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ORIGINAL ARTICLE**Randomized Controlled Trial**

- 21 Double-blind randomized controlled study of the efficacy, safety and tolerability of eszopiclone *vs* placebo for the treatment of patients with post-traumatic stress disorder and insomnia
Dowd SM, Zalta AK, Burgess HJ, Adkins EC, Valdespino-Hayden Z, Pollack MH

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Randomized Controlled Trial

Double-blind randomized controlled study of the efficacy, safety and tolerability of eszopiclone vs placebo for the treatment of patients with post-traumatic stress disorder and insomnia

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Abstract

BACKGROUND

Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD). Given the relationship between sleep disturbance and PTSD, there has been a relative paucity of studies examining the potential therapeutic impact of using pharmacotherapy to target sleep disturbance in patients with PTSD. Eszopiclone (ESZ) is a non-benzodiazepine γ -aminobutyric acid-A receptor agonist indicated for the treatment of sleep and may affect sleep in patients with PTSD.

AIM

To evaluate the efficacy of ESZ *vs* placebo (PBO) for patients with PTSD and insomnia.

METHODS

The study was a 12-wk, double blind, randomized controlled trial with 3 mg of ESZ ($n = 13$) or PBO ($n = 12$).

RESULTS

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Patients in both arms experienced significant improvement in PTSD symptoms as assessed by the Clinician-Administered PTSD Scale for DSM-IV (CAPS): ESZ ($t_{11} = -3.12$, $P = 0.005$) and PBO ($t_{11} = -3.5$, $P = 0.002$) and by self-report with the Short PTSD Rating Interview (ESZ $t_{11} = -3.38$, $P = 0.003$ and PBO $t_{11} = -4.48$, $P = 0.0005$). There were no significant differences between treatments on the CAPS ($t_{22} = -0.13$, $P = 0.70$) or the Short PTSD Rating Interview ($t_{22} = -0.58$, $P = 0.56$). Similarly, both treated groups improved on sleep measures as assessed by the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI) and on total sleep time (TST) and sleep latency assessed by actigraphy with no significant differences between groups (PSQI $t_{22} = -0.24$, $P = 0.81$; total sleep time $t_{10} = 0.13$, $P = 0.90$ and sleep latency $t_{10} = 0.68$, $P = 0.50$). There was a significant correlation between improvement in sleep and overall improvement in PTSD as measured by change scores on the PSQI and CAPS, $r(8) = 0.79$, $P = 0.01$ for ESZ treated subjects, but not for those treated with PBO $r(9) = 0.16$, $P = 0.69$. Adverse events of ESZ were consistent with the known profile of the medication including dysgeusia (30%, mild), sedation (20%, mild) and headache (20%, moderate to severe).

CONCLUSION

Results do not support the hypothesis of a specific positive effect of ESZ compared to PBO for measures of PTSD and associated sleep disturbance.

Key words: Trauma; Sleep disturbance; Hypnotic; Post-traumatic stress disorder

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Core tip: Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD) yet few studies have examined the impact of psychopharmacotherapy. Results from this randomized controlled parallel study in individuals with PTSD and sleep disturbance did not demonstrate a significant relative improvement for eszopiclone (ESZ) vs placebo treated patients. Although patients receiving ESZ did experience significant improvement in measures of PTSD and sleep disturbance, placebo treated patients also significantly improved on these outcomes. Thus the potential role for ESZ in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken.

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INTRODUCTION

Sleep disturbance is a core feature of post-traumatic stress disorder (PTSD) and is reported by 70%-91% of patients with PTSD in civilian and combat veteran populations^[1]. Dysregulated sleep is associated with a number of adverse consequences and in the aftermath of trauma exposure is a marker and perhaps risk factor for the development of PTSD or may contribute to its persistence^[2-4]. Disturbed sleep among individuals with PTSD is associated with measures of poorer clinical status including depression and suicidality, poorer perceived physical health and somatization and increased rates of alcohol and substance use, and decreased overall quality of life and functioning^[3,5-7]. In addition, sleep deprivation in preclinical studies led to impaired extinction learning in fear conditioned rats, a possible explanation for the impact of sleep disturbance a finding of potential relevance in explaining the persistence of PTSD in individuals with ongoing sleep disturbance^[8].

Given the relationship between sleep disturbance and PTSD, there has been a relative paucity of studies examining the potential therapeutic impact of using pharmacotherapy to target sleep disturbance in patients with PTSD. Serotonin reuptake inhibitors including selective serotonin reuptake inhibitors and serotonin-

noradrenaline reuptake inhibitors are commonly used to treat PTSD. Sertraline and paroxetine are Food and Drug Administration approved for this indication however they were found to either worsen sleep disturbance or sleep was not assessed in individuals with PTSD^[9]. The antidepressant trazodone, often used in low doses to treat insomnia, was reported effective for the treatment of PTSD as well as sleep disturbance in a small open trial^[10]. Prazosin, an α_1 -adrenergic receptor antagonist was found to be beneficial in reducing trauma related nightmares and overall global illness in several placebo (PBO) controlled trials in military and civilian PTSD patients^[11]. A related compound, α -1 adrenergic antagonist doxazosin has been reported useful for PTSD related sleep disturbance in an open trial and also demonstrated efficacy in a randomized controlled trial of the extended release formulation for PTSD related sleep disturbance and overall PTSD symptoms^[12,13]. Alternatively, studies of psychotherapy interventions found improvement in sleep quality and symptoms of PTSD. In a randomized controlled trial of sexual assault survivors using Imagery Rehearsal therapy a modified Cognitive Behavioral Therapy technique focused on sleep education, changing an aspect of a nightmare and rehearsing it daily, there was significant improvement in nightmares, sleep quality and overall PTSD symptoms^[14,15].

Benzodiazepines are often used in the treatment of PTSD because of their anxiolytic and hypnotic effects. One clinical trial with alprazolam demonstrated no significant benefit for PTSD, and a small PBO controlled trial of clonazepam for PTSD-related sleep disturbance, reported no significant benefit for the benzodiazepine^[16,17]. Treatment guidelines discourage the use of benzodiazepines in the treatment of PTSD because of lack of demonstrated efficacy, concerns related to abuse and dependence, and potential adverse impact on exposure based cognitive-behavioral therapy^[18]. Among the non-benzodiazepine γ -aminobutyric acid-A receptor agonist hypnotics several case reports of veterans treated with the hypnotic zolpidem showed improvement in PTSD associated insomnia^[19].

Eszopiclone (ESZ) is a non-benzodiazepine γ -aminobutyric acid-A receptor agonist indicated for the treatment of sleep onset and maintenance^[20]. In addition to effects on primary insomnia, ESZ has been studied as augmentation to selective serotonin reuptake inhibitors for the treatment of major depression and generalized anxiety disorder^[21,22]. In a small 7-wk crossover study, 3 wk of ESZ was associated with short-term improvement in overall PTSD severity as well as sleep disturbance^[23]. In the present report, we present findings from a 12 wk randomized parallel PBO controlled trial to evaluate the relative efficacy, safety and tolerability of ESZ and PBO for the treatment of PTSD and associated sleep disturbance.

MATERIALS AND METHODS

The study was a 12-wk, double blind, randomized controlled trial with 3 mg of ESZ or PBO at bedtime with a one-month follow-up visit. Investigators were blind to the randomization sequence, which was designed by the Medical Center's research pharmacy. Recruitment began in September of 2012 and completed in 2015. Randomization was stratified by symptom severity as measured by a Clinician-Administered PTSD Scale for DSM-IV score of > 75 (CAPS)^[24]. Safety evaluations, included assessment of medication use and drug allergies, and laboratory results (CBC, chemistry, pregnancy, thyroid function, EKG, urine toxicology screen and urinalysis). A study physician performed a medical history and physical exam and evaluated lab results to rule out excluded medical conditions. Diagnosis was determined with the Structured Clinical Interview for the DSM-IV^[25].

The primary outcome measure to assess for efficacy for PTSD symptomatology was change in CAPS, which was assessed six times throughout the study. The CAPS is a 30-item, structured interview assessing the presence and severity of the DSM-IV PTSD criteria with demonstrated validity and reliability. The primary outcome measure for efficacy on sleep symptomatology was change in the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI), which was administered weekly^[26]. The PSQI with PTSD Addendum is a 13-item, well-validated and reliable patient administered scale with higher scores reflecting poorer sleep.

The secondary outcome measures included the: (1) Short PTSD Rating Interview (SPRINT) to assess for PTSD symptomatology, a 10-item, valid and reliable clinician-administered scale assessing core and related symptoms of PTSD collected weekly; (2) Self-report sleep diary to assess for change in insomnia including sleep latency and total sleep time recorded daily for 12 wk; and (3) Actigraphy to assess for change in sleep, including total sleep time, initial insomnia and number of awakenings^[27]. Actigraphy data was collected daily for the week between baseline and week 1 as well

as between week 11 and week 12. Additional clinician-rated instruments included a measure of depression and global clinical severity with the Montgomery-Asberg Depression Rating Scale, and the Clinical Global Impression Scale^[28,29]. A measure of global functioning was also completed using the Range of Impaired Functioning Tool (LIFE-RIFT)^[30].

Inclusion and exclusion criteria

Subjects included male and female outpatients, aged 18-65 years of age with a primary DSM-IV diagnosis of PTSD and confirmed with CAPS score of > 45 . Associated sleep disturbance was operationalized as (1) positive score on diagnostic criterion item D1: "difficulty falling or staying asleep"; (2) sleep latency > 30 min; and (3) total sleep time < 6.5 h at least three times per week over the previous month. A lifetime history of psychotic disorders was exclusionary, as was a history of alcohol/substance abuse in the last 3 mo. Concurrent use of antidepressants or benzodiazepines (on a stable dose for at least 6 wk) was allowed. Patients receiving current psychotherapy initiated within 3 mo of randomization or ongoing psychotherapy of any duration directed specifically toward treatment of PTSD and/or sleep disturbance (*e.g.*, CBT) were excluded, but general supportive individual, couple/family therapy > 3 mo duration was permitted. Patients who had current legal actions related to trauma or an ongoing relationship with their assailant were also excluded.

Informed consent

Informed consent was obtained prior to the initial assessment. The study was approved by the Institutional Review Board of Rush University Medical Center and was registered on ClinicalTrials.gov (Identifier: NCT01605253).

Statistics

The primary analysis used last observation carried forward approach in a modified intent to treat population that excluded subject who did not receive at least 1 dose of study drug. Baseline to endpoint (week 12) change scores were examined on the primary and secondary measures. All tests were 2-tailed with significance set at an α of 0.05. Correlations were completed comparing change scores on scales measuring sleep and PTSD.

RESULTS

There were no significant differences in demographics between groups at baseline. Of the 25 randomized subjects (13 ESZ, 12 PBO) 9 did not complete the study (ESZ = 6, PBO = 3). Four experienced worsening symptoms (2 ESZ, 2 PBO), 1 had memory disturbance (ESZ) and 4 were lost to follow up (3 ESZ, 1 PBO). Baseline demographics and clinical characteristics of the 25 randomized patients are presented in Table 1. The nature of the traumas included sexual assault or abuse ($n = 6$), physical abuse or assault ($n = 6$), observed violence to or death of a loved one ($n = 3$), military combat related trauma ($n = 1$), medical trauma ($n = 2$), car accident ($n = 5$), fire ($n = 1$) and accident ($n = 1$). A complete set of actigraphy data was obtained on a total of 12 subjects, 6 in the ESZ group and 6 in the PBO group. Only three subjects received concomitant medication, all in the PBO group, 2 received an antidepressant and 1 a benzodiazepine.

PTSD assessments

In the last observation carried forward, both treatment groups experienced significant improvement on the CAPS, (ESZ $t_{11} = -3.12$, $P = 0.005$ and PBO $t_{11} = -3.5$, $P = 0.002$) and the SPRINT (ESZ $t_{11} = -3.38$, $P = 0.003$ and PBO $t_{11} = -4.48$, $P = 0.0005$) (Table 2). However, there was no significant difference in outcome for ESZ *vs* PBO treated patients as reflected by the CAPS ($t_{22} = -0.13$, $P = 0.70$) nor the SPRINT ($t_{22} = -0.58$, $P = 0.56$). In a post-hoc analysis to determine if the core symptoms of PTSD were improved apart from effects on specific sleep symptoms, analyses were performed after removing the sleep items on the CAPS (item B2 and D1). There were no significant treatment effects for the remaining PTSD items of the CAPS ($t_{22} = 0.25$, $P = 0.81$).

Sleep assessments

There were no significant differences between ESZ and PBO on changes in the total score of the PSQI ($t_{22} = -0.24$, $P = 0.81$). Of the 12 subjects with complete actigraphy data, changes in total sleep time and latency were also not significantly different between ESZ and PBO ($t_{10} = 0.13$, $P = 0.90$ and $t_{10} = 0.68$, $P = 0.50$, respectively),

Table 1 Baseline demographic and clinical characteristics of patient (*n* = 25)

Characteristics	Eszopiclone (<i>n</i> = 13)	Placebo (<i>n</i> = 12)	Total sample (<i>n</i> = 25)
Age, mean \pm SD	38 \pm 11.6	48 \pm 11.3	43 \pm 12.2
Sex, male, <i>n</i> (%)	8 (54)	7 (58)	15 (60)
Race, <i>n</i> (%)			
White	4	2	6 (24)
African American	7	7	14 (56)
Hispanic	1	1	2 (8)
Mixed	1	2	3 (12)
Education status, college graduate, <i>n</i> (%)	5	4	9 (36)
Duration of illness in years, mean \pm SD	5 \pm 7	7 \pm 8	6 \pm 8
Current comorbidity, <i>n</i> (%)			
Major depressive disorder	7	7	14
Social anxiety disorder	2	1	3
Generalized anxiety disorder	0	1	1
Lifetime depression, <i>n</i>	8	9	17
Lifetime alcohol or substance abuse or dependency, <i>n</i>	8	3	11
Concomitant antidepressant, <i>n</i>	0	2	2
Concomitant benzodiazepine, <i>n</i>	0	1	1
Drop-outs	6	3	9

consistent with results from the self-reported Total Sleep Time and Latency as assessed by the PSQI. In those treated with ESZ, there was a correlation between improvement in sleep and overall improvement in PTSD as measured by change scores on the PSQI and CAPS, $r(8) = 0.79$, $P = 0.019$. This was not true for those treated with PBO $r(9) = 0.16$, $P = 0.69$.

There was a correlation between the PSQI improvement and SPRINT improvement but this is the case only for the ESZ group $r(8) = 0.89$, $P = 0.002$ and not PBO at week 12 $r(9) = 0.58$, $P = 0.10$. In addition, there was a correlation in the ESZ group with improvement on TST with improvement on the SPRINT $r(8) = -0.71$, $P = 0.05$ but again, not in the PBO group $r(9) = -0.51$, $P = 0.16$.

Additional assessments

There were no significant differences in between ESZ and PBO change scores on the MADRAS ($t_{22} = -0.73$, $P = 0.47$) and the Clinical Global Impression - Severity Scale ($t_{22} = 1.00$, $P = 1.00$). Total change scores on the Range of Impaired Functioning Tool were also not significantly different between the two groups ($t_{22} = 0.916$, $P = 0.369$).

Adverse events

The most common adverse events experienced by subjects receiving ESZ were consistent with the known side effect profile for the drug and included dysgeusia (30%, mild), sedation (20%, mild) and headache (20%, moderate to severe). Adverse events in the subjects receiving PBO included most commonly dysgeusia (25%, mild) and a change in urine color or smell (25%, mild). Other adverse events in the PBO group included headache (16%, mild) and dry mouth (16%, mild). In order to enhance blinding, a trace amount of vitamin B was added to the PBO capsule, which may have contributed to some of these reported adverse events however was unlikely to affect sleep.

DISCUSSION

Results from this randomized controlled parallel study in individuals with PTSD and sleep disturbance did not demonstrate a significant relative improvement for ESZ *vs* PBO treated patients. Although patients receiving ESZ did experience significant improvement in measures of PTSD and sleep disturbance, PBO treated patients also significantly improved on these outcomes. Of note, improvement in PTSD symptoms as assessed by both clinician and self-reports for the ESZ but not PBO treated patients was correlated with improvements in sleep suggesting the potential importance of

Table 2 Outcome measures – completers

Measure	Eszopiclone		Placebo		<i>t</i> (df)	<i>P</i> value
	Baseline (mean ± SD)	Endpoint (mean ± SD)	Baseline (mean ± SD)	Endpoint (mean ± SD)		
CAPS total score	65 ± 22.04	40 ± 20.13	64 ± 10.93	41 ± 16.94	-0.13 (22)	0.70
SPRINT total score	22 ± 5.55	13 ± 6.58	24 ± 3.61	14 ± 4.79	-0.58 (22)	0.56
PSQI total score	12.58 ± 3.12	8.38 ± 3.35	12.33 ± 3.94	7.44 ± 2.31	0.24 (22)	0.81
Total sleep time	6.75 ± 2.11	7.00 ± 1.82	6.15 ± 1.74	6.78 ± 1.26	0.13 (10)	0.41
Sleep latency	31.11 ± 26.54	39.70 ± 48.16	44.06 ± 37.55	37.42 ± 26.27	0.68 (10)	0.77
MADRAS total score	24.25 ± 7.28	18.33 ± 9.59	25.56 ± 9.46	21.00 ± 10.80	0.73 (22)	0.47
CGI severity	4.42 ± 0.79	4.00 ± 0.95	4.50 ± 0.80	4.08 ± 0.79	0.00 (22)	1.00
LIFE-RIFT total score	13.50 ± 2.64	11.92 ± 4.14	13.58 ± 2.87	12.83 ± 3.22	0.92 (22)	0.37

CAPS: Clinician-Administered Post-Traumatic Stress Disorder Scale; SPRINT: Short Post-Traumatic Stress Disorder Rating Interview; PSQI: Pittsburgh Sleep Quality Index with Post-Traumatic Stress Disorder Addendum; CGI: Clinical Global Impression; LIFE-RIFT: Range of Impaired Functioning Tool.

this specific association for the active treatment *vs* PBO effect. Potential reasons for the negative findings in this study include the significant positive response of the PBO treated patients, the greater amounts of drop out amongst the ESZ *vs* PBO treated patients (50% *vs* 25%), and higher rates of past alcohol and substance abuse in the ESZ treated patients (62% *vs* 25%) with these latter two factors approaching but not achieving statistical significance given the small sample size.

This overall finding was in contrast to a report from an earlier small ($n = 24$) randomized PBO controlled crossover study with ESZ that demonstrated significant positive effects on PTSD and sleep for ESZ relative to PBO^[22]. However, in that study, response to PBO was minimal, rate of drop out for both treatment groups was 7%, and the rates of past alcohol and substance abuse was lower (37%) than for ESZ treated patients in the current study.

Thus the potential role for ESZ in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken. In addition to the current negative study, a recent 26 wk multi-centered, double-blind PBO controlled study of prazosin in veterans from 13 Veterans Affairs Medical Centers found no benefit for the active agent over PBO or overall PTSD symptomatology^[31]. The data from insomnia focused CBT appears to improve sleep but no other symptoms of PTSD. However, the data from Imagery Rehearsal therapy for the treatment of PTSD is positive, suggesting a therapeutic role for affected patients^[15]. Thus, further work is necessary to establish the potential role and patient population of sleep disturbance targeted pharmacotherapy for the treatment of patients with PTSD.

ARTICLE HIGHLIGHTS

Research background

Sleep disturbance is a frequent concern and an important component of post-traumatic stress disorder (PTSD). It is associated with several adverse consequences and may be a marker and risk factor for developing PTSD. It is also possible that it contributes to the difficulty treating PTSD. Preclinical studies have found impaired extinction learning in fear conditioned rats, a possible explanation for the impact of sleep disturbance.

Research motivation

There are few studies focused on the use of pharmacotherapy targeting sleep disturbance. However there is evidence that sleep disturbance among patients with PTSD are associated with increased rates of depression, suicidal ideation, increased use of alcohol and substances and poorer functioning.

Research objectives

The main objective was to examine the possible benefits of eszopiclone on sleep disturbance in PTSD.

Research methods

The study was a randomized controlled parallel study of participants with PTSD and sleep disturbance. We collected both self-report and clinician administered measures of PTSD and sleep quality. In addition, actigraphy data were collected and compared to patient's self-report sleep logs.

Research results

The study did not find a significant relative improvement for those treated with eszopiclone compared to placebo. Those participants receiving eszopiclone experienced significant improvement in symptoms of PTSD and sleep disturbance, as did the participants receiving placebo. However, clinician and self-report measures of PTSD were correlated with improvement in sleep for the eszopiclone, but not placebo-treated patients, suggesting the potential importance of this specific association for the active treatment *vs* placebo effect. Interestingly, there were greater amounts of dropouts amongst the eszopiclone *vs* placebo treated patients. In addition, there were higher rates of past alcohol and substance abuse in the eszopiclone treated patients with two factors approaching, but not achieving statistical significance. Due to the small sample size, the potential role for eszopiclone in the treatment of PTSD remains uncertain until a larger more definitive trial is undertaken

Research conclusions

The findings of this study have contributed to the mixed evidence exploring pharmacotherapy in the treatment of sleep disturbance in patients with PTSD.

Research perspectives

Further work is needed to determine the potential role for pharmacotherapy targeting sleep disturbance in patients with PTSD.

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