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Brief Report

ADJUNCTIVE RISPERIDONE TREATMENT AND SLEEP SYMPTOMS IN COMBAT VETERANS WITH CHRONIC PTSD

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Sleep disturbances are core symptoms of posttraumatic stress disorder (PTSD) and are often resistant to treatment. One reason for the recent use of atypical antipsychotics in PTSD appears to be their effects on sleep. Study objectives were (1) to evaluate preliminarily the sleep effects of adjunctive risperidone, and (2) to evaluate the use of sleep diaries versus the more standard retrospective sleep assessments. This was a pilot, open-label, 12-week, flexible-dose trial of adjunctive risperidone in male veterans with a primary diagnosis of chronic, combat-related PTSD, partially responsive to current medications. Diagnostic interviews were administered at baseline, and PTSD ratings were obtained at baseline and at 6 and 12 weeks. Self-report sleep measures, including morning logs, were obtained at baseline and 6 weeks. Seventeen patients completed at least 6 weeks of the trial. Global ratings of sleep disturbance improved. Changes in frequency of awakenings and reductions in trauma-related dreams were only evident via morning log assessments. Nighttime awakening frequency derived from the sleep logs but not from the Pittsburgh Sleep Quality Index (PSQI) decreased significantly. There were no changes in the PSQI nightmare item; however, sleep log data indicated a reduced proportion of traumatic dreams at 6 weeks. Preliminary results suggest that adjunctive risperidone may benefit sleep disturbances associated with chronic PTSD. Prospective logs may be more sensitive to change than are retrospective scales. Depression and Anxiety 23:489–491, 2006. Published 2006 Wiley-Liss, Inc.†

Sleep disturbances including nightmares and insomnia are core symptoms of posttraumatic stress disorder (PTSD) according to DSM-IV-TR [American Psychiatric Association, 2000]. PTSD is frequently comorbid with mood, anxiety, and alcohol and substance use disorders [Kessler et al., 1995] that likely further contribute to sleep difficulties. Selective serotonin reuptake inhibitors (SSRIs), which are considered first-line medications for chronic PTSD, are not documented to benefit sleep [Friedman et al., 2000]. Findings from a state prescription database [Mellman et al., 2003] indicated that atypical antipsychotics, benzodiazepines and other hypnotics, and trazodone were more frequently prescribed for PTSD and for major depression disorder (MDD) co-occurring with PTSD than for MDD alone. This suggests that prescriptions for patients with PTSD often target sleep disturbance.

Specific data on medication efficacy for sleep disturbance in chronic PTSD are limited. Pilot studies have suggested that atypical antipsychotics target sleep symptoms [David et al., 2004; Hamner et al., 2003a, 2003b; Stein et al., 2003]. Stein et al. stated that the

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benefit of adjunctive olanzapine was largely attributable to improved sleep. The noradrenergic α-1 receptor blocker prazosin decreased nightmares and insomnia in a controlled trial [Raskind et al., 2003]. Risperidone is an atypical antipsychotic medication that has significant α-1 antagonism [Richelson, 1999].

It is unclear how best to measure changes in sleep disturbance in PTSD. Objective recordings might provide a gold standard; however, subjective reports and objective indices can be discordant in PTSD [Klein et al., 2003], and subjective reports are relevant to clinical response. Most studies utilize retrospective ratings of the prior 1–2 weeks or month. Anecdotal observations suggest that a decrease in nightmares is heralded by shifts toward less trauma-replicating dreams [Mellman et al., 1999; Raskind et al., 2000]. Prospective diaries may be more sensitive to eliciting these and other subjective changes in sleep.

The objectives of this study were to evaluate preliminarily (1) the effects of adjunctive risperidone on nightmares and sleep disruption, and (2) the sensitivity to change of sleep diaries in relation to the more standard retrospective instruments.

This open-label, 12-week, flexible-dose trial of adjunctive risperidone treatment in male combat veterans with chronic PTSD was approved by the Department of Veterans Affairs Institutional Review Board. General findings were presented in a previous report [David et al., 2004]. The focus of this study is changes in sleep variables at 6 weeks.

Twenty male Vietnam combat veterans were recruited through the PTSD program at the Miami Veterans Administration Medical Center (VAMC). Subjects were included if they met DSM-IV criteria for PTSD as their primary diagnosis, had only partial response to their present medications, were alcohol and drug-free for at least 2 months, were medically stable, had been on stable doses of other psychotropic medications for at least 4 weeks, were not currently taking other antipsychotic medications, and did not meet current or lifetime diagnostic criteria for a schizophrenia-spectrum disorder or mania. Two subjects were excluded due to abnormal baseline tests, and one was lost to follow-up. Seventeen subjects completed at least 6 weeks of the trial, and 14 subjects completed each set of sleep logs.

Lifetime and current psychiatric diagnoses were evaluated by the Mini-International Neuropsychiatric Interview [MINI; Sheehan et al., 1998]; PTSD severity was measured with the Clinician-Administered PTSD Scale [CAPS; Blake et al., 1990] at baseline, 6 weeks, and 12 weeks. Sleep assessments included the Pittsburgh Sleep Quality Index [PSQI; Buysse et al., 1989] and sleep/dream diaries that patients completed for three consecutive nights at baseline and at 6 weeks. The sleep diaries created by T. A. Mellman had been used and validated in previous studies [Mellman et al., 1999, 2001]. Dream diary reports were reviewed by the investigative team for consistency between the content and self-ratings of similarity to combat experiences. Descriptions were categorized as trauma dreams if the patient verified that the content was *quite a bit like* or *exactly like* combat experiences and distressing. Ratings for sleep variables were compared by paired *t*-tests between baseline and 6-weeks. PTSD severity was also compared between baseline and 12 weeks.

Subjects were males with a mean age of 53.7 ± 3.8 years (range, 50–66 years); 35.3% were white, 41.2% were black, and 23.5% were Hispanic; 52.9% of subjects were married. Education level was 13.0 ± 1.66 years (range, 11–17 years). All subjects had a principal diagnosis of PTSD and met full current criteria for the disorder; 14 subjects (82.4%) also had MDD, 9 (52.9%) had dysthymia, and 7 (41.2%) had an additional anxiety disorder. Twelve subjects (70.6%) had alcohol abuse in remission, and 7 (41.2%) subjects had substance abuse in remission. Fourteen subjects (82.4%) had current or lifetime psychotic features. This high rate is related to the original study having a focus on psychotic symptom response [David et al., 2004]. Six subjects met current ($n = 5$) or lifetime ($n = 1$) diagnostic criteria for MD with psychotic features; the rest of the patients with psychotic features had combat-themed hallucinations that were nonbizarre in nature but not considered flashbacks [David et al., 1999]. All subjects (100%) were taking stable doses of antidepressants at the time of study enrollment; 35% were taking a mood stabilizer, and 41% were taking an anxiolytic.

Risperidone was started at 1 mg at bedtime, and the dose was increased gradually until subjects reported improvement in target symptoms and/or developed mild and tolerable side effects. The mean maximum dose of risperidone was 2.3 ± 0.6 mg (range, 1–3 mg) per day.

Results are shown in the Table 1. Total CAPS score and the sleep items B-2—"recurrent distressing dreams of the event" and D-1—"difficulty falling or staying asleep" were improved at 6 weeks. The PSQI global score decreased; however, there were no significant changes in the PSQI number of awakenings or

TABLE 1. Outcome variables

Variable	Baseline	Six weeks	Significance
CAPS Total	91.4 ± 11.8	80.7 ± 20.5	$t = 2.3$, $df = 16$, $P = .04$
CAPS B-2	5.4 ± 1.9	3.8 ± 2.8	$t = 2.2$, $df = 16$, $P = .04$
CAPS D-1	6.4 ± 1.1	4.6 ± 2.4	$t = 2.9$, $df = 16$, $P = .01$
PSQI Total	15.9 ± 3.1	12.6 ± 5.2	$t = 2.2$, $df = 13$, $P = .05$
PSQI awakenings	3.0 ± .0.0	2.7 ± .0.6	$t = 1.7$, $df = 13$, NS
PSQI bad dreams	2.7 ± 0.5	2.5 ± .0.8	$t = 1.1$, $df = 13$, NS
Sleep diary awakenings	2.8 ± .0.9	1.9 ± .0.8	$t = 3.8$, $df = 13$, $P = .003$
Percent of sleep diaries with trauma dreams	38.0 ± 36.7	19.0 ± 21.5	$t = 2.3$, $df = 13$, $P = .04$

frequency of bad dreams. Sleep log ratings of nighttime awakenings decreased, but there were no significant changes for sleep latency or duration. There was a reduction in the proportion of diaries documenting trauma dreams at 6 weeks. Risperidone dose correlated negatively with the 6-week PSQI item of number of awakenings per night [$r = -.64$, $n = 14$, $P = .015$) and with the PSQI global score at a trend level ($r = -.52$, $n = 14$, $P = .06$).

In this open-label study of combat veterans with chronic PTSD and prior treatment resistance, the addition of risperidone was associated with improvement in overall PTSD symptoms and specific sleep variables. Sleep diaries appear to be more sensitive to detecting changes than the PSQI and may therefore be a potentially useful method for detecting therapeutic changes in a chronic PTSD population.

These results are preliminary, due to lack of a control condition, a small number of subjects, and ongoing psychosocial interventions. Larger, placebo-controlled trials are needed to confirm that risperidone is beneficial for sleep problems in chronic PTSD. The yield of such studies may be enhanced by the use of morning diaries for recording sleep and dream patterns.

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