous studies have estimated insomnia complaints to occur in up to 90% of patients with MDD,[1,2] but more recent reviews have reported this number around 35%.[3] Approximately 76% and 80% of patients with MDD experience difficulty initiating and maintaining sleep, respectively.[4] Conversely, among patients with insomnia, 29.4% suffer from MDD.[5] One community-based survey found that patients with insomnia were nearly 10 times more likely to also have clinically significant depression.[6] Chronic insomnia may contribute to MDD[7–9] by increasing its risk[8,10–12] and likelihood of relapse.[5] Moreover, insomnia is among the most common residual symptoms of MDD, and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) and other antidepressants can cause insomnia.[13] Sleep disturbances marked by sleep maintenance symptoms are prominent in patients with MDD[3,14]; the strong association between these disturbances and later MDD onset suggests that they may represent prodromal symptoms and/or contribute to its onset.[11]

Rather than treating insomnia as a symptom of MDD, it is now recommended that each condition be treated independently.[9] Until recently, there has been a paucity of data on the use of both benzodiazepine and nonbenzodiazepine hypnotic agents in the treatment of patients with insomnia and a comorbid psychiatric disorder. Studies conducted over the past few years have shown positive results with escitalopram and either zolpidem extended-release or eszopiclone in patients with insomnia and generalized anxiety disorder[15,16] and for fluoxetine and eszopiclone in patients with combined insomnia and MDD.[17] Data from 1 study in patients with comorbid MDD showed a median sleep onset latency of 125.4 minutes at baseline compared with 30 minutes after 8 weeks of combination therapy with eszopiclone and fluoxetine and 45.5 minutes in patients receiving placebo and fluoxetine.[17]

A number of investigations have demonstrated that zolpidem extended-release is safe and effective in the treatment

of patients with insomnia. In one 3-week, double-blind, randomized, placebo-controlled trial, adult patients with primary insomnia who took nightly zolpidem extended-release experienced significant improvements on polysomnographic measures of sleep induction (sleep onset latency) and sleep maintenance (number of awakenings and wake time after sleep onset).[18] A separate 24-week, randomized, placebo-controlled investigation in patients with primary insomnia showed that zolpidem extended-release taken 3 to 7 nights/wk improved sleep induction and maintenance for up to 6 months, based on subjective patient reports.[19] This evidence suggests that short- and long-term administration of zolpidem extended-release relieves both sleep-onset and sleep-maintenance symptoms of insomnia. Other data indicate a lack of significant drug-drug interaction when zolpidem is administered concomitantly with SSRIs, with no clinically significant changes detected in pharmacokinetic parameters.[20,21]

The goal of this study was to evaluate the effect on insomnia of nightly therapy with zolpidem extended-release 12.5 mg/night administered concomitantly with escitalopram 10 mg/d to patients with MDD and insomnia. Other sleep-related measures examined were sleep-related next-day functioning, cognitive and physical functioning, quality of life (QoL), and possible rebound effects. The potential effect of combination zolpidem extended-release/escitalopram on depressive symptoms was also evaluated.

METHOD

Patients

Men and women between the ages of 21 and 64 years, inclusive, were eligible to participate if they met criteria for MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[1] and structured psychiatric interview, using the Mini International Neuropsychiatric Interview.[22] Other inclusion criteria were (1) sleep disturbances occurring ≥ 3 nights per week for ≥ 4 weeks prior to study entry; (2) total sleep time < 6.5 hours and/or sleep onset latency > 30 minutes on ≥ 3 of the 7 nights 1 week prior to randomization, based on results of the specifically designed Morning Sleep Questionnaire (MSQ) during screening[23]; (3) a score between 6 and 15, inclusive (to target mild to moderate MDD), on the 16-item Quick Inventory of Depressive Symptomatology Self-Report ($QIDS\text{-}SR_{16}$)[24]; and (4) newly diagnosed MDD or the demonstration of symptoms of relapse/recurrence during a period of no antidepressant medication for depression. Reproductive-age females were required to have a negative urine pregnancy test prior to randomization and had to use acceptable methods of contraception (steroidal contraceptive/double-barrier/intrauterine device) throughout the study. Patients receiving long-term medication regimens were required to have been stabilized for ≥ 28 days prior to screening.

Patients were excluded from participation if they had a current episode of MDD that was "severe," "severe with psychotic features," that required hospitalization, or if their current MDD followed a history of suicidal attempts or if they had "active" suicidal ideation. Also excluded were pregnant/lactating women and patients with a history of mania, manic episode, bipolar disorder, a primary sleep disorder (ie, sleep apnea, restless leg syndrome, night terrors), myasthenia gravis, history of alcoholism or drug addiction, drug abuse (including alcohol) within the past 24 months, or a positive urine drug screen for drugs of addiction or compounds that would interfere with assessment of a hypnotic agent. Persons who reported shift work or a requirement for a regular change in sleep schedule of ≥ 6 hours during the prior 28 days were excluded, as were patients taking a benzodiazepine or SSRI for > 2 days within the 28 days before randomization and patients with a known allergy or hypersensitivity to escitalopram or zolpidem or a prior failure to respond to escitalopram for depression. Finally, patients were ineligible if they had any untreated, clinically significant renal, endocrine, gastrointestinal, hepatic, respiratory, cardiovascular, neurologic, hematologic, oncologic, immunologic, or cerebrovascular disease, malignancy, or abnormal prestudy laboratory values requiring intervention.

During the study, use of prescription/nonprescription drugs/herbal therapies with sedative effects for the purpose of inducing sleep or relieving jet lag was not permitted. The regular use of benzodiazepines, anxiolytics, and antidepressants except escitalopram was also prohibited. Nonsedating antihistamines were recommended for patients who required medication for allergies. Other concomitant therapies considered necessary by the investigator and not specifically disallowed by the protocol were permitted.

Study Design

This was a 24-week, 2-phase, double-blind, randomized, parallel-group, placebo-controlled investigation to assess efficacy and safety of zolpidem extended-release for reduction of insomnia symptoms in patients with MDD and insomnia. The study was conducted at 41 centers in the United States between February 15, 2006, and June 28, 2007. The protocol and its amendments were in compliance with Good Clinical Practices and recommendations of the 18th World Health Congress[25] and were approved by the institutional review board at each site. All patients provided written informed consent prior to participating in study-related procedures. The study was registered at clinicaltrials.gov (NCT00296179).

Patients were screened for eligibility for 7 ± 2 days. Initially, all participants underwent a physical examination with vital signs (respiration rate, systolic/diastolic blood pressures, and heart rate), medical history, medication review, laboratory testing, urinalysis, urine drug screen, and urine pregnancy test, if applicable. A sleep history was obtained, a psychiatric interview was conducted, and the patients completed the self-rated $QIDS\text{-}SR_{16}$. Patients who continued to meet eligibility criteria were instructed on how to complete the MSQ via an interactive voice response system and told to complete the MSQ daily for approximately 7 days before

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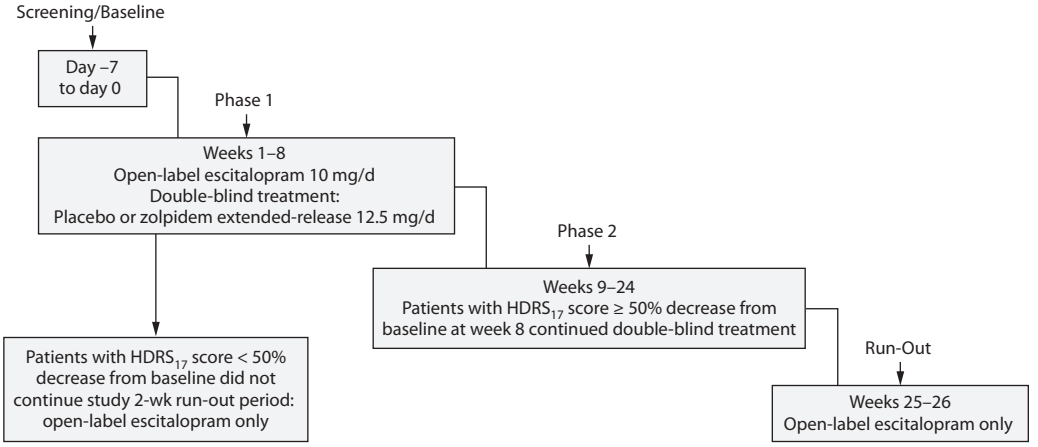
Figure 1. Study Design



Abbreviation: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

the baseline visit. At the baseline visit, laboratory, urinalysis, urine drug screen, and screening period MSQ data were used to determine eligibility. Because some benzodiazepines have a long half-life, patients whose urine drug screen was positive for benzodiazepines but met all other entry criteria could continue completing the MSQ and undergo a second urine drug screen 7 days later.

Patients were randomly assigned to a treatment group based on a nonstratified, 4-per-block randomization schedule generated by the study sponsor. Using a centralized interactive voice response system operated by the ClinPhone Group (Perceptive Infomatics, Waltham, Massachusetts), patients were assigned in a 1:1 ratio to receive adjunctive double-blind treatment with nightly zolpidem extended-release 12.5 mg or matching placebo. All patients received open-label escitalopram 10 mg (based on previous research),[26] to be taken each morning. During phase 1, patients returned to the clinic for safety and efficacy assessments at weeks 2, 4, 6, and 8 and were to complete the MSQ daily; during phase 2, clinic assessments were carried out at weeks 12, 16, 20, and 24, and the MSQ was to be completed ≥ 2 representative days/wk. A 2-week run-out period occurred, when patients took only open-label escitalopram, after randomized treatment was finished at the end of phase 1 for patients not continuing on to phase 2, or at the end of phase 2 (Figure 1).

Assessments

Primary efficacy measure. The primary efficacy measure was change from baseline in total sleep time at week 8, based on item 5 of the MSQ ("How long did you sleep last night?"), a 9-item self-administered questionnaire. The week 8 total sleep time value was the mean of values obtained between weeks 6 and 8.

Secondary efficacy measures. Secondary core sleep measures derived from the MSQ included total sleep time at all other study time points, sleep onset latency, number of awakenings, wake time after sleep onset, and sleep quality graded on a 4-point scale from excellent (score = 1) to poor (score = 4). Core sleep measures were also derived from the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), a clinician-rated scale that measures the severity of each depression-related symptom and that contains 3 insomnia-related items,[27] and the Patient Global Impression of Insomnia Treatment (PGI-IT) scale, a 5-item, patient-completed scale that evaluates patient opinions about an insomnia treatment over the last week, including treatment helpfulness to sleep, sleep latency, total sleep time, sleep quality, and medication strength.[28,29]

Measures of sleep-related daytime symptoms were derived from the MSQ and included morning concentration ability (scale: 1 = excellent to 4 = poor), morning energy (scale: 1 = high to 3 = low), and impact of sleep on daily activities (scale: 1 = not at all to 5 = could not do any work); the Sleep Impact Scale (SIS), a self-administered, 35-item questionnaire that assesses the effect of sleep problems over the last 2 weeks on 7 domains of functioning (daily activities, emotional well-being, emotional impact, energy/fatigue, social well-being, mental fatigue, and satisfaction with sleep), each calculated from ratings (on a 5-point Likert scale) assessing how much particular activities or feelings were affected by sleep problems[30]; the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH-CPFQ),[31] a self-administered 7-item questionnaire that assesses physical and cognitive functioning, graded on a 6-point scale, ranging from "greater than normal" (a score of 1) to "totally absent" (a score of 6); and the Health Care Resource Utilization (HRU) form,[32] which quantifies the use of health care services related to insomnia or anxiety and daily productivity over the past week, via reporting of time lost from daily activities, social activities, work, and school; productivity while at work and school; the amount/number of health care resources used; and number of caregiver hours used.

Depression was assessed by the $HDRS_{17}$ and a major depression symptom review, wherein an interviewer marks the presence or absence of each of the 9 MDD criteria listed

in the *DSM-IV-TR* and indicates whether the patient met criteria for the presence of at least 5 symptoms, with 1 being either "depressed mood" or "loss of interest or pleasure." Depression treatment response was defined as categorical values indicating whether or not the patient showed 50% or greater reduction from baseline on the $HDRS_{17}$ total score at each visit. This was calculated for patients in phase 1. All patients who entered phase 2 had treatment response at week 8. Remission of depression was defined as an $HDRS_{17}$ total score ≤ 7. Depression relapse was defined as a categorical variable indicating whether a patient had relapsed at each visit in phase 2. A patient was considered "relapsed" if 1 or both of the following occurred: the patient had 5 or more symptoms from the major depression symptom review, and at least 1 of these was "depressed mood" or "loss of interest or pleasure" and/or the patient had an $HDRS_{17}$ score that was greater than or equal to his or her baseline value.

Overall functioning and QoL were evaluated by the Clinical Global Impressions (CGI)-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). The CGI has 2 components that measure clinician judgments about patient's mental illness.[33] The CGI-S is a global judgment of the current severity of mental illness, rated on a scale of 1 (normal) to 7 (most extremely ill). The CGI-I is a global judgment about how much improvement occurred since inclusion in the study, rated on a scale of 1 (very much improved) to 7 (very much worse). CGI-I was to be rated without regard to the clinician's judgment whether improvement was due to the study treatments. The Q-LES-Q, a patient-rated instrument, was measured using a scale from 1 (lowest satisfaction/participation) to 5 (highest level). The scale yields scores in the following: physical health/activities, feelings, work, household duties, school/course work, leisure time activities, social relations, and general activities.[34]

Safety measures. Safety was evaluated based on adverse event reporting coded by the Medical Dictionary for Regulatory Activities,[35] version 8.1 codes. The intensity (mild, moderate, severe) of each adverse event and relationship to the study drug were noted. Also examined were laboratory results, physical examination, vital signs, and sleep characteristics measured by the MSQ during the 2-week run-out.

Schedule of assessments. At the baseline visit, investigators reviewed screening data from the MSQ, conducted a physical examination with vital signs, reviewed concomitant medications, and completed the $HDRS_{17}$ and CGI-S; patients completed the MGH-CPFQ, Q-LES-Q, HRU, and SIS. During phase 1 (weeks 1 through 8), the MSQ was completed daily (between 5 AM and 1 PM via interactive voice response system or interactive Web response system); during phase 2 (weeks 9 through 24) it was completed twice weekly, and it was completed daily during the run-out periods (weeks 9 and 10; weeks 25 and 26). During visits at weeks 2, 4, 6, 8, 12, 16, 20, and 24, investigators completed the $HDRS_{17}$, CGI-S, and CGI-I, while patients completed the PGI-IT and HRU; the MGH-CPFQ, SIS, and Q-LES-Q were completed at each visit except at weeks 2 and 6. At all visits, the use of concomitant medications was recorded, and patients were queried about adverse events, which could be reported at any time. Major depression symptom review was completed only during phase 2. Drug accountability was measured at week 26. At final study evaluation at week 26 or early discontinuation, investigators conducted a physical examination, vital signs, obtained samples for laboratory testing and urinalysis, and completed the $HDRS_{17}$, CGI-I, and the major depression symptom review; patients completed the MGH-CPFQ, SIS, and Q-LES-Q.

Statistical Analysis

Sample size determination. Using means and SDs determined in prior clinical studies with zolpidem extended-release, it was estimated, that 130 patients per treatment arm were required to have 90% power to detect a difference between treatment groups using a 2-sided *t* test when $\alpha = .05$ in order to achieve a 27-minute difference between treatment groups in mean change in total sleep time from baseline to week 8 (with SD = 67 minutes for the placebo arm and SD = 64.5 minutes for active treatment). Assuming that 48.7% of patients would fail screening and that 30.9% of patients would discontinue prior to study completion, it was estimated that 735 patients would need to be screened to randomize 377 patients and obtain 260 patients.

General overview. Descriptive statistics were evaluated within study phases for each treatment arm and visit for the intent-to-treat (ITT) and per-protocol populations. Inferential analyses were also performed using these populations within both phases. Analysis of covariance (ANCOVA) was used to examine treatment effects for all continuous efficacy variables while adjusting for sex and baseline values. Differences between treatment means and 95% confidence intervals were calculated via least squares mean.

Normality of the primary end point, total sleep time, and certain secondary end points (ie, sleep latency, number of awakenings, and wake time after sleep onset) were determined by visual inspection of histograms. If data deviated from normal distribution, either appropriate transformation of data was performed or Mann-Whitney tests were utilized. Missing data values were assigned using last observation carried forward (LOCF) for the primary efficacy analysis and most secondary analyses, except that baseline values were not carried forward into the randomized treatment period. For analyses involving both the randomized treatment and follow-up periods, LOCF was utilized within each period, but values were not carried forward across the 2 periods. For categorical efficacy variables, the Mantel-Haenszel test was performed to evaluate treatment effects while controlling for sex.

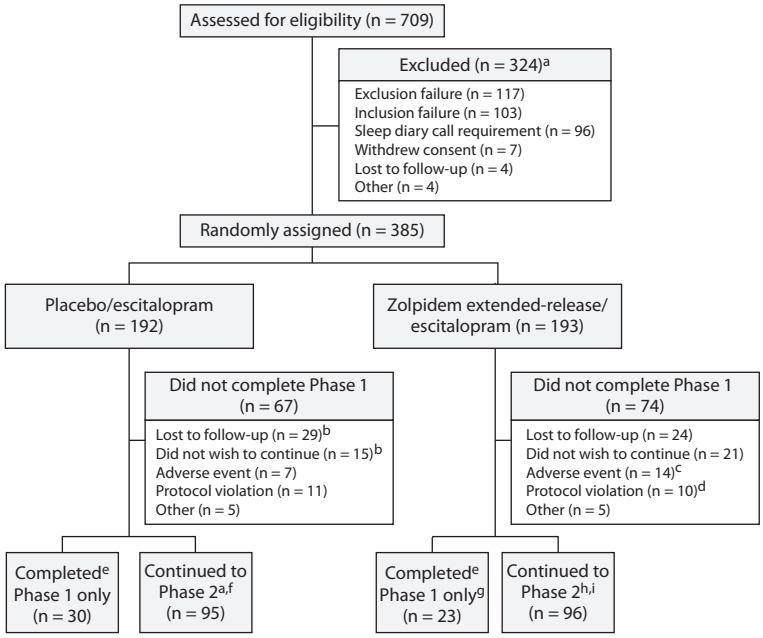
Primary efficacy analysis. Change from baseline to week 8 in total sleep time was examined in the ITT population using an ANCOVA model with treatment group and sex as fixed effects and baseline total sleep time as the covariate. Primary analysis was performed on the ITT population while supporting analysis was performed on the per-protocol population. All missing values were imputed via LOCF.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (ITT)

Characteristic	Phase 1		Phase 2	
	Placebo/Escitalopram (n = 190)	Zolpidem Extended-Release/ Escitalopram (n = 190)	Placebo/Escitalopram (n = 94)	Zolpidem Extended-Release/ Escitalopram (n = 93)
Demographic				
Age, mean (SD), y[a]	43.0 (11.2)	42.9 (12.0)	43.6 (11.1)	43.6 (11.6)
Gender, n (%)[a]				
Male	69 (36.3)	70 (36.8)	33 (35.1)	29 (31.2)
Female	121 (63.7)	120 (63.2)	61 (64.9)	64 (68.8)
Race, n (%)[a]				
White	140 (73.7)	142 (74.7)	76 (80.9)	75 (80.6)
African American	32 (16.8)	32 (16.8)	9 (9.6)	14 (15.1)
Asian	3 (1.6)	3 (1.6)	0 (0.0)	1 (1.1)
Multiracial	2 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)
Other	13 (6.8)	13 (6.8)	8 (8.5)	3 (3.2)
Weight, mean (SD), kg[a]	85.8 (21.0)	83.5 (20.0)	86.0 (22.0)	86.9 (20.9)
Height, mean (SD), cm[a]	168.4 (10.6)	169.0 (9.6)	167.8 (11.3)	168.5 (9.2)
Clinical				
QIDS score, mean (SD)	12.6 (2.4)	12.6 (2.4)[a]	12.1 (2.6)	12.5 (2.4)
Sleep history				
Sleep < 6.5 h, n (%)[a,b]	187 (98.4)	180 (94.7)	92 (97.9)	89 (95.7)
Sleep onset latency > 30 min, n (%)[a,b]	178 (93.7)	163 (85.8)	88 (93.6)	80 (86.0)
Snoring, n (%)	68 (35.8)	50 (26.3)	37 (39.4)	29 (31.2)[a]
Nighttime breathing pauses/ gasping/choking, n (%)[a]	7 (3.7)	2 (1.1)	4 (4.3)	1 (1.1)
Uncomfortable leg sensations prior to falling asleep, n (%)	20 (10.5)	8 (4.2)[c]	6 (6.4)	2 (2.2)[a]

[a]Not significant; $P > .05$ versus placebo, based on 1-way analysis of variance methods for interval variables or χ^2 tests for categorical variables.
[b]≥ 3 nights/wk over the last 4 weeks.
[c]$P = .0292$ from Fisher exact test.
Abbreviations: ITT = intent-to-treat, QIDS = Quick Inventory of Depressive Symptomatology.

Figure 2. Patient Disposition: Phase 1



[a]A patient could fall into more than 1 category of reason for exclusion.
[b]Two patients were eligible for continuation to phase 2 at week 8 but did not continue or return for the final phase 1 follow-up visit.
[c]One additional patient completed investigational product and completed the study but discontinued escitalopram because of an adverse event.
[d]One patient was eligible for phase 2 at week 8 but did not comply with the study medication regimen or return for the final phase 1 follow-up visit.
[e]Patients who completed phase 1 visits through the follow-up visit at week 10.
[f]One patient was not eligible for phase 2 but inadvertently entered into phase 2.
[g]One patient was eligible for phase 2 at week 8 but did not wish to continue into phase 2; this patient completed phase 1 only.
[h]Patients were eligible for phase 2 if they had a depression treatment response at week 8. Depression treatment response was defined as a ≥ 50% decrease from baseline in 17-item Hamilton Depression Rating Scale total score.
[i]Two patients were not eligible for phase 2 but inadvertently entered into phase 2.

Secondary efficacy analyses. To evaluate treatment effects based on continuous secondary efficacy variables, an ANCOVA model similar to that used for the primary efficacy analysis was employed. For categorical variables, separate Mantel-Haenszel tests were performed, with sex effects controlled for.

Safety analyses. Data derived from the safety population, (patients who took at least 1 dose of study drug in phase 1) were used to evaluate safety. Frequency distributions of adverse events by treatment arm were generated. Adverse event intensity was graded as mild, moderate, or severe, and relationship to study drug was indicated by the investigator.

RESULTS

Study Population, Patient Disposition, and Treatment Compliance

Baseline demographic and clinical characteristics of study participants (phase 1 and phase 2) are summarized in Table 1. Treatment groups were demographically and clinically similar at baseline. No notable differences were seen between the groups with regard to MDD or most insomnia symptoms at screening. A total of 65.1% of patients in the placebo/escitalopram group and 61.7% of patients in the zolpidem extended-release/escitalopram group completed phase 1 of the trial (Figure 2); 63.2% and 69.8% of patients completed phase 2, respectively. The most common reason for discontinuation was "lost to follow-up" in both groups and phases. There were no statistically significant differences in treatment adherence/compliance between the groups ($P > .05$ for all comparisons), with compliance defined as the percentage of placebo/escitalopram and zolpidem extended-release/escitalopram ingested by patients as determined by tablet counts. Mean and median compliance in both groups and phases was between 91% and 98%.

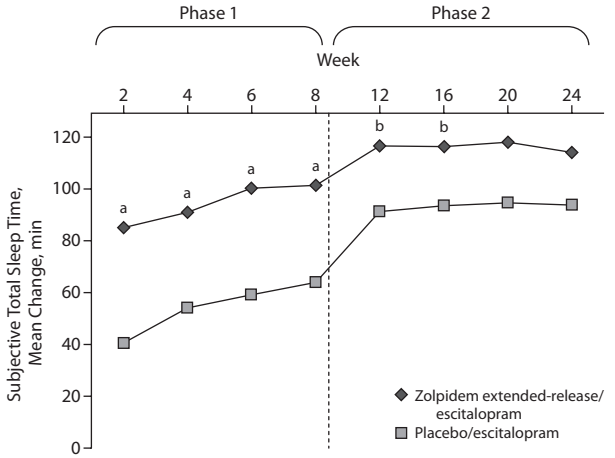
Phase 1 Findings: Primary Efficacy Analyses

Total sleep time. Mean total sleep time at baseline was similar between the placebo/escitalopram (300.2 minutes) and zolpidem extended-release/escitalopram groups (304.0 minutes). Treatment with zolpidem extended-release/escitalopram resulted in significantly greater improvement in total sleep time in MDD patients with insomnia than did treatment with placebo/escitalopram. The difference between treatment groups was statistically significant at each assessment point during phase 1 (Figure 3). The least squares mean difference between the treatment groups in the change from baseline total sleep time ranged from 37.9 to 45.5 minutes ($P < .0001$ for all comparisons). The zolpidem extended-release/escitalopram group at week 8 had a total sleep time of approximately 7 hours.

Phase 1 Findings: Secondary Efficacy Analyses

Other sleep characteristics. The zolpidem extended-release/escitalopram group reported statistically significant improvements in sleep characteristics measured by the MSQ: sleep onset latency, wake time after sleep onset, number of awakenings, and sleep quality (Figure 4A–4D). Mean sleep onset latency (108.0 vs 94.1), wake time after sleep onset (73.4 vs 78.3), number of awakenings (2.4 vs 2.3), and sleep quality (2.8 for both) at baseline were similar between the placebo/escitalopram and zolpidem extended-release/escitalopram groups, respectively. The differences between treatment groups were statistically significant at all time points during phase 1 (all P values $< .001$). Total improvement in insomnia-only $HDRS_{17}$ items was also significantly greater ($P < .001$ for all) in the zolpidem extended-release/escitalopram group throughout phase 1.

Figure 3. Mean Change From Baseline in Total Sleep Time, ITT Phase 1 (n = 380) and Phase 2 (n = 187)

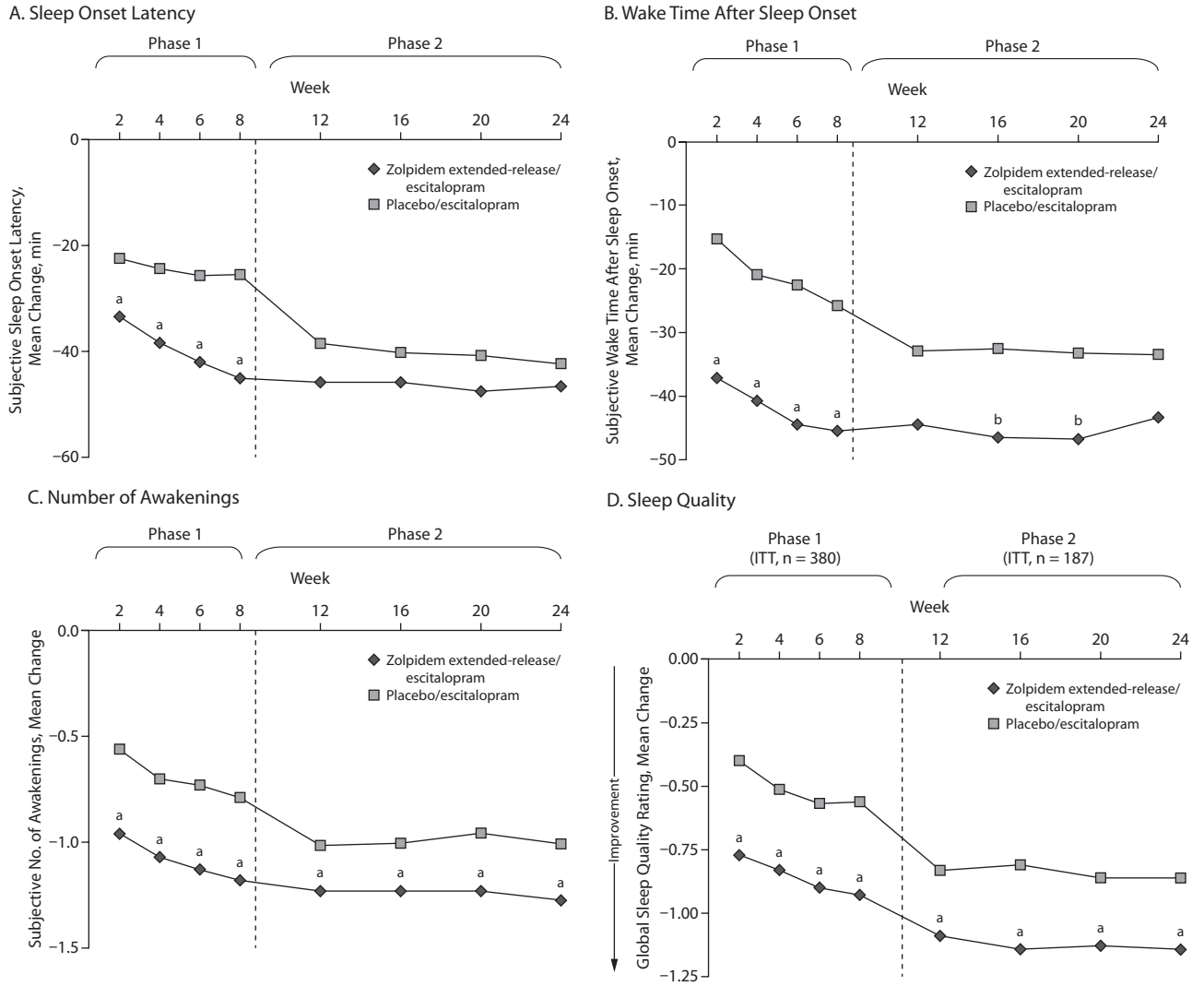


[a]$P < .0001$ versus placebo, based on analysis of covariance (ANCOVA) model.
[b]$P < .05$ versus placebo, based on ANCOVA model.
Abbreviation: ITT = intent to treat.

Next-day functioning. Evaluation of SIS responses at week 8 (Table 2) revealed statistically significant differences ($P < .05$) favoring zolpidem extended-release/escitalopram on all of the SIS domain scores except mental fatigue. While there were no significant differences at week 8 between the 2 groups in the degree of improvement in functioning and QoL on the Q-LES-Q (with the exception of household duties assessments), there were significantly greater improvements with zolpidem extended-release/escitalopram in the MGH-CPFQ total score, wakefulness/alertness, energy, memory/recall, and mental acuity but not in motivation/enthusiasm, attention focus/sustain, or ability to find words, compared with the placebo/escitalopram group ($P < .05$). Additionally, treatment with zolpidem extended-release/escitalopram was associated with significantly greater improvements in some aspects of sleep-related next-day functioning, specifically morning energy, sleep impact on daily activities, and morning concentration ability than placebo/escitalopram (Figure 5A–5C).

Depressive symptoms. Mean $HDRS_{17}$ score at baseline was similar between the placebo/escitalopram (21.0) and zolpidem extended-release/escitalopram groups (20.7). Decreases from baseline $HDRS_{17}$ total scores were comparable throughout phase 1 (Figure 6). By the end of phase 1, 58.4% and 63.7% of patients in the placebo/escitalopram and zolpidem

Figure 4. Mean Change From Baseline in Subjective (A) Sleep Onset Latency, (B) Wake Time After Sleep Onset, (C) Number of Awakenings, and (D) Sleep Quality



[a]$P \leq .001$ versus placebo/escitalopram, based on analysis of covariance (ANCOVA) model.
[b]$P < .05$ versus placebo/escitalopram based on ANCOVA model.
Abbreviation: ITT = intent-to-treat.

extended-release/escitalopram groups, respectively, met the criteria for depression treatment response (≥ 50% reduction from baseline $HDRS_{17}$ total score). The difference between groups was not statistically significant ($P = .2889$). While a greater number of patients in the zolpidem extended-release/escitalopram group were responders at each of the other visits (weeks 2, 4, and 6; data not shown), differences were not statistically significant ($P > .05$ for all). Further, at the end of phase 1, 45.0% and 54.5% of patients in the placebo/escitalopram and zolpidem extended-release/escitalopram groups, respectively, met the criteria for depression treatment remission ($HDRS_{17}$ total score ≤ 7).

PGI-IT. Mean PGI-IT at baseline was similar between the placebo/escitalopram and zolpidem extended-release/escitalopram groups (~ 4.1 for both). The zolpidem extended-release/escitalopram group rated their insomnia treatment significantly superior ($P < .0001$) to the placebo/escitalopram group at all visits in phase 1, including week 8 (Figure 7), in concordance with their improved sleep characteristics.

CGI-S and CGI-I. The severity of mental illness (evaluated via CGI-S) and global improvement of mental illness (assessed by CGI-I) were comparable between treatment groups throughout phase 1. At week 8, mean CGI-I ratings for the zolpidem extended-release/escitalopram and placebo/escitalopram groups were 2.45 and 2.54, respectively. These differences were not statistically significant.

Phase 2 Findings: Primary Efficacy Analyses

Total sleep time. Mean total sleep time at baseline was similar between the placebo/escitalopram (313.8 minutes) and zolpidem extended-release/escitalopram groups (311.8 minutes). Although the mean total sleep time difference between the zolpidem extended-release/escitalopram group and the placebo/escitalopram group was smaller in phase 2

Table 2. Mean Change From Baseline in the SIS, MGH-CPFQ, and Q-LES-Q During Phases I and II (ITT)[a]

	Phase 1 (wk 8)							Phase 2 (wk 24)						
	Placebo/Escitalopram			Zolpidem Extended-Release/ Escitalopram				Placebo/Escitalopram			Zolpidem Extended-Release/ Escitalopram			
Assessment	n	Baseline Mean	Mean Change (SD)	n	Baseline Mean	Mean Change (SD)	P^b	n	Baseline Mean	Mean Change (SD)	n	Baseline Mean	Mean Change (SD)	P^b
SIS														
Daily activities	149	37.2	19.9 (22.9)	154	36.8	25.6 (24.9)	.0356	87	NA	30.7 (26.2)	84	NA	37.9 (24.1)	.0217
Emotional well-being	149	32.9	25.5 (25.0)	154	32.3	30.5 (24.4)	.0483	87	NA	31.8 (25.1)	84	NA	40.3 (23.7)	.0101
Emotional impact	149	28.3	25.5 (28.4)	154	27.9	41.3 (25.5)	<.0001	87	NA	38.1 (29.5)	84	NA	47.8 (26.7)	.0061
Energy/fatigue	149	27.5	23.3 (27.8)	154	28.2	35.2 (26.7)	<.0001	87	NA	34.5 (25.9)	84	NA	45.6 (24.7)	.0022
Social well-being	149	40.2	24.8 (25.5)	154	39.5	32.4 (28.0)	.0044	87	NA	33.7 (23.3)	84	NA	41.5 (25.6)	.0104
Mental fatigue	149	44.8	22.1 (26.9)	154	42.2	27.3 (27.2)	.0557	87	NA	31.9 (24.7)	84	NA	36.3 (26.8)	.1657
Satisfaction with sleep	148	23.0	21.8 (25.9)	154	22.6	39.1 (23.7)	<.0001	87	NA	34.7 (25.4)	84	NA	47.4 (24.0)	.0006
MGH-CPFQ														
Total score	149	26.7	−8.0 (7.4)	154	27.4	−9.7 (6.6)	.0203	87	26.6	−9.8 (6.4)	84	27.0	−10.8 (6.3)	.4098
Motivation/enthusiasm	149	4.2	−1.6 (1.4)	154	4.3	−1.8 (1.2)	.0886	87	4.2	−1.7 (1.4)	84	4.2	−2.0 (1.1)	.2158
Wakefulness/alertness	149	3.9	−1.1 (1.3)	154	4.0	−1.4 (1.0)	.0039	87	3.9	−1.5 (1.1)	84	3.9	−1.5 (1.1)	.8138
Energy	149	4.2	−1.3 (1.4)	154	4.2	−1.6 (1.3)	.0147	87	4.1	−1.6 (1.3)	84	4.2	−1.8 (1.2)	.2431
Attention, focus/sustain	149	3.8	−1.2 (1.3)	153	3.9	−1.4 (1.3)	.1044	87	3.9	−1.5 (1.1)	84	3.9	−1.6 (1.1)	.7893
Memory/recall	149	3.6	−0.9 (1.3)	154	3.7	−1.2 (1.1)	.0125	87	3.6	−1.1 (1.3)	84	3.7	−1.4 (1.2)	.5378
Ability to find words	148	3.4	−0.9 (1.2)	154	3.5	−1.0 (1.1)	.5487	87	3.4	−1.1 (1.1)	84	3.5	−1.3 (1.2)	.9818
Mental acuity	149	3.6	−0.9 (1.2)	154	3.7	−1.3 (1.1)	.0313	87	3.6	−1.2 (1.0)	84	3.6	−1.4 (1.1)	.4773
Q-LES-Q														
Overall life satisfaction	146	41.0	21.9 (25.2)	153	40.1	25.3 (22.2)	.1519	86	42.7	29.1 (26.8)	84	47.1	31.9 (25.3)	.5721
Physical health/activities	149	40.4	16.4 (21.2)	154	40.4	19.8 (19.4)	.0551	84	40.7	22.1 (21.8)	84	40.7	28.9 (20.0)	.0231
Feelings	148	47.7	16.4 (19.0)	153	47.1	18.7 (17.0)	.2559	87	49.1	23.8 (19.2)	84	48.4	27.1 (17.9)	.2087
Work	111	53.0	13.5 (23.9)	111	52.1	17.4 (19.4)	.1818	64	57.3	16.7 (21.8)	66	54.8	24.8 (20.2)	.0661
Household duties	140	51.4	12.9 (23.6)	150	48.7	19.7 (23.6)	.0267	82	55.4	18.4 (22.8)	82	48.5	28.6 (25.8)	.1578
School/course work	12	36.8	6.9 (26.3)	13	34.4	18.5 (26.3)	.2526	9	36.5	22.2 (17.4)	7	36.1	5.4 (9.9)	.0420
Leisure activities	148	47.9	15.1 (24.7)	154	46.1	19.1 (22.2)	.1513	87	50.3	21.4 (25.1)	84	47.8	27.9 (22.4)	.0882
Social relations	149	49.1	15.0 (20.4)	153	47.1	19.6 (19.7)	.1357	87	50.9	23.4 (20.0)	83	49.3	27.5 (20.6)	.1984
General activities	147	47.8	16.6 (18.0)	154	44.7	20.2 (16.6)	.1415	86	50.0	21.4 (19.5)	84	45.6	28.0 (18.4)	.1602
Medication satisfaction	142	64.9	65.1 (24.7)	145	66.7	70.5 (22.0)	.0557	83	73.7	70.2 (23.0)	82	80.3	78.7 (20.1)	.0116

[a]Data shown are mean values observed at weeks 8 and 24.
[b]*P* values obtained are versus placebo, based on an analysis of covariance model with treatment and gender as fixed effects and baseline value as the covariate.
Abbreviations: ITT = intent-to-treat, MGH-CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, NA = not available, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SIS = Sleep Impact Scale.

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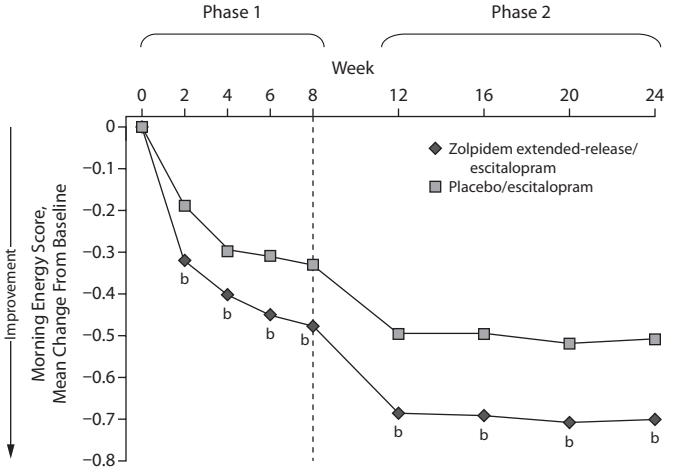
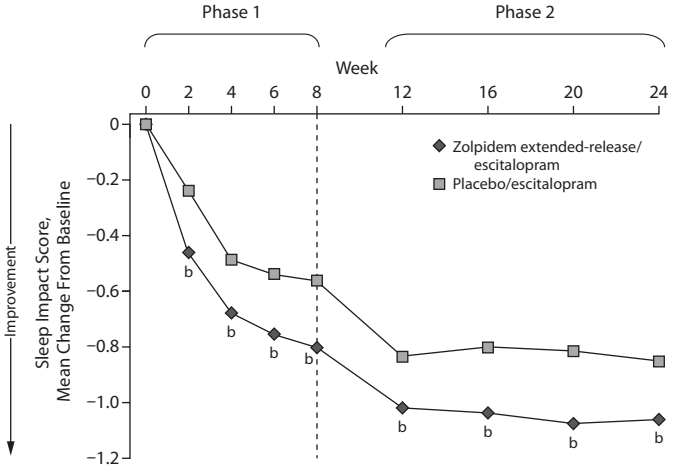
Figure 5. Mean Change From Baseline in Morning Sleep Questionnaire Measures of Next-Day Functioning at End of Phase 1 (week 8) and End of Phase 2 (week 24)[a]

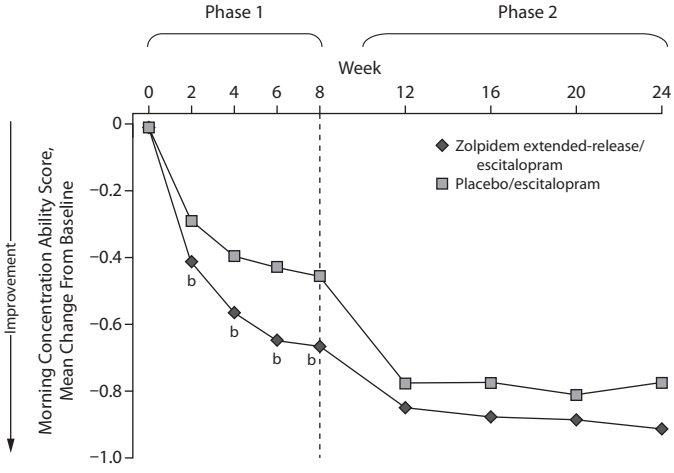
A. Mean Change From Baseline in Patient-Reported Next-Day Functioning: Morning Energy



B. Mean Change From Baseline in Patient-Reported Next-Day Functioning: Sleep Impact on Daily Activities



C. Mean Change From Baseline in Patient-Reported Next-Day Functioning: Morning Concentration Ability



[a]For each measure, lower ratings indicate greater improvement.
[b]$P < .05$ versus placebo/escitalopram, from an analysis of covariance model with treatment group and sex as the fixed effect terms and baseline value as the covariate.

(after the loss of treatment nonresponders; approximate least squares mean difference of 20 minutes), the superiority ($P < .05$) of zolpidem extended-release/escitalopram was maintained through week 16 but not at weeks 20 and 24 (Figure 3).

Phase 2 Findings: Secondary Efficacy Analyses

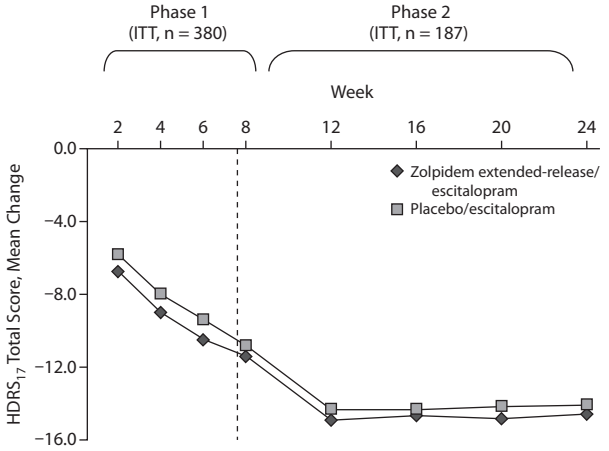
Other sleep characteristics. Throughout phase 2 (after removal of nonresponders to treatment), the zolpidem extended-release/escitalopram treatment group continued to show significantly greater improvement at each visit in number of awakenings and sleep quality ($P \leq .001$; Figure 4C and 4D). The zolpidem extended-release/escitalopram group showed significant treatment differences only at weeks 16 and 20 in wake time after sleep onset (Figure 4B), with no significant differences observed in sleep onset latency during phase 2 (Figure 4A). Mean sleep onset latency (87.7 vs 89.6), wake time after sleep onset (65.1 vs 67.4), number of awakenings (2.4 vs 2.0), and sleep quality (3.1 vs 3.0) at baseline were similar between the placebo/escitalopram and zolpidem extended-release/escitalopram groups, respectively. The $HDRS_{17}$ total score of insomnia-only items demonstrated statistically greater improvement in the zolpidem extended-release/escitalopram group throughout phase 2 ($P < .05$ for all).

Next-day functioning. Treatment with zolpidem extended-release/escitalopram was associated with statistically significant differences ($P < .05$) on all of the SIS domain scores at week 24 except mental fatigue (Table 2). The treatment groups did not exhibit significant differences (Table 2) in any of the MGH-CPFQ subscales at week 24.

On 2 of the 10 Q-LES-Q subscales (physical health/activities and medication satisfaction) (Table 2), the advantages of zolpidem extended-release/escitalopram were significant ($P < .05$), whereas on 1 of the subscales (school/course work), the advantage for placebo/escitalopram was significant ($P < .05$). Treatment with zolpidem extended-release/escitalopram resulted in significantly greater improvement on the MSQ items morning energy and sleep impact on daily activities (both P values $< .05$) but not for morning concentration ability, throughout phase 2 (Figure 5A, 5B, and 5C).

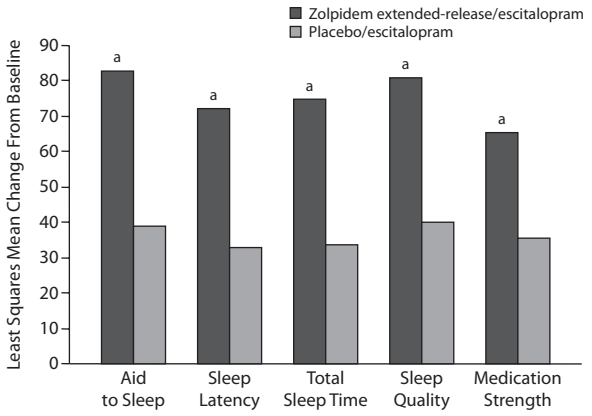
Depressive symptoms. At baseline, mean $HDRS_{17}$ total scores for patients who continued to phase 2 were similar in the placebo/escitalopram group (mean = 20.69, SD = 4.321) and zolpidem extended-release/escitalopram group (mean = 20.06, SD = 4.053); $P = .3076$. In phase 2, both groups experienced improvements in treatment remission ($HDRS_{17}$ score ≤ 7) and depression symptoms ($HDRS_{17}$ total score) (Figure 6), although this improvement was not statistically significant between treatment groups. The difference between rates of depression relapse did not significantly differ between the 2 treatment groups at any visit in phase 2 (week 24, 6.4% relapse in the placebo/escitalopram group vs 3.2% in zolpidem

Figure 6. Mean Change From Baseline in 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$) Total Score



Abbreviation: ITT = intent-to-treat.

Figure 7. Subjects Indicating Positive Responses on the Patient Global Impression of Insomnia Treatment at Week 8[a]



[a]$P < .0001$, intent-to-treat population.

extended-release/escitalopram group; $P = .285$). Remission was not measured in phase 2.

PGI-IT. At all visits in phase 2, patients in the zolpidem extended-release/escitalopram group rated their insomnia treatment significantly higher ($P < .001$; data not shown) than the placebo/escitalopram group. This finding is in agreement with their improvements in sleep characteristics.

CGI-S and CGI-I. Ratings of severity of mental illness (measured by CGI-S) by clinicians were comparable between treatment groups throughout phase 2. Clinician ratings of global improvement of mental illness (measured by CGI-I) were also comparable. There were no statistically significant treatment group differences on these measures (data not shown).

Health Care Resource Utilization

While the data were analyzed only descriptively, the treatment groups appeared comparable in their use of health care services. The sample sizes for some variables included in the HRU form were small, and there were floor effects for the report of usage for several of the health resources related to insomnia and anxiety.

Safety and Tolerability

A greater percentage of patients experienced at least 1 treatment-emergent adverse event (TEAE) during phase 1 in the zolpidem extended-release/escitalopram treatment group (140 patients, 72.9%) than in the placebo/escitalopram group (126 patients, 66.3%). Common TEAEs seen in > 5% of the safety population are summarized in Table 3. The most frequently reported TEAEs (experienced by ≥ 5% of patients) seen more often in patients receiving zolpidem extended-release/escitalopram than in placebo/escitalopram patients during phase 1 were nausea (10.9% vs 8.4%), somnolence (8.9% vs 8.4%), dry mouth (6.8% vs 5.3%), dizziness (6.3% vs 2.1%), sedation (5.7% vs 4.7%), fatigue (5.7% vs 3.7%), upper respiratory tract infection (5.7% vs 2.1%), and decreased libido (5.2% vs 3.2%). During phase 2, 57.3% of patients receiving zolpidem extended-release/escitalopram and 60.0% of patients receiving placebo/escitalopram experienced TEAEs, with headache (8.3% vs 6.3%), diarrhea (8.3% vs 4.2%), and nasopharyngitis (5.2% vs 5.3%) the most frequently reported. The overall incidence of TEAEs was lower during phase 2 than phase 1. Throughout the study, most TEAEs were mild or moderate in intensity. Combining phases I and II, a total of 27 severe TEAEs were reported (14 in the placebo/escitalopram group and 13 in the zolpidem extended-release/escitalopram group); none occurred in > 1 patient. Five patients experienced a serious TEAE during treatment. In phase 1, chest pain was experienced by 1 patient in the placebo/escitalopram group, and aneurysm and suicidal ideation were experienced by 2 patients in the zolpidem extended-release/escitalopram group. A suicide was attempted by 1 patient in the placebo/escitalopram group during phase 2, and congestive cardiac failure was experienced by 1 patient in the zolpidem extended-release/escitalopram group. No deaths occurred. Only 1 serious adverse event (chest pain), which occurred in the placebo/escitalopram group, was attributed to study treatment. One serious posttreatment adverse event of craniosynostosis was observed in a newborn following unintended maternal exposure during the first trimester of pregnancy. (The investigator reported this adverse event as related to the investigational product and escitalopram.)

Seven patients receiving zolpidem extended-release/escitalopram experienced a total of 8 amnesia events (5 mild and 3 moderate) in phase 1 (none in phase 2), although no patients discontinued the study medication due to amnesia. The patients in 6 cases recovered without sequelae, with the incidents resolving within 2 to 112 days. All 8 events were considered related to zolpidem extended-release, but 6 events were also considered related to escitalopram. Three other patients had TEAEs related to memory ("forgetfulness," "impaired memory," and "retrograde amnesia"). These events resolved within 1 to 6 days.

A greater proportion of patients in the zolpidem extended-release group discontinued their medication during phase 1

Table 3. Treatment-Emergent Adverse Events (TEAEs) Reported by >5% of Patients in Either Treatment Group (safety population)

	Phase 1		Phase 2	
Adverse Event	Placebo/Escitalopram (n = 190), n (%)	Zolpidem Extended-Release/ Escitalopram (n = 192), n (%)	Placebo/Escitalopram (n = 95), n (%)	Zolpidem Extended-Release/ Escitalopram (n = 96), n (%)
Any TEAE	126 (66.3)	140 (72.9)	57 (60.0)	55 (57.3)
Headache	34 (17.9)	27 (14.1)	6 (6.3)	8 (8.3)
Nausea	16 (8.4)	21 (10.9)	…	…
Somnolence	16 (8.4)	17 (8.9)	…	…
Dry mouth	10 (5.3)	13 (6.8)	…	…
Dizziness	4 (2.1)	12 (6.3)	…	…
Sedation	9 (4.7)	11 (5.7)	…	…
Fatigue	7 (3.7)	11 (5.7)	…	…
URTI	4 (2.1)	11 (5.7)	…	…
Libido decreased	6 (3.2)	10 (5.2)	…	…
Diarrhea	12 (6.3)	9 (4.7)	4 (4.2)	8 (8.3)
Nasopharyngitis	…	…	5 (5.3)	5 (5.2)

Abbreviation: URTI = upper respiratory tract infection.

Table 4. Mean Change in Subjective Total Sleep Time During Run-Out Period (intent-to-treat)[a]

	Phase 1				Phase 2			
	Placebo/ Escitalopram		Zolpidem Extended-Release/ Escitalopram		Placebo/ Escitalopram		Zolpidem Extended-Release/ Escitalopram	
Follow-Up Interval	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Night 1	22	10.7 (112.5)	18	25.9 (135.5)	25	85.9 (118.6)	28	–5.4 (159.8)[b]
Night 2	27	35.7 (122.3)	20	72.1 (132.4)	29	106.2 (79.1)	37	37.4 (139.5)
Night 3	27	53.3 (108.9)	23	64.2 (93.3)	38	112.9 (75.4)	40	47.5 (121.8)[b]
Nights 4–14	35	30.2 (67.1)	26	81.7 (78.5)[c]	47	96.5 (80.1)	58	54.2 (117.3)[b]

[a]Mean change from baseline in subjective total sleep time, in minutes.
[b]$P \leq .034$ versus placebo, based on an analysis of covariance model with treatment group and gender as the fixed effects terms and baseline value as the covariate.
[c]$P = .004$ versus placebo, based on an analysis of covariance model with treatment group and gender as the fixed effects terms and baseline value as the covariate.

due to a TEAE than did patients in the placebo group (7.8% vs 3.7%, respectively). Psychiatric disorders led to discontinuation in 6 patients in the zolpidem extended-release/escitalopram group and 1 patient in the placebo/escitalopram group; 3 events (anxiety, restlessness, and hallucination) were considered possibly related to zolpidem extended-release and escitalopram, and 1 event (hypnopompic hallucination) was considered related to zolpidem extended-release. In phase 2, 1 patient in each group discontinued medication due to a TEAE. Physical examination findings, vital signs, and laboratory values revealed no clinically meaningful differences between groups.

Discontinuation Effects on Sleep

The number of available MSQ reports was low in both run-out phases, especially for nights 1 and 2, with only 18 to 37 patients in either treatment group reporting MSQ data. Among patients who underwent the escitalopram-only run-out period at the end of phase 1, patients in both groups reported increases from baseline total sleep time for all run-out intervals examined (Table 4). The increase for mean change total sleep time in the zolpidem extended-release group was significantly greater for the night 4 to 14 interval versus placebo ($P = .004$).

At the end of phase 2, the zolpidem extended-release/escitalopram group reported a decrease from baseline in mean total sleep time on run-out night 1 (–5.4 minutes) while the placebo/escitalopram group reported an increase of 85.9 minutes ($P \leq .034$). The placebo/escitalopram and zolpidem extended-release/escitalopram groups slept longer than at baseline at all other run-out intervals.

DISCUSSION

Zolpidem extended-release 12.5 mg given concomitantly with escitalopram 10 mg to patients with MDD and insomnia led to significantly greater increases in total sleep time than placebo/escitalopram during phase 1. Among patients who continued into phase 2, statistically significant increases from baseline total sleep time with zolpidem extended-release/escitalopram were observed to week 16; however, these changes were more modest.

The effects on sleep parameters observed in this study are comparable to those described with zolpidem extended-release in a 24-week study in patients with primary chronic insomnia[19] and in an 8-week study in patients with insomnia and comorbid generalized anxiety disorder.[15] In this study, total sleep time increased from baseline by 101 minutes at week 8, compared with 64 minutes in the placebo group. In the studies by Krystal et al[19] and Fava et al,[15] increases in total sleep time with zolpidem extended-release at study end were approximately 115 and 106 minutes, respectively.

Moreover, sleep onset latency, number of awakenings, wake time after sleep onset, and sleep quality were significantly more improved with zolpidem extended-release than placebo. Improvements in sleep parameters were also seen in an earlier study of combination eszopiclone and fluoxetine for patients with insomnia and MDD, with a median increase from baseline total sleep time of 120 minutes.[17] In another study, coadministration of eszopiclone and escitalopram was well tolerated and associated with significantly improved sleep, daytime functioning, anxiety, and depression symptoms in patients with insomnia and generalized anxiety disorder.[16]

Besides complaints of insomnia, patients with MDD also suffer from symptoms of impaired functioning, including diminished ability to think or concentrate.[1] The present findings suggest improved insomnia symptoms had a positive impact on a few sleep-related next-day functioning measures, based on statistically significant improvements from baseline during phase 1 on MSQ next-day items, the SIS, and MGH-CPFQ. Patients given zolpidem extended-release reported more morning energy, better ability to concentrate, and less impact of insomnia on daily activities during phase 1. These improvements are similar to those seen in studies of zolpidem extended-release in patients with primary insomnia[19] and of eszopiclone in patients with comorbid MDD.[17] During phase 2, improvements were maintained for some MSQ and SIS measures, including morning energy and sleep impact on daily activities, but not for other measures.

Neither $HDRS_{17}$ total scores (with or without insomnia items) nor response or remission rates in this study differed between treatment groups. These results differ from those reported in a study of eszopiclone and fluoxetine,[17] which showed significantly greater proportions of patients in response or remission at 8 weeks among those given eszopiclone/fluoxetine (59% and 42%, respectively) than among patients given placebo/fluoxetine (48% and 33%, respectively).[17]

These findings suggest that insomnia and insomnia-related daytime symptoms respond differently from, and independently of, depression symptoms. Additionally, while eszopiclone and zolpidem extended-release impact insomnia symptoms effectively at the initiation of therapy, they may have different profiles, including their pharmacologic affinities for γ-aminobutyric acid type A receptor subtypes.[36] However, only a direct comparison in randomized controlled trials could truly differentiate the distinct effects of these compounds on sleep and depression in the population with MDD and insomnia.

The current study detected no statistically significant difference in depression relapse rates between the groups during phase 2; however, although the rates were extremely small, there were almost twice as many relapses in the placebo/escitalopram group. This raises the question of whether this difference might have become significant with a longer follow-up period. Further research using more naturalistic long-term follow-up methods is necessary.

Daily cognitive, physical, and next-day functioning measures after treatment with zolpidem extended-release demonstrated significant improvements in some SIS and MGH-CPFQ items during phase 1 but no significant differences in QoL improvements on the Q-LES-Q (only the household duties item was significantly different) between the 2 groups. Although all SIS items except mental fatigue and 3 of 10 Q-LES-Q items achieved significance in phase 2, no MGH-CPFQ items maintained significance. Both CGI-S and CGI-I failed to demonstrate significant differences in the 2 groups in either phase with zolpidem extended-release therapy. Further research is needed to clarify these findings, as few studies of patients with insomnia have demonstrated enhanced sleep without associated improvements in disability, impairment, and/or QoL.[37]

Clinical Relevance of the Present Study

This study suggests that a number of clinical benefits, particularly in terms of sleep and next-day functioning, can be achieved by adding a nonbenzodiazepine hypnotic to an antidepressant among patients with insomnia and mild-to-moderate MDD. This is consistent with previous reports of the benefits of augmentation of antidepressants from the outset of treatment in MDD.[38,39] However, neither $HDRS_{17}$ total scores (with or without insomnia items) nor MDD response or remission rates in this study differed between the 2 treatment groups, suggesting a relative lack of enhancement of antidepressant effect when zolpidem extended-release is added to escitalopram compared to placebo added to escitalopram. Recently, a paradigm shift in treating insomnia and coexisting psychiatric disorders has occurred; insomnia is regarded as an independent disorder, comorbid with anxiety or mood disorders albeit with a bidirectional influence.[5–8,40] Analyses of depression and insomnia derived from the present investigation may be relevant to this new paradigm. For example, one could argue that insomnia is secondary to MDD, for in patients given placebo/escitalopram there was no longer a separation from placebo on certain sleep measures (eg, sleep onset latency) after their depression responded. The fact that insomnia and sleep-related next-day functioning improved as much as they did in these patients with mild-to-moderate MDD strongly suggests that MDD and insomnia represent at least 2 different dimensions of a single disorder, if not 2 separate disorders. These findings indicate that the presence of MDD does not diminish the efficacy of insomnia pharmacotherapy with zolpidem extended-release. The study found greater benefits in some measures of cognitive, physical, and next-day functioning in the zolpidem extended-release group than in the placebo group, despite no significant differences in QoL and depressive symptoms. This supports the model of initiating and monitoring the treatment of insomnia and depression simultaneously.

The effects of zolpidem extended-release in patients with MDD suggest the importance of considering both sleep maintenance and latency. During phase 2, improvements in sleep latency with zolpidem extended-release were

marginally greater than with placebo, although not statistically significant at study end. In contrast, measures of sleep maintenance showed more consistent and significantly greater improvements during long-term treatment; sleep quality was also significantly better with zolpidem extended-release than with placebo throughout phase 2. This may be particularly relevant to patents with MDD, as middle and late insomnia tend to be prominent in this population.[14,18]

Safety

A major drawback to this treatment approach would be a decrease in safety or tolerability, but this does not appear to be the case. No clear differences in study completion rates were observed between the groups in either phase of the trial (61%–70% for both groups in both phases). Adverse events were similar in frequency, nature, and intensity, as reported in previous trials.[18,19,41] Despite the use of combination therapy, there was a low discontinuation rate due to adverse events in both groups (7.8% and 3.7%, respectively). Few serious or unusual adverse events occurred; during phase 1, 7 patients experienced a total of 8 transient, nonglobal amnesia events while receiving zolpidem extended-release; most were mild, and none of these patients withdrew from the study. These findings are similar to those observed in short-term pivotal trials of zolpidem extended-release.[18,42] With longer-term treatment during phase 2, few adverse events were reported, and only 1 patient in each group discontinued due to an adverse event. Moreover, no excess of psychiatric- or central nervous system–related adverse events were seen in patients treated with zolpidem extended-release in this phase, suggesting that such adverse events emerge early in treatment with zolpidem extended-release.

This investigation found little evidence of clinically significant rebound insomnia with abrupt cessation of zolpidem extended-release therapy. During phase 1 run-out, total sleep time was greater than at baseline for both groups and numerically favored zolpidem extended-release, consistent with findings during the run-out period in a trial of eszopiclone and fluoxetine in patients with comorbid MDD.[43] Other trials have demonstrated evidence of a rebound event on the first night of abrupt discontinuation that was absent by the second night.[18,42] During phase 2 run-out in the current study, there was no significant reduction in total sleep time compared with baseline; a mild decrease from baseline total sleep time (–5.4 minutes) was seen on night 1, while on subsequent nights total sleep time was greater than at baseline. This is similar to the absence of rebound insomnia seen in a 24-week study of zolpidem extended-release in patients with primary insomnia; in that study, no statistically significant worsening from baseline sleep parameters was observed during the run-out period, although the placebo group described significantly better sleep parameters for the initial discontinuation night in terms of longer total sleep time and a shorter wake time after sleep onset.[19] The similarity of these results suggests a low likelihood of clinically significant rebound insomnia on abrupt discontinuation of insomnia treatment in patients with or without MDD.

Limitations of the Study

The primary limitation of this investigation is the use of self-reported measures rather than objective measurement of sleep parameters (ie, sleep studies) and activity (ie, actigraphy). This is problematic, and may result in an overestimate of the effect of treatment. Another limitation is the number of comparisons conducted between the placebo and zolpidem extended-release treatment groups. Because no corrections were made for multiple comparisons, the risk of type II errors is increased; results seen with all secondary efficacy analyses must therefore be considered exploratory. Nevertheless, the robust effects on sleep measures with zolpidem extended-release (in many cases significant to $P < .001$) suggest that the findings concerning sleep improvements are reliable and valid. Moreover, similar findings on both the total sleep time and the MSQ-derived secondary sleep measures were observed in other studies of zolpidem extended-release in patients with insomnia and psychiatric comorbidity.[15,19]

The lack of an active comparator group is also a limitation; this investigation does not distinguish the effects on sleep by zolpidem extended-release from those seen with other, similar agents. Furthermore, the study did not examine the potential effects of adjunctive zolpidem extended-release in patients first stabilized on an SSRI, which is likely to be more relevant to the clinical presentation of insomnia in patients with depression, who tend to report persistent insomnia after initiating SSRI treatment. However, the present findings are similar to those of a previous investigation conducted under such conditions.[44] One 4-week, placebo-controlled study performed with zolpidem 10 mg nightly in patients with mild to moderate depression, receiving stable doses of an SSRI, reported increases in total sleep time, a reduced number of awakenings, and greater sleep quality, as in the current study.[44] The current study did not examine the potential impact on sleep with the concomitant double-blind administration of escitalopram; effects might be altered if patients are not aware that they are taking an antidepressant. However, the antidepressant response rate seen here with escitalopram at week 8 (63.7%) was similar to, or slightly higher than, that seen in double-blind trials of this drug in patients with depression, based on the Montgomery-Asberg Depression Rating Scale (mean response rate, 52.9%).[45] It is also worth noting that recent studies have suggested that higher doses of escitalopram may increase the response rate of MDD.[46]

Finally, it is also possible that the mild to moderate severity of depressive symptoms (score between 6 and 15 [inclusive] on the QIDS-SR_{16} at baseline) may have had a negative impact on the study's ability to detect a significant effect of the zolpidem augmentation on depressive symptoms because of a flooring effect, since the severity of depression was greater on average in the eszopiclone study in MDD.[17]

CONCLUSIONS

Zolpidem extended-release, given in combination with escitalopram, improved total time spent asleep and

some measures of sleep and sleep-related next-day functioning to a greater degree than placebo. Such treatment did not, however, significantly enhance the antidepressant effects of escitalopram or improve QoL. Among patients who were antidepressant responders, continuing therapy with the combination of zolpidem extended-release and escitalopram demonstrated sustained efficacy for several insomnia symptoms for up to 24 weeks, with little evidence of rebound insomnia upon abrupt cessation of zolpidem extended-release. The safety and tolerability of the combination therapy were generally comparable to those seen with placebo and escitalopram, with the exception of amnesia, and consistent with the previously reported safety profiles of both agents. Further research into the impact of insomnia treatment concomitantly with antidepressant treatment on clinical response, remission, and relapse in patients with insomnia and MDD is warranted.

Drug names: escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), zolpidem (Ambien, Zolpimist, and others).

Author affiliations: Massachusetts General Hospital, Depression Clinical and Research Program, Boston (Dr Fava); Montefiore Medical Center/Albert Einstein College of Medicine, Psychiatry Department, Bronx, New York (Dr Asnis); Eastside Comprehensive Medical Center, New York, New York (Dr Shrivastava); South East Health Consultants, Charleston, South Carolina (Dr Lydiard); NorthCoast Clinical Trials Inc, Beachwood, Ohio (Dr Bastani); Depression and Anxiety Disorders Research Institute, University of South Florida, Tampa, Florida (Dr Sheehan); and Henry Ford Hospital Sleep Disorders Center, Detroit, Michigan (Dr Roth).

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