Eszopiclone Co-Administered With Fluoxetine in Patients With Insomnia Coexisting With Major Depressive Disorder

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Background: *Insomnia and major depressive disorder (MDD) can coexist. This study evaluated the effect of adding eszopiclone to fluoxetine.*

Methods: *Patients who met DSM-IV criteria for both MDD and insomnia (n = 545) received morning fluoxetine and were randomized to nightly eszopiclone 3 mg (ESZ+FLX) or placebo (PBO+FLX) for 8 weeks. Subjective sleep and daytime function were assessed weekly. Depression was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and the Clinical Global Impression Improvement (CGI-I) and Severity items (CGI-S).*

Results: *Patients in the ESZ+FLX group had significantly decreased sleep latency, wake time after sleep onset (WASO), increased total sleep time (TST), sleep quality, and depth of sleep at all double-blind time points (all $p < .05$). Eszopiclone co-therapy also resulted in: significantly greater changes in HAM-D-17 scores at Week 4 ($p = .01$) with progressive improvement at Week 8 ($p = .002$); significantly improved CGI-I and CGI-S scores at all time points beyond Week 1 ($p < .05$); and significantly more responders (59% vs. 48%; $p = .009$) and remitters (42% vs. 33%; $p = .03$) at Week 8. Treatment was well tolerated, with similar adverse event and dropout rates.*

Conclusions: *In this study, eszopiclone/fluoxetine co-therapy was relatively well tolerated and associated with rapid, substantial, and sustained sleep improvement, a faster onset of antidepressant response on the basis of CGI, and a greater magnitude of the antidepressant effect.*

Key Words: Insomnia, major depressive disorder, comorbidity, adjunctive antidepressant therapy, antidepressant remission rates, eszopiclone

Insomnia is a prevalent disorder with important clinical and socioeconomic consequences. Insomnia is, however, unrecognized or overshadowed by comorbid conditions such as depression. Affective disorders and chronic insomnia may coexist and depression might be the most prevalent comorbid condition seen among insomnia patients (Ford et al 1989).

The relationship between insomnia and major depressive disorder (MDD) is complex from both pathophysiologic and treatment standpoints (Fava 2004). Insomnia is one of the diagnostic criteria of MDD and, accordingly, is reported in more than 90% of depressed patients (Thase 1999). Insomnia might persist after remission of depressive symptoms (Nierenberg et al 1999), might be a marker for depression recurrence (Perlis et al 1997), might be associated with non-response to antidepressant medication (Casper et al 1994), is independently associated with poor quality of life in depressed patients (McCall 2001), and might be associated with an increased risk of suicidal behavior (Agargun et al 1997).

Although few question the need to treat either primary insomnia or MDD, there is no consensus on whether and how to treat insomnia when it co-occurs with MDD. The first-choice psychiatric treatment of insomnia in depressed patients is to add trazodone in addition to the antidepressant medication prescribed (Dording et al 2002); however, there have been no systematic, large-scale, well-controlled studies examining the utility of either this combination or of trazodone specifically as a treatment for insomnia. Although there are preliminary data on the use of trazodone in this setting, there is also evidence that this strategy might in fact worsen the sleep disturbance in those with insomnia co-occurring with MDD (Reynolds et al 1991). In contrast, the treatment of insomnia with hypnotic agents has a solid empirical foundation.

Clinical guidelines advocate antidepressant monotherapy for the treatment of insomnia associated with MDD (Mendelson 1995; National Institutes of Health 1991; Walsh and Sugerman 1989). This viewpoint portrays insomnia as a symptom that is a "secondary" manifestation of underlying MDD, the fundamental pathophysiological entity, whereas the associated insomnia is without independent importance. Direct treatment of the sleep disturbance is assumed to be unnecessary and/or ineffective as long as the underlying mood disturbance persists. The currently available evidence indicates that in many patients this assumption does not hold (Lichstein 2000).

Thus, contrary to the guidelines, insomnia symptoms might require specific attention, and reluctance to treat insomnia might hinder overall symptom relief for many patients. These observations support a re-evaluation of how to optimally treat insomnia comorbid with MDD and suggest the possibility that targeted insomnia treatment might be indicated.

The nonbenzodiazepine eszopiclone is a γ-aminobutyric acid (GABA)-receptor agonist approved for the long-term treatment of sleep onset and sleep maintenance insomnia and has demonstrated safety and sustained efficacy in patients with insomnia (Krystal et al 2003; Roth et al 2005; Scharf et al 2005; Zammit et al 2004). The potential for eszopiclone to improve sleep main-

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tenance without tolerance makes it a viable adjunctive agent candidate. The purpose of the present study was to evaluate the patient-reported hypnotic efficacy and safety of eszopiclone administered concurrently with fluoxetine as initial therapy in patients with a new episode of both insomnia and MDD. This study also assessed the impact of concurrent eszopiclone treatment on depressive symptomatology and daytime function and additionally evaluated the effects of discontinuing eszopiclone.

Methods and Materials

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 67 sites in the United States. The study consisted of subjects with MDD and comorbid insomnia treated daily for 10 weeks with fluoxetine hydrochloride (starting dose 20 mg; dose range: 20–40 mg/day) and randomized to also receive either eszopiclone 3 mg or placebo nightly for 8 weeks, followed by a 2-week single-blind placebo run-out period. 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). Subjects were compensated for their time during the study, as approved by the institutional review boards involved.

Patients and Screening

All patients were required to be 21–64 years old (inclusive) and meet DSM-IV criteria for MDD and for insomnia associated with MDD. The current depressive episode was required to have lasted 2 weeks to 6 months (inclusive), and the insomnia symptoms must not have predated the symptoms of MDD by more than 10 weeks. Additionally, patients were required to have a score of ≥ 14 after subtracting the three sleep-related item scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17; Hamilton 1960). Patients had to report total sleep time (TST) ≤ 6.5 hours, sleep latency ≥ 30 min, and wake time after sleep onset (WASO) ≥ 45 min per night at least three times per week for the preceding month. Finally, patients were required to either not be taking antidepressant medications at screening or to be taking a sub-therapeutic antidepressant dose with the approval of the investigator to taper the medication. Patients were required to have not been receiving antidepressant medication for at least 14 days before randomization for all drugs except fluoxetine (35 days) and antipsychotic medications (30 days). Other chronic prescription medications not suspected to affect depressive symptoms or sleep-wake function that were taken at a stable dose for at least 30 days before screening were allowed. Over-the-counter medications and mild to moderate alcohol consumption not intended for soporific use were also allowed. Patients were additionally excluded if they: 1) had a known sensitivity to any selective serotonin reuptake inhibitor (SSRI), zopiclone, or eszopiclone; 2) were a significant suicide risk as determined by clinical interview; 3) had a previous episode of MDD that was refractory to treatment with an SSRI; 4) had a psychiatric or personality disorder that might compromise the ability to evaluate safety and efficacy of study medication; 5) had insomnia associated with another sleep disorder or had any condition that impacted or was likely to impact sleep; 6) had a history of drug or alcohol abuse or dependence in the previous 6 months or positive urine test at screening; or 7) had evidence of clinically unstable or uncontrolled serious medical conditions.

Study Procedures

Figure 1 summarizes the study from screening through completion. The HAM-D-17 used to assess eligibility was determined with patient self-report with an Interactive Voice Recording System (IVRS). Sites were informed of patient eligibility but were not given the actual score of the patient-rated HAM-D-17. Patients meeting screening criteria at Visit 1 were instructed to call the IVRS daily for the next 3–7 days to assess baseline sleep and daytime function. Patients with a minimum of three complete IVRS assessments were scheduled for a study initiation clinic visit. At this visit, the patient's baseline Insomnia Severity Index (ISI), HAM-D-17 (clinician-administered), and Clinical Global Impression severity (CGI-S) item were assessed. Note that patients were not required to meet HAM-D entry criteria at this time and that the HAM-D-17 and CGI-S scores collected were used for the patient's baseline measures. This was done to avoid the regression to the mean phenomenon that is commonly seen in depression studies. Patients then received open-label fluox-

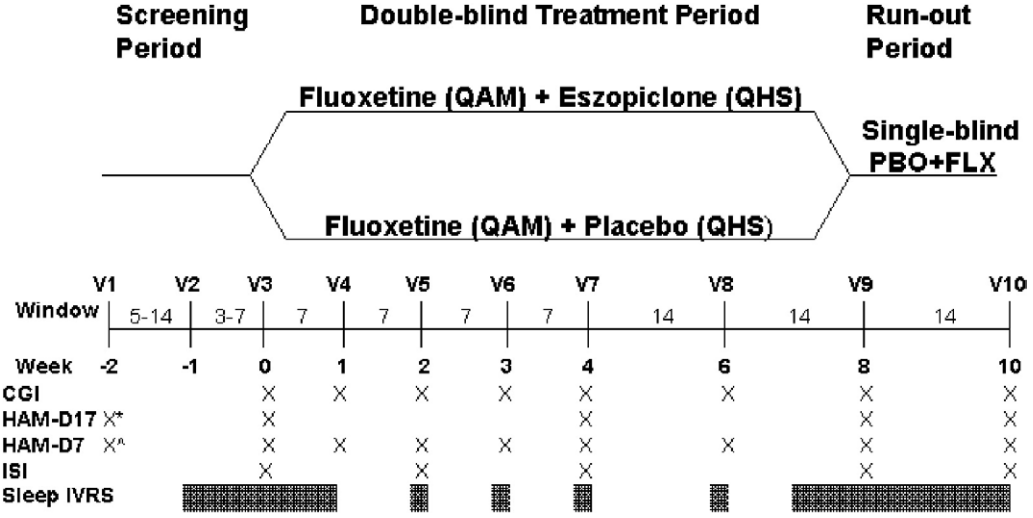

Figure 1. Summary of study schematic from screening through study completion. *Screening 17-item Hamilton Rating Scale for Depression (HAM-D17) was self-administered by patient with Interactive Voice Response System (IVRS); all other HAM-D17s were clinician-administered; ^HAMD7 collected via IVRS before visit on visit day (includes Bech & Maier subscales); **shaded bars** represent days when sleep assessments were collected via IVRS. PBO+FLX, placebo plus fluoxetine; CGI, Clinical Global Impression; ISI, Insomnia Severity Index.