Eszopiclone for the Treatment of Posttraumatic Stress Disorder and Associated Insomnia: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: The development of novel strategies for the treatment of posttraumatic stress disorder (PTSD) represents a critical public health need. We present the first prospective, randomized, double-blind, placebo-controlled trial of a non-benzodiazepine hypnotic agent for the treatment of PTSD and associated insomnia.

Method: Twenty-four patients with PTSD by *DSM-IV* criteria and sleep disturbance were treated in a randomized, double-blind, placebo-controlled crossover study of 3 weeks of eszopiclone 3 mg at bedtime compared to placebo. The primary outcome measures were changes in scores on the Short PTSD Rating Interview (SPRINT) and the Pittsburgh Sleep Quality Index (PSQI). The data were collected from April 2006 to June 2008.

Results: Three weeks of eszopiclone pharmacotherapy was associated with significantly greater improvement than placebo on PTSD symptom measures including the SPRINT ($P = .032$) and the Clinician-Administered PTSD Scale ($P = .003$), as well as on measures of sleep including the PSQI ($P = .011$) and sleep latency ($P = .044$). Greater improvement with eszopiclone on PTSD measures was present even when specific sleep-related items were excluded. Adverse events were consistent with the known profile of the drug.

Conclusions: This study provides initial evidence that pharmacotherapy with eszopiclone may be associated with short-term improvement in overall PTSD severity as well as associated sleep disturbance. Longer, more definitive study of eszopiclone in PTSD is warranted.

Trial Registration: clinicaltrials.gov Identifier: NCT00120250

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Posttraumatic stress disorder (PTSD) is among the most common psychiatric conditions in the population, with an overall lifetime prevalence in the United States of 6.8%.[1] PTSD is associated with increased morbidity, disability, and mortality among affected individuals as well as elevated rates of comorbidity and suicidality.[2–4]

Sleep disturbance is a core feature of PTSD, included in 2 of the 3 major symptom clusters (ie, hyperarousal and reexperiencing) in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), and is common among patients with PTSD, reported in more than two-thirds of affected individuals.[5] Disturbed sleep associated with PTSD is linked to increased depression, suicidality, substance use, and decreased quality of life and functioning.[6–9] Sleep disturbance in the aftermath of trauma exposure is a marker for the subsequent development of PTSD,[10] and sleep disturbances may both worsen and prolong the course of extant PTSD.[11] Further, preclinical evidence suggests that sleep deprivation leads to impaired extinction learning in fear-conditioned rats,[12] a finding of potential relevance in explaining the maintenance of PTSD in individuals with persistent sleep disturbance.

Eszopiclone is a non-benzodiazepine γ-aminobutyric acid-A (GABA-A) receptor agonist indicated for the treatment of sleep onset and maintenance insomnia.[13,14] It is classified as a schedule IV medication, although abuse, dependence, or serious withdrawal effects have not been reported.[15] It has also demonstrated efficacy as augmentation for the treatment of insomnia with major depressive disorder[16] and with generalized anxiety disorder.[17]

Given the high prevalence and morbid impact of sleep disturbance associated with PTSD and the prior evidence of potential benefit of eszopiclone for primary insomnia and affective states, this study was designed to provide an initial examination of the short-term efficacy and tolerability of eszopiclone for the treatment of *DSM-IV* PTSD and concomitant insomnia. We hypothesized that, compared to placebo, 3 weeks of eszopiclone would lead to greater reduction in both PTSD severity and insomnia.

METHOD

The study was a 7-week, randomized, double-blind, placebo-controlled crossover study with eszopiclone 3 mg and placebo at bedtime, comprising 3 weeks on each randomized treatment arm, with an intervening washout week. Investigators were blind to the randomization sequence, which was developed by the research pharmacy and blocked by antidepressant use.

The primary outcome measure to assess efficacy for PTSD symptomatology was change in Short PTSD Rating Interview (SPRINT)[18] scores, which were assessed weekly. The SPRINT is a 10-item, clinician-administered scale assessing core and related symptoms of PTSD. The primary outcome

measure for efficacy on sleep symptomatology was change in scores on the Pittsburgh Sleep Quality Index (PSQI),[19] which was also administered weekly. The PSQI is a 24-item, patient-administered scale with demonstrated validity and reliability assessing 7 sleep-related domains.

Key secondary measures included the (1) Clinician-Administered PTSD Scale (CAPS),[20] administered at baseline and week 3; and (2) sleep latency and total sleep time, derived from a subject-completed daily sleep diary reviewed weekly at each study visit by the clinician. The CAPS is a well-validated, highly detailed measure of the presence and severity of the *DSM-IV* PTSD criteria. (It was not administered more frequently in an attempt to avoid potential distress associated with its repeated administration.) Adverse events were assessed at each visit by open query and rated as mild, moderate, or severe.

Diagnosis

Men and women outpatients, aged 18–64 years, were eligible for study inclusion if they had a primary *DSM-IV* diagnosis of PTSD, by structured interview,[21] with associated sleep disturbance, operationalized as (1) positive score on item D1: "difficulty falling or staying asleep"; (2) sleep latency ≥ 30 minutes; and (3) total sleep time ≤ 6.5 hours at least 3 times per week over the previous month. Patients with concurrent depression or anxiety disorders were eligible if PTSD was judged to be the predominant disorder (ie, causing the patient the most distress). A lifetime history of psychotic disorders was exclusionary, as was a history of alcohol/substance abuse in the last 3 months or dependence in the last 6 months. Concurrent antidepressants (at a stable dose for ≥ 4 weeks prior to randomization) were permitted, but other psychotropic agents were excluded. Patients in current cognitive-behavioral therapy or in any psychotherapy initiated less than a month prior to randomization were excluded, as were individuals with current legal actions related to the trauma.

Informed Consent/Ethics Review

Patients received and signed informed consent prior to study entry. The study was approved by the Institutional Review Board of the Massachusetts General Hospital and was registered on clinicaltrials.gov (NCT00120250). Data were collected from April 2006 to June 2008.

Statistics

Subjects were randomized in double-blind fashion with equal probability to initiate treatment with either eszopiclone or placebo first. All patients receiving at least 1 dose of study drug and having at least 1 postbaseline efficacy assessment were included in the analyses. The standard *t* test method for crossover trials examining treatment effect and accounting for period effect[22] was utilized, after first testing to assure no carryover was present before examination of data from phase 1 and 2. Baseline to end point change within each phase was examined, utilizing a modified intent-to-treat approach including participants who had at least 1 on-medication visit in each phase in crossover analyses. This crossover method was used to analyze each of the continuous primary outcome measures (change from baseline to week 3, and change from week 4 to week 7 in the total score on the SPRINT and PSQI) as well as for secondary measures, sleep latency and total sleep time. The change in the CAPS was assessed in phase 1 only (baseline to week 3). All tests were 2-tailed, with significance set at an α of .05. Descriptive statistics are provided for all safety variables.

Table 1. Baseline Demographic and Clinical Characteristics of Patients (n = 24) With Posttraumatic Stress Disorder and Associated Insomnia Enrolled in a 7-Week Trial of Eszopiclone and Placebo

Characteristic	All Patients (n = 24)
Age, mean (SD), y	42.0 (10.3)
Sex, female, n (%)	17 (70.8)
Race, white, n (%)[a]	17 (73.9)
Education status, college graduate, n (%)	9 (37.5)
Duration of illness, mean (SD), y	19.0 (14.3)
Current comorbidity, n (%)	
Major depressive disorder	11 (45.8)
Dysthymia	3 (12.5)
Agoraphobia	1 (4.2)
Social anxiety disorder	5 (20.8)
Generalized anxiety disorder	3 (12.5)
Panic disorder	2 (8.3)
Lifetime depression, n (%)	17 (70.8)
Lifetime alcohol or substance abuse or dependency, n (%)	9 (37.5)
Concomitant medications, n (%)	
Antidepressant	5 (20.8)

[a]Data missing for 1 patient.

RESULTS

Of the 27 subjects initially randomized, 2 dropped out after baseline without subsequent evaluation (1 each assigned to eszopiclone and placebo) and 1 discontinued within the first week because of unwillingness to monitor sleep (assigned to placebo). Baseline demographic and clinical characteristics of the remaining 24 randomized patients are presented in Table 1. The mean ± SD duration of PTSD was 19.0 ± 14.3 years, with over half the subjects with a current comorbid mood or anxiety disorder, and over a third with a lifetime history of alcohol or other substance abuse or dependence. The nature of the traumas included sexual assault or abuse (41%, n = 10), physical abuse or assault (25%, n = 6); observed violence to or death of a loved one (17%, n = 4), and other (17%, n = 4), including one combat-related trauma. The majority of patients (79%, n = 19) received the study medication as monotherapy.

Sleep Measures

Treatment with eszopiclone was associated with greater improvement in sleep compared to placebo, as reflected by a significantly greater reduction in PSQI score ($P = .011$, Table 2). Sleep latency was also significantly reduced with eszopiclone compared to placebo ($P = .044$). There was also a nonsignificant increase in total sleep time at the level of a statistical trend ($P = .061$).

Table 2. Outcome Measures for Patients (n = 24) With Posttraumatic Stress Disorder and Associated Insomnia Enrolled in a 7-Week Trial of Eszopiclone and Placebo[a]

	Eszopiclone		Placebo				
Measure	Baseline, Mean ± SD	End Point, Mean ± SD	Baseline, Mean ± SD	End Point, Mean ± SD	Crossover Analysis Mean Difference (95% CI)	*t* (*df*)	*P*
Sleep measure							
PSQI item							
Total score	11.52 ± 3.50	8.30 ± 3.28	11.13 ± 3.33	11.29 ± 3.86	−3.5 (−6.0 to −0.9)	−2.79 (22)	.011
Subjective sleep quality	2.0 ± 0.66	1.13 ± 0.54	1.88 ± 0.80	1.71 ± 0.62	−0.71 (−1.3 to −0.2)	−2.64 (22)	.015
Sleep latency	2.08 ± 1.10	1.0 ± 0.93	2.0 ± 0.98	1.79 ± 1.06	−0.88 (−1.5 to −0.3)	−2.98 (22)	.007
Sleep duration	1.83 ± 0.87	1.08 ± 0.88	1.67 ± 0.76	1.33 ± 0.82	−0.42 (−0.9 to 0.09)	−1.71 (22)	.103
Sleep efficiency	1.96 ± 1.20	1.25 ± 1.39	2.04 ± 1.12	1.96 ± 1.27	−0.63 (−1.6 to 0.3)	−1.39 (22)	.177
Sleep disturbances	1.57 ± 0.66	1.09 ± 0.51	1.54 ± 0.66	1.42 ± 0.58	−0.34 (−0.7 to 0.0)	−2.27 (21)	.034
Use of sleep medication	0.54 ± 1.10	1.88 ± 1.48	0.46 ± 1.06	1.75 ± 1.51	0.04 (−1.0 to 1.1)	0.086 (22)	.933
Daytime dysfunction	1.63 ± 0.77	0.83 ± 0.76	1.54 ± 0.93	1.42 ± 0.65	−0.67 (−1.2 to −0.1)	−2.56 (22)	.018
Sleep latency, min	65.71 ± 67.15	25.83 ± 17.55	49.17 ± 29.51	55.83 ± 82.39	−46.5 (−91.7 to −1.4)	−2.14 (22)	.044
Total sleep time, min	319.38 ± 79.18	390.0 ± 83.46	338.09 ± 57.41	362.38 ± 67.30	52.6 (−2.6 to 107.7)	1.99 (19)	.061
PTSD measure							
SPRINT score	22.13 ± 4.86	16.13 ± 4.56	21.92 ± 5.46	19.88 ± 5.47	−4.0 (−7.5 to −0.37)	−2.29 (22)	.032
CAPS score[b]	75.08 ± 14.43	53.92 ± 17.05	68.08 ± 21.67	67.50 ± 20.83	−20.6 (−33.3 to −7.8)	−3.34 (22)	.003

[a]All means represent combined phase 1 and 2 data.
[b]CAPS means, CI, and analysis with phase 1 data only (baseline and week 3).
Abbreviations: CAPS = Clinician-Administered PTSD Scale, PSQI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder, SPRINT = Short PTSD Rating Interview.

Post hoc crossover analyses of the subscales of the PSQI were consistent with the overall results for sleep measures. Eszopiclone was associated with significant improvement in PSQI subscales assessing subjective sleep quality, sleep latency, sleep disturbances, and daytime dysfunction (all *P* values < .05, see Table 2). Eszopiclone was not associated with significant change in the sleep duration, sleep efficiency, or use of sleep medications subscales (note: additional sleep medication use was prohibited in the trial).

PTSD Measures

Eszopiclone was associated with significant improvement in PTSD symptomatology as measured by the SPRINT ($P = .032$) relative to placebo in the crossover trial (see Table 2). In phase 1, the CAPS was also significantly reduced with eszopiclone (n = 12) compared to placebo (n = 12) ($P = .003$). To determine if PTSD core symptoms were improved apart from effects on specific sleep symptoms, post hoc crossover analyses were performed after removing the sleep item (item 4) from the SPRINT; there was a significant treatment effect for the remaining PTSD items of the SPRINT ($t_{22} = -2.39$, $P = .026$), with a mean difference of 3.71 points (95% CI, 0.49 to 6.93 points), indicating greater symptom reduction among the eszopiclone-treated patients. Similar findings were obtained in phase 1 only analyses (n = 24) after removing the sleep and distressing dream items (items B2 and D1) from the CAPS; there was a significant treatment effect for the remaining PTSD items of the CAPS (placebo: mean ± SD increase = 0.08 ± 15.9 vs eszopiclone: mean ± SD decrease = 18.25 ± 10.6: $t_{22} = 3.32$, $P = .003$).

Additionally, in post hoc follow-up analysis we examined the effect of eszopiclone compared to placebo on PTSD symptoms after excluding the 5 individuals who were receiving stable concomitant antidepressants; there was a similar significant reduction in PTSD symptoms in the eszopiclone monotherapy subset as measured by crossover analyses with the SPRINT ($t_{17} = -2.67$, $P = .016$, with a mean difference of 4.99 points with a 95% CI of 1.04 to 8.95) and for phase 1 analyses with the CAPS (placebo: mean ± SD increase 3.75 ± 16.1 vs eszopiclone mean ± SD decrease 21.2 ± 13.0: $t_{17} = 3.73$, $P = .002$).

A total of 4 of the initial 27 patients (14.8%) dropped out after randomization (2 on eszopiclone treatment and 2 on placebo), with 3 of these lost to follow-up and 1 unwilling to monitor their sleep. The adverse events experienced by patients receiving eszopiclone were of mild to moderate severity, with the most common comprising unpleasant taste (dysgeusia; 32%), sedation (16%), and headaches (12%).

DISCUSSION

This study is, to our knowledge, the first prospective, randomized, placebo-controlled trial of a non-benzodiazepine hypnotic agent for the treatment of PTSD. Results from this study are consistent with the hypothesis that eszopiclone would lead to greater improvement than placebo in measures of both sleep and PTSD. Improvement in PTSD was reflected by significantly greater reduction in scores on the SPRINT and the CAPS. Improvement in sleep was reflected by significantly greater reductions in scores on the PSQI, as well as sleep latency, with greater improvement in total sleep time at the level of a trend. Adverse events with eszopiclone in this trial were consistent with its known profile[13,14]; dropout rates were modest, with 2 of 27 patients (7%) each discontinuing treatment with eszopiclone and with placebo.

The PTSD experienced by subjects was relatively chronic, with a mean duration of illness of close to 20 years. Over two-thirds of patients had current or past affective disorder comorbidity, and over a third had lifetime alcohol or other substance abuse, suggesting that this was a clinically relevant, significantly ill group of individuals. However, conclusions from this randomized controlled trial are limited by its small

sample size. Further, we opted in this initial study to examine the impact of treatment over a relatively brief 3-week time period in anticipation of the agent's acute effects on sleep and utilized a crossover design to increase the power of a relatively small study sample; these design features, however, preclude examination of the degree and course of treatment response over time, as well as the potential loss of response or emergent adverse effects with a longer treatment course.

Common adverse effects associated with eszopiclone administration included dysgeusia, headache, sedation, dry mouth, and dyspepsia.[23] Although not observed in this trial, depression has been reported as consequent to administration of hypnotics, including eszopiclone, and its potential emergence should be monitored.[24] Further, although abuse, dependence, or serious withdrawal effects have not been reported,[15] eszopiclone is classified as a schedule IV medication, and an unpublished report notes that high doses of eszopiclone (ie, 6 and 12 mg) may produce euphoria similar to the effects of 20 mg of diazepam in patients with a history of benzodiazepine abuse.[23,25] These data suggest that care should be taken in the administration of eszopiclone to individuals with a substance abuse diathesis, an important clinical consideration given the elevated rates of alcohol and drug abuse among individuals with PTSD. Our findings in this brief initial trial suggest that examination of these important issues in a larger, longer, and more definitive non-crossover, parallel-design, controlled study is warranted. In addition, the majority of patients (79%) received eszopiclone as monotherapy, precluding the ability to comment on its efficacy as an augmentation agent, although the overall positive findings in a chronic population suggest that this question may be worth examining.

It should be noted again that subjects were selected for this study on the basis of having significant sleep disturbance as well as PTSD; the efficacy of this intervention in individuals with PTSD without significant sleep disturbance was not addressed. However, the finding of greater improvement with eszopiclone in PTSD symptomatology even after removal of sleep-related items is consistent with similar findings from studies in generalized anxiety disorder[17] and depression.[16] This finding may be attributable to a number of factors. It is possible that eszopiclone administration may have direct effects on PTSD symptomatology beyond the known sleep effects. Although speculative, a direct PTSD effect may be related in part to its activity across a relatively broad range of GABA-A receptor subunits,[26,27] including the GABA α3 subunit, which may be relevant for anxiolytic activity,[28] and the GABA α5 subunit, which is critical in the extinction of learned fear in the hippocampus, a process relevant for recovery from PTSD.[29] Alternatively, treatment of the insomnia may have contributed to an overall salutary effect on PTSD, consistent with controlled studies in PTSD with prazosin[30] and Imagery Rehearsal Therapy,[31] in which interventions specifically targeting nightmares and other sleep disruptions had a positive effect on the overall PTSD syndrome.

While a number of pharmacologic and psychosocial interventions are commonly used for the treatment of PTSD, relatively few systematic data from randomized controlled trials specifically address the treatment of associated sleep disturbance in PTSD.[32] In large randomized controlled trials, selective serotonin reuptake inhibitors (SSRIs) have been associated with a small but significant improvement in sleep in participants with PTSD,[33] although adverse effects, including insomnia,[34] increased arousal, periodic leg movements, and reduced rapid eye movement sleep, and total sleep time,[35,36] have also been reported. Studies examining the efficacy of sedating antidepressants (ie, amitriptyline or mirtazapine) for PTSD show weak results or are small and methodologically limited.[37,38] Further, although consensus treatment guidelines[39] and survey data[40] suggest the efficacy of trazodone for the treatment of sleep disturbance in PTSD, there is no controlled study of this indication. Although benzodiazepines are commonly administered for PTSD[41] and may improve associated anxiety, data from small controlled studies demonstrate no substantial overall benefit for PTSD or on specific sleep parameters.[42,43] Data from controlled trials in PTSD with the atypical antipsychotics are also mixed; augmentation studies with olanzapine and risperidone[44,45] in refractory patients have demonstrated significant improvement in sleep and other symptoms of PTSD, but a small olanzapine monotherapy study showed no improvement on either.[46]

Data examining the targeting of insomnia in PTSD with hypnotics are limited. In a case series of patients with combat-related PTSD, administration of the non-benzodiazepine hypnotic zolpidem was associated with improved sleep, although effects on other PTSD symptoms were not reported.[47] Recently, a randomized trial of 32 patients with chronic combat-related PTSD and insomnia reported that 2 weeks of augmentation of SSRIs with hypnotherapy but not zolpidem resulted in improvement in PTSD symptoms.[48] These negative findings for zolpidem are consistent with studies of zolpidem augmentation of SSRIs in generalized anxiety disorder[49] and depression,[50] which demonstrate salutary effects on insomnia but no significant effect on mood or anxiety. The discrepant findings regarding the efficacy of eszopiclone and zolpidem for PTSD and other affective disorders may be attributable in part to methodological differences across trials as well as to the relative specificity of zolpidem for the α1 GABA-A receptor subunit compared to the broader range of eszopiclone across GABA-A receptor subunits.[26,27]

Given its high prevalence, morbid impact, and the persistent distress of many affected individuals despite current standard interventions, the development of novel, effective interventions for PTSD represents a critical public health need. This study provides initial evidence that eszopiclone pharmacotherapy (administered generally as monotherapy in this trial) may be associated with improvement in overall PTSD severity as well as in associated sleep disturbance. Additional study of eszopiclone for PTSD with larger samples over a longer period of time to address issues including the durability and magnitude of treatment effects as well as potential adverse effects over time and following discontinuation, the underlying therapeutic mechanisms, and the relative effects of monotherapy and augmentation strategies are warranted.

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Drug names: eszopiclone (Lunesta), mirtazapine (Remeron and others), olanzapine (Zyprexa), risperidone (Risperdal and others), trazodone (Oleptro and others), zolpidem (Ambien, Edluar, and others).

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