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Placebo-Controlled Comparison of Prazosin and Cognitive-Behavioral Treatments for Sleep Disturbances in US Military Veterans

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Abstract

Objective—Pharmacological and cognitive-behavioral treatments targeting insomnia and nightmares have been shown to be effective in the treatment of military veterans with sleep complaints comorbid with symptoms of stress-related disorders, including Post-Traumatic Stress Disorder (PTSD), but the two approaches have not been directly compared. This randomized controlled trial compared the effects of prazosin vs. a behavioral sleep intervention (BSI), targeting nightmares and insomnia against a placebo pill control condition on sleep and daytime symptoms.

Methods—Fifty United States military veterans (mean age 40.9 years, SD = 13.2 years) with chronic sleep disturbances were randomized to prazosin (n = 18), BSI (n = 17), or placebo (n = 15). Each intervention lasted eight weeks. Participants completed self-report measures of insomnia severity, sleep quality, and sleep disturbances. All kept a sleep diary throughout the intervention period. Polysomnographic studies were conducted pre- and post-intervention.

Results—Both active treatment groups showed greater reductions in insomnia severity and daytime PTSD symptom severity. Sleep improvements were found in 61.9% of those who completed the active treatments and 25% of those randomized to placebo.

Conclusion—BSI and prazosin were both associated with significant sleep improvements and reductions in daytime PTSD symptoms in this sample of military veterans. Sleep-focused treatments may enhance the benefits of first-line PTSD treatments.

Keywords

Insomnia; nightmares; behavioral sleep treatments; PTSD; prazosin; sleep

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Introduction

Sleep disturbances are highly prevalent in combat-exposed military veterans, including recent cohorts of military personnel serving in Iraq and Afghanistan (1, 2). These observations are consistent with previous findings among other military cohorts (3–6). Three studies have found that sleep disturbances are strongly correlated with PTSD symptom severity and other poor psychological outcomes in military personnel deployed to combat theaters (7–9). In light of the growing recognition that sleep disturbances are a risk factor for poor psychological and physical health outcomes (e.g., 10, 11), there is a pressing need to identify effective treatments targeting veterans' chronic stress-related sleep complaints.

Prazosin, an alpha-1 antagonist, and cognitive-behavioral techniques have been shown to be effective for the treatment of nightmares, non-nightmare distressed awakenings, and insomnia among adults with PTSD, including military veterans (12–17). Improvements in sleep seen with prazosin are accompanied by significant improvements in daytime symptoms of PTSD (12–16). Prazosin may attenuate central noradrenergic tone during sleep and especially during Rapid Eye Movement (REM) sleep (13, 18) to reduce nightmares and complaints of insomnia comorbid with PTSD. Non-pharmacological sleep-focused interventions are also effective in reducing nightmares and insomnia. For nightmares, Imagery Rehearsal Therapy (IRT) is a technique in which trauma-related or non-trauma related nightmares are rescripted into non-distressing dream scenarios (19–24), which are then mentally rehearsed daily. Nightmares are significantly reduced within six weeks and improvements are maintained over time (20, 25). For the treatment of insomnia, techniques known as stimulus control (26) and sleep restriction (27) have been shown to be highly effective in young, middle-age, and older adults with primary insomnia or insomnia comorbid with other psychiatric or medical conditions, including military veterans (28–32). The behavioral sleep intervention in the present study (BSI) integrated each of these approaches.

The effectiveness of prazosin and BSI for nightmares and insomnia has not been directly compared in veterans who have chronic sleep complaints comorbid with PTSD, subthreshold PTSD symptoms, or other psychiatric and medical comorbidities commonly seen in this population. Therefore, the aim of this eight-week randomized clinical trial was to compare the effects of prazosin, BSI, and a placebo conditioning on sleep, nightmares, and daytime psychiatric symptoms in military veterans with a primary sleep complaint comorbid with stress-related psychiatric symptoms. We hypothesized that both prazosin and BSI would show greater improvements in all domains relative to a placebo pill condition. Also, a four-month follow-up was conducted under naturalistic conditions to explore the sustainability of acute treatment effects.

Methods

This study was approved by the University of Pittsburgh Institutional Review Board (IRB), the VA Pittsburgh Healthcare System IRB, and the Department of Defense Human Research Protection Office.

Participants

Recruitment was conducted between October 2006 and March 2010, using television, radio, and newspapers advertisements, recruitment flyers posted in public areas, and referrals and mass mailing conducted by the VAPHS. One hundred forty-four US military veterans who were 18 years old and older provided written, informed consent (Figure 1). The primary inclusion criteria were having served or serving in the US military and current sleep complaints. DD Form 214 documentation of prior military service, a form issued by the

Department of Defense upon a military service member's separation from active-duty military, was obtained from all participants to verify military service.

Participants completed an extensive physical and psychiatric evaluation that included a detailed physical examination, a series of self-report questionnaires, and clinician-administered interviews to assess PTSD (33), psychiatric history (34), and sleep disorders using a locally developed structured interview previously used in clinical studies (e.g., 28, 35, 36).

A screening polysomnogram (PSG) was used to exclude those with an apnea-hypopnea index greater than 15 events per hour. Consistent with prior studies (12, 37), eligible veterans endorsed clinically meaningful sleep disturbances, which was determined by a score ≥ 3 of the nightmare item of the Clinician-Administered PTSD Scale. Participants also had to endorse a score > 5 on the Pittsburgh Sleep Quality Index (38), indicative of clinically significant sleep complaints. The complaints of sleep disturbances had to be accompanied by at least one daytime functional impairment or sleep disruption, and had to be persistent for more than one month(39).

Exclusion criteria included: 1) unstable medical conditions; 2) resting blood pressure less than 90/60 during the physical examination (to reduce the risk of hypotension with prazosin); 3) history of bipolar or psychotic disorder, 4) current (< 3 months) substance/alcohol abuse or dependence; 5) positive drug screen; or 6) diagnosis of obstructive sleep apnea. Those using a beta-blocker or another alpha-1 antagonist were also excluded to avoid their potential synergistic effects with prazosin (e.g., orthostatic hypotension, syncope).

Randomization and Treatment Delivery

A permuted block design randomization was stratified by use of an antidepressant (yes/no) and age group (18–36, 37 years old and older). Participants were first randomized in a 1:2 manner to BSI versus medication, with the medication arm being randomized again in a 1:1 manner to prazosin or placebo. The medication arms were delivered in a double-blind design.

Each treatment was delivered weekly, over an eight-week period. Sleep and side-effects were assessed weekly by the therapist for BSI participants, and the study physician for the others. Blood pressure was monitored weekly in the medication groups. The Asberg Side Effect Scale (ASES; 40), the patient self-report and clinician-administered Clinical Global Impression Improvement (CGI-I) structured the study clinicians' assessments. Post-treatment CGI-I ratings were conducted by independent assessors (also blind to medication randomization).

A masters' level licensed therapist delivered BSI intervention over eight consecutive weeks, including at least five weekly in-person sessions and up to three telephone contacts. BSI is a manualized treatment that combines education and behavioral techniques to reduce nightmares and insomnia (28, 41). All visits consisted of an individual 45-minute session. Sessions were audiotaped and rated to verify delivery integrity. The core BSI components included 1) education about nightmares and implementation of IRT (week 1); education about sleep and insomnia (week 2); 3) stimulus control and sleep restriction (week 3); and 4) adherence monitoring and adjusting the recommended sleep-wake schedule and imagery rehearsal practice to address problems in implementation (week 4 through 8). At each session's conclusion, participants received a wrist actigraph to wear for the next 7 consecutive days to document adherence to the therapist's recommended sleep schedule.

Participants randomized to prazosin or placebo took an oral dose of four capsules each night. The total assigned dose was distributed among the 4 capsules. One-week medication supplies were provided in daily dose dispensers. Participants were instructed to take the medication 30 minutes prior to bedtime, and not to engage in any activities that would prevent them from going to bed. Prazosin was titrated up from an initial oral dose of 1 mg, increasing the following weeks to 2mg, 4 mg, 6 mg, 10 mg, and 15 mg. The decision to alter or stop the scheduled dose increase was made weekly by the blinded physician, in coordination with the research pharmacist (who was operating outside the double blind) based on response, risks, and side effects. The therapeutic goal was to achieve complete absence of nightmares, and diary-based sleep latency and wake time after sleep onset both lower than 30 minutes. Adherence was monitored weekly by reviewing participants' medication recording on the abbreviated Pittsburgh Sleep Diary (PghSD; 42), and upon return of the previous week's medication and dispenser at each weekly visit. At the end of the treatment phase, the final mean nightly dose of prazosin was 8.9 mg (SD = 5.7 mg; 1mg to 15 mg), and the equivalent final nightly mean dose of placebo was 10.4 mg (SD = 5.7 mg; 1mg to 15 mg), $t(24) = .66, p = 0.52$.

Four months post-treatment, measures of global clinical improvements and self-report measures of sleep and psychiatric symptoms were obtained.

Outcome measures

The global primary outcome measures included the clinician- and patient-reported versions of the CGI-I Scale. Both are a seven-point Likert scale assessing the magnitude of perceived change (1 = markedly improved, 4 = unchanged, 7 = markedly worse). Ratings were obtained at baseline, weekly at each intervention visit, at post-treatment, and at the 4-month follow-up.

The Insomnia Severity Index (ISI; 43), the Pittsburgh Sleep Quality Index (PSQI; 38), the PSQI Addendum for PTSD (PSQI-A; 44), and the PghSD were used as primary outcome measures, and were completed at baseline, post-treatment, and four-month follow-up. Participants completed the sleep diary during the pre-intervention baseline, through the intervention period, and post-treatment. The diaries provided estimates of sleep latency, total sleep time, sleep efficiency (defined as the ratio of total sleep time/total time spent in bed), wake time after sleep onset, total sleep time, and nightmare frequency. Nightmare frequency as determined as the mean number of nightmares recalled upon awakening each morning per week, which was logged in the sleep diary. Because trauma-exposed individuals with chronic nightmares reported a broad range of dysphoric dreams (2–5), participants were asked to log all distressing dreams (nightmares) they experienced. This broader definition of nightmares was intended to provide a more ecologically valid assessment of the effects of prazosin or BSI on distressing dreams in military veterans with PTSD symptoms. Weekly averages for sleep latency, wake time after sleep onset, total sleep time, and sleep efficiency were computed for subsequent analyses.

Secondary sleep measures included sleep parameters obtained on laboratory PSG studies, and self-report measures of daytime symptom severity using the PTSD Checklist (PCL; 45), Beck Depression Inventory (BDI; 46), the Beck Anxiety Inventory (BAI; 47), and the Sheehan Disability Scale (SDS; 48). Pre- and post-treatment, participants completed two consecutive nights of PSG. Sleep latency, total sleep time, sleep efficiency, wake time after sleep onset, REM sleep and NREM sleep parameters were determined according to previously described scoring methods and procedures (e.g., 36, 49). Post-treatment PSG studies were conducted prior to breaking the blind of medication randomization, when participants were on the highest tolerated doses of prazosin or placebo for least three weeks.

For the PSG studies, and consistent with instructions given to participants during the entire trial, medication was taken at the participants' usual bedtime.

Data Analysis

Prior to analyses, all variables were examined for normality and transformations were used where necessary (see footnotes in Tables 2 and 3). Demographic and service record characteristics were first compared among the three treatment groups using analyses of variance (ANOVAs) for continuous variables, and chi squared test or Fisher's exact test for categorical variables. Pre- to post treatment differences in sleep diary measures, PSG sleep and secondary outcomes were assessed using mixed-effect models for the intent-to-treat groups. Group and time were defined as the fixed effects with subjects as the random effect, where significant group by time interactions indicated statistically different levels of improvement over time between the treatment groups. Because the BSI group showed no variation in nightmares post-treatment, a non-parametric Fisher Exact test. Post-hoc comparisons using the modeled data were conducted for significant main effects to test all pairwise comparisons. Specifically, contrast statements were used to test for differences in slopes in models where Group X Time interactions were significant. The slopes of the three groups were tested using three contrast statements to test slopes of BSI vs. prazosin; BSI vs. placebo; and prazosin vs. placebo. For variables where there was a significant group effect, three contrast statements were used to test over all level of BSI vs. prazosin; BSI vs. placebo; and prazosin vs. placebo. The step-down Bonferroni method of Holm was used to correct for multiple comparisons with the primary sleep outcomes (i.e., ISI, PSQI, diary-based sleep latency, wake time after sleep onset, total sleep time, and sleep efficiency).

Response rates grouping the two active treatments relative to the placebo condition were assessed using two different criteria with chi squared analyses. Consistent with previous clinical trials, the first criterion defined treatment response as the percentage of subjects who were found to be "much improved" (score of 2) or "very much improved" (score of 1) at the end of the trial on the clinician-administered CGI. The second criterion defined treatment response as a reduction of ≥ 7 points on the ISI, or a decrease of ≥ 3 points on the PSQI, or a reduction of $\geq 50\%$ on nightmare frequency pre- to post-treatment.

Results

Sample characteristics (Figure 1 and Table 1)

Of the 144 veterans who initially provided written consent, 87 met one or more of the exclusionary criteria and were excluded (Figure 1). Fifty-seven eligible participants were randomized to one of the three treatment conditions, and 50 initiated at least one intervention session and were included in the analyses. Excluded participants were older (48.2 years old (SD = 12.1) vs. 40.9 years old (SD = 13.2): $t(142) = 3.35$, $p < .001$) and reported lower combat exposure on the Combat Exposure Scale (CES; (50); (9.5 (SD = 12.3) vs. 14.9 (SD = 11.8): $t(94) = -2.17$, $p < .04$) than veterans who were included in the study. Demographic and clinical data for the three groups are presented in Table 1. Veterans included in the analyses were mainly men (90%, $n=45$) and Caucasian (82%, $n=41$). The majority had served in the Army (82%, $n=42$), and had served in Iraq or Afghanistan (48%, $n=24$), the first Gulf War (18%, $n=9$), or in Vietnam (12%, $n=6$). The mean CAPS score for current PTSD was 40.0 (SD = 22.4), indicating mild to moderate current daytime PTSD symptom severity. Fifty-eight percent ($n=29$) met all DSM-IV diagnostic criteria for current PTSD, whereas 42% endorsed subthreshold PTSD symptoms. Thirty percent ($n=15$) met diagnostic criteria for comorbid insomnia (formerly insomnia related to another mental health disorder). Psychiatric comorbidity was low in this sample; only one veteran presented with comorbid depression, and two veterans met criteria for current generalized anxiety

disorder. Of the 50 participants who were randomized and initiated treatment, a total of 17 participants were taking at least one prescribed medication (six in BSI, four in placebo, and seven in prazosin). In the BSI group, five were on monotherapy (citalopram, trazodone, oxycodone, sertraline, hydrocodone), and one was on polytherapy (bupropion plus gabapentin). In the prazosin group, three were on monotherapies (hydrocodone, clonazepam, citalopram), and four had polytherapies (citalopram plus quetiapine, quetiapine plus trazodone, alprazolam and diazepam, and citalopram plus mirtazapine). In the placebo group, two were on monotherapy (eszopiclone, tramadol), and two were on polytherapy (gabapentin plus trazodone, and amitriptyline plus citalopram plus topiramate). Groups did not differ on age, race, service branch, combat theater, combat exposure, concurrent use of antidepressant, psychotropic medications, psychiatric comorbidity, PTSD severity, or gender.

Sleep treatment outcomes (Tables 2 and 3)

Reductions on insomnia severity as measured by the ISI were significantly greater in the BSI and prazosin groups compared to the placebo group post-treatment ($F(2, 37) = 6.06, p < .01$), which remained significant after correction for multiple comparisons. All three groups showed improvements over time on overall sleep quality and nocturnal sleep disturbances as measured by the PSQI (Main effect of time: $F(1, 37) = 31.61, p < .01$) and PSQI-A (Main effect of Time: $F(1,37) = 17.36, p < .01$), respectively. No significant Treatment X Time interactions were observed for these measures.

No significant Group X Time interactions were found on any of the sleep diary measures. All groups showed improvements in sleep latency ($F(1,30) = 26.09, p < .01$), wake time after sleep onset ($F(1,29) = 13.84, p < .01$), total sleep time ($F(1,29) = 4.41, p = .04$), and sleep efficiency ($F(1,29) = 19.93, p < .01$). Pre- to post-treatment changes on mean weekly nightmare were greater for the BSI and prazosin groups than for the placebo group (exact $p=0.045$, Mean (SD) = -1.00 (1.38) vs. Mean (SD) 0.11 (0.78), respectively).

Using the CGI-defined criterion for treatment response, no statistically significant differences were detected between the 2 active treatments (13 responders out of 21 veterans who completed the trial and the placebo group (3 responders out of 12 veterans who completed the trial) (Fisher Exact $p = .07$). For the CGI-defined response criterion, the power to detect a significant difference between active and inactive treatments using a two-sided test, and an alpha of 0.05 was 58%, based on the observed rates of responders of 13/21 in the BSI and PRZ groups (61.6%; 95% Confidence Interval [CI] = 40.8% to 79.3%) vs. PBO (25%, 95% CI = 8.3% to 53.9%).

Using the sleep-specific criterion of treatment response, completers randomized to prazosin or BSI showed a higher rate of treatment response based on this criterion, 22 of the 28 veterans (78.6%; $22/28 = 78.57\%$, 95% CI = 60.28–89.70%) completed the treatment course with BSI or prazosin met criteria for treatment response Compared to five of the 13 veterans (38.5%; 95% CI = 17.66–64.86%) who completed the placebo course (Fisher exact $p < .02$).

Polysomnography and daytime symptom severity (Tables 2 and 3)

Objective sleep parameters derived from polysomnographic studies indicated no statistically significant Treatment $\times$ Time interactions for sleep latency, wake time after sleep onset, or sleep efficiency.

No significant Treatment $\times$ Time interactions were observed for the daytime PTSD symptom severity measured by the PCL ($F(2,32) = 1.80, p = .18$), BDI, ($F(2,37)=1.57, p=0.22$), BAI ($F(2,35)=1.64, p=0.21$), or SDS ($F(2,37)=0.23, p=0.80$).

Adverse Effects

There were no significant changes in systolic or diastolic blood pressure measurements over the eight treatment visits in the prazosin and placebo groups ($F(7,126) = .38, p = .92$; and $F(7,126) = .51, p = .83$, respectively). No falls or syncopal episodes occurred. Mild orthostatic symptoms were sporadically reported in 13 veterans over the course of the interventions (4 with prazosin, 4 with placebo, and with 5 with BSI). The frequency of side effects as measured by the Asberg did not differ across treatment groups, and decreased over the eight-week period in all three groups. Most common side effects in both the prazosin and placebo groups were drowsiness, physical tiredness, headaches, and dry mouth. Two veterans withdrew from the placebo because of side effects (heart palpitations and dizziness), and one participant randomized to prazosin was withdrawn due to cataplexy-like symptoms upon morning awakening. For the BSI group, similar side effects were reported, and included headaches, drowsiness, muscle tiredness of stiffness, and dry mouth.

Follow-up Study (Table 2)

Four months after terminating the acute treatment phase, improvements in insomnia severity continued to be greater in the BSI group compared to the prazosin group (Group by Time interaction: $F(2,71)=3.47, p < 0.04$, at follow-up: $t(71)= 2.71, p < 0.009$). No Group by time interaction were observed for overall sleep quality and disruptive nocturnal behaviors at follow up, but a mean effect of time was observed for both measures (PSQI: ($F(1,72)=56.98, p < 0.001$) and PSQIA: ($F(1,72)=25.70, p < 0.001$). Similarly, no Group by Time interaction was observed on the PCL, BDI, BAI, or SDS, but a main effect of time was observed for all measures (PCL: $F(1,72)=26.56, p < 0.001$, BAI: $F(1,70)=30.80, p < 0.001$, BDI: $F(1,72)=23.78, p < 0.001$; and SDS: $F(1,72) = 8.61, p < 0.005$).

Discussion

To our knowledge, this is the first study targeting chronic sleep disturbances in military veterans that directly compares the effects of a sleep-targeted cognitive-behavioral treatment versus prazosin and placebo condition for controlling for the non-specific effects of treatment. The results suggest that both BSI and prazosin are more effective than placebo for self-reported and clinician-rated global clinical improvements, and reductions in prospective self-reported and diary-based measures of sleep continuity and nightmare frequency. Although subjective sleep improvements tended to be greater in veterans who were randomized to BSI or prazosin, self-report measures of sleep quality and severity of nocturnal sleep disturbances were improved in all three treatment groups over time. Both active treatments were associated with greater rates of treatment response than the placebo condition, but did not differ from one another. Findings from this study replicate previous findings (e.g., 12, 16, 32, 37, 41) showing that prazosin and behavioral interventions targeting sleep complaints in trauma-exposed samples are associated with clinically meaningful improvements in sleep complaints. However, prazosin was not associated with reductions in nightmares as previously reported (12, 13, 16). This may be attributable to the inclusion of veterans with low nightmare frequency, the use of prospective sleep and dream diaries, or the inclusion of veterans who endorsed subsyndromal symptoms of PTSD (42% of the sample). Improvements in daytime symptoms were substantial in all three treatment conditions, but did not statistically differ on the clinician-administered and self-report measures of PTSD, depression, anxiety, and disability. The latter contrasts with previous studies that showed significant improvements in daytime symptoms of PTSD, depression, and anxiety following sleep treatment (12, 13, 16). Marked improvements in daytime symptoms levels may be more easily detectable in patients with more severe psychiatric symptoms, compared to mild to moderate pre-treatment symptom levels observed in the current sample. Generally mild improvements across symptom domains may have resulted

from introducing daily (e.g., medication intake, sleep diaries) and weekly (in-person or telephone visits) routines in veterans' lives throughout the study.

Treatment response rates as defined by subjective insomnia and sleep quality measures were significantly higher in the two active treatment groups, while the CGI-defined treatment response rates only showed a trend for differences among the three groups. This divergence may be attributable to the small sample size, and to the use of sleep-focused measures with greater sensitivity for measuring nightmare frequency, insomnia severity, and sleep quality compared to a global rating scale. Similarly, diary-based and self-report sleep measures indicated modest but significant improvements in sleep and dreaming quality in the BSI group relative to prazosin and placebo. PSG measures did not differ pre- or post-treatment for any of the three groups. The latter suggests that PSG may not be the method of choice to study the mechanisms of effective sleep-focused treatments. Instead, sleep neuroimaging methods may be necessary to capture neurobiological changes that may underlie sleep disturbances and sleep treatment responses.

Interestingly, three treatment groups did not differ at the four-month follow-up assessment. In those who received the active treatments, improvements were maintained over time. The naturalistic design of the follow-up study limits possible extrapolations regarding the factors that may have contributed to sleep improvements over time in all three treatment groups, especially because veterans randomized to placebo were strongly encouraged to seek sleep-specific treatments. More frequent symptom monitoring over time will be necessary in future studies to clarify the course of sleep and daytime symptoms in military veterans, and the relationships between nighttime and daytime functioning.

Although the comparison of two active treatments for sleep disturbances in a group of US military veterans is unique, the present study has some limitations. First, with the exclusion of nearly 65% veterans who were initially screened ($n = 1531$), the 50 veterans who initiated treatment may not represent all military veterans who endorse clinically significant sleep complaints. Second, the specific medication exclusions were intended to optimize safety and minimize adverse side effects to a possible randomization to prazosin. As a result of these criteria, the test of the effects of BSI was limited to veterans who were also eligible to complete an 8-week course of prazosin. In typical clinical settings, BSI may provide an alternative treatment option for veterans who cannot use prazosin or who do not respond to pharmacological sleep treatments. Further evaluation of the broader effectiveness of prazosin and BSI is needed in a more inclusive sample. Third, the absence of an inactive therapy-placebo control group against the BSI condition also limits the study interpretation. Although participants randomized to the placebo condition received informational brochures from the American Academy of Sleep Medicine on healthy sleep and insomnia (which can be considered a non-pharmacological treatment as usual for sleep disturbances), this condition did not account for the length of time spent face-to-face with an experienced BSI interventionist. Our study design did not fully account for the length of time spent face-to-face with the experienced BSI therapist, and the selected statistical approach may have biased the findings toward BSI. Replication in larger and more heterogeneous samples is necessary to ascertain the robustness of the observed effects. The absence of more frequent, weekly independent clinical ratings of improvements also constitutes one of the limitations of the present study. Finally, testing the impacts of combining BSI and prazosin relative to the effects of either treatment alone may provide a novel approach to effectively reduce otherwise treatment resistant chronic sleep disturbances in military veterans.

In summary, sleep complaints are highly prevalent and chronic in military veterans, and have been associated with poor psychiatric and physical outcomes. The present findings suggest that behavioral interventions targeting sleep disturbances offer modestly greater

benefits compared to prazosin, and that both BSI and prazosin constitute viable options for the treatment of chronic sleep complaints in those with PTSD symptoms. Further comparative effectiveness research, as well as partnerships with community-based health providers who serve veterans, are also need to enhance the availability of resources to address their sleep disturbances.

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Figure 1.
CONSORT Chart.

Figure 2. Percentage of participants in the three treatment groups who were very improved much or much on the clinician rated (a) and patient-rated (b) global improvement scales post-treatment and at the four-month follow-up.

Table 1

Demographic for participants who initiated to one of the three treatment conditions.

	BSI N=17	Prazosin N=18	Placebo N=15	Test Statistic
Mean Age (SD)	40.0 (14.1)	39.4 (11.9)	43.6 (14.0)	F (2,47)=0.46, p=0.63
% Male (n)	82.4 (14)	88.9 (16)	100.0 (n=15)	Fisher Exact p=0.30
% Caucasian (n)	70.6 (12)	83.3 (15)	93.3 (14)	Fisher Exact p=0.31
Combat Theater				
% Operations Iraqi/Enduring Freedom (n)	47.1 (8)	44.4 (8)	53.3 (8)	
% Persian Gulf War (n)	17.7 (3)	33.3 (6)	0.0 (0)	Fisher Exact p=0.11
% Vietnam (n)	11.8 (2)	5.6 (n=1)	20.0 (3)	
% Other theater of operations (n)	0.0 (0)	11.1 (2)	0.0 (0)	
% No conflict (n)	23.5 (4)	5.6 (1)	26.7 (4)	
Mean Combat Exposure Score (SD)	9.6 (9.9) n=16	17.1 (10.8) n=17	18.1 (13.5) n=14	F (2,44) =2.60, p=0.09
Mean Past Month Score on the Clinician Administered PTSD Scale (SD)	35.5 (23.0)	47.0 (23.9)	36.7 (19.0)	F (2,47)=1.41, p=0.25
% using antidepressants, hypnotics, benzodiazepines, opiate agonists, trazodone, antipsychotics prescribed for sleep, or anticonvulsants (n)	35.3 (6)	44.4 (7)	40.0 (4)	Fisher Exact p=0.93
SCID Primary Diagnosis				
% No Diagnosis on axis I	5.9 (1)	5.6 (1)	6.7 (1)	n/a
% Current Posttraumatic stress disorder (n)	41.2 (7)	72.2 (13)	60.0 (9)	Fisher Exact p=0.58
% Generalized anxiety disorder (n)	5.9 (1)	5.6 (1)	0.0 (0)	n/a
% Major depressive disorder, recurrent episode, unspecified (n)	5.9 (1)	0.0 (0)	0.0 (0)	n/a
% Primary Insomnia or Insomnia related to another disorder (n)	41.2 (7)	16.7 (3)	33.3 (5)	n/a

Table 2

Mean scores pre- and post-treatment on subjective sleep and symptom measures, and on objective, polysomnographic measures for the behavioral sleep intervention (BSI), prazosin (PRZ), and placebo (PBO) groups.

	Pre-treatment			Post-treatment			Follow-up		
	BSI N=17	PRZ N=18	PBO N=15	BSI N=13	PRZ N=15	PBO N=13	BSI N=12	PRZ N=12	PBO N=11
<u>Sleep questionnaires</u>									
ISI ^f	16.5 (4.0)	16.4 (4.4)	14.8 (3.7)	6.8 (5.0)	9.3 (7.2)	11.8 (5.0)	5.5 (5.0)	7.0 (4.7)	8.7 (5.1)
				n=12			n=11		
PSQI	10.3 (3.4)	11.6 (3.1)	10.5 (3.6)	5.5 (3.2)	7.6 (2.9)	8.9 (3.4)	5.5 (4.1)	5.9 (2.2)	7.5 (3.4)
					n=14				
PSQIA ^f	3.1 (2.9)	4.8 (3.8)	4.1 (3.6)	1.1 (1.5)	2.2 (3.1)	3.2 (3.1)	0.7 (2.0)	1.8 (2.1)	1.8 (1.7)
				n=12					
<u>Sleep diary measures</u>									
Sleep latency ³	31.2 (18.0)	31.6 (17.6)	38.0 (29.3)	10.8 (5.9)	20.5 (8.1)	21.4 (14.2)	-	-	-
	n = 15		n = 14	n = 12	n = 13	n = 10			
Wake time after sleep onset ^f	28.0 (32.2)	31.1 (32.5)	27.9 (17.3)	9.7 (7.6)	12.1 (11.5)	18.3 (19.7)	-	-	-
	n = 15		n = 13	n = 12	n = 13	n = 10			
Total sleep time	389.4 (92.0)	365.3 (81.7)	413.5 (48.4)	406.5 (71.0)	372.3 (68.3)	-	-	-	-
	n = 15		n = 13	n = 12	n = 13	n = 10			
Sleep Efficiency ⁴	85.5 (9.8)	84.5 (11.8)	85.8 (8.0)	94.8 (3.0)	92.2 (4.3)	90.1 (5.2)	-	-	-
	n = 15		n = 13	n = 12	n = 13	n = 10	-	-	-
Nightmare Frequency	.09 (1.4)	1.0 (1.1)	0.4 (1.1)	0.0 (0.0)	0.3 (0.8)	0.5 (1.1)	-	-	-
	n = 15	n = 15	n = 13	n = 12	n = 12	n = 10	-	-	-
<u>PSG Measures</u>									

	Pre-treatment				Post-treatment				Follow-up			
	BSI N=17	PRZ N=18	PBO N=15	BSI N=13	PRZ N=15	PBO N=13	BSI N=12	PRZ N=12	PBO N=11			
Sleep latency ³	29.5 (22.5)	31.3 (35.4)	20.1 (19.0)	18.2 (11.9)	17.1 (12.2)	14.7 (8.7)	-	-	-			
				n=12	n=13	n=12						
Wake time after sleep onset ²	64.2 (46.6)	43.4 (29.8)	32.5 (32.6)	45.1 (19.7)	31.0 (24.0)	33.0 (24.5)	-	-	-			
				n=12	n=13	n=12						
Total sleep time	340.9 (75.0)	355.7 (83.6)	365.1 (75.0)	355.6 (64.9)	409.3(69.9)	389.7 (40.0)	-	-	-			
				n=12	n=13	n=12						
Sleep Efficiency ⁴	78.9 (1(2.1)	82.0 (11.4)	87.1 (8.1)	84.5 (6.5)	89.2 (7.1)	89.1 (5.0)	-	-	-			
				n=12	n=13	n=12						
% REM	23.4 (5.3)	25.1 (3.8)	24.0 (4.8)	23.7 (5.3)	25.7 (6.1)	25.1 (5.5)	-	-	-			
				n=12	n=13	n=12						
% Slow wave sleep	6.4 (5.8)	3.9 (4.8)	4.5 (5.4)	6.3 (7.1)	4.7 (5.1)	4.9 (6.4)	-	-	-			
				n=12	n=13	n=12						
REM density ^{*2}	10.8 (5.9)	11.5 (8.3)	8.3 (3.8)	10.8 (3.8)	10.2 (5.4)	7.1 (3.5)	-	-	-			
				n=12	n=13	n=12						
<u>Symptom Measures</u>												
PCL ²	36.5 (13.8)	43.9 (17.3)	35.0 (14.1)	27.1 (7.5)	33.3 (16.4)	35.1 (14.3)	25.9 (8.2)	27.6 (11.7)	31.2 (13.5)			
				n=12								
BDI ¹	8.5 (5.4)	13.3 (9.1)	8.7 (9.1)	6.0 (5.4)	9.4 (9.7)	8.5 (9.5)	4.8 (5.0)	5.2 (4.2)	6.9 (6.3)			
				n=12								
BAI ¹	5.6 (5.6)	9.1 (8.6)	6.9 (7.1)	5.8 (6.7)	5.8 (5.3)	5.4 (7.4)	3.3 (5.7)	2.5 (2.8)	4.9 (5.4)			
		n=17		n=12		n=12						
SDS ³	5.2 (5.6)	7.4 (7.3)	6.3 (7.5)	4.0 (5.5)	5.5 (8.3)	5.7 (7.7)	3.9 (4.7)	1.9 (3.6)	3.6(4.5)			
				n=12					n=11			

ISI = Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; PSQI-A: PSQI Addendum for PTSD; PSG = polysomnography; REM = Rapid eye movement; PCL = PTSD Checklist; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SDS = Sheehan Disability Scale

* REM density was determined using an automated measure of the mean number of rapid eye movements per minute of REM sleep for the whole night.

- 1 Transformation of raw data for analyses using $\sqrt{x + 1}$
- 2 Transformation of raw data for analyses using $\sqrt{x}$
- 3 Transformation of raw data for analyses using $\ln(x)$
- 4 Transformation of raw data for analyses using $\ln(100-x)$

Table 3

Statistical parameters for pre- to post-treatment comparisons in the behavioral sleep intervention (BSI) and two medication groups (DRUG; prazosin vs. placebo).

Beta (standard error)							Type 3 Tests of Fixed Effects		
Variables	Intercept	Group (BSI)	Group (DRUG)	Time	Group*Time (BSI)	Group*Time (DRUG)	Group	Time	Group*Time
<u>Sleep Questionnaires</u>									
ISI ¹	3.95 (0.19)	0.21 (0.26)	0.20 (0.25)	-0.45 (0.21)	-1.05 (0.31)	-0.63 (0.29)	F(2,37.0)=0.41, p=0.67	F(1,37.0)=69.45, p<.01	F(2,37.0)=6.06, p<.01
PSQI	10.47 (0.85)	-0.17 (1.16)	1.14 (1.15)	-1.60 (1.09)	-3.24 (1.53)	-2.36 (1.51)	F(2,37.0)=0.83, p=0.45	F(1,37.0)=31.61, p<.01	F(2,37.0)=2.38, p=0.11
PSQI-A	2.14 (0.19)	-0.26 (0.26)	0.15 (0.26)	-0.25 (0.18)	-0.25 (0.26)	-0.31 (0.25)	F(2,37.0)=1.35, p=0.27	F(1,37.0)=17.36, p<.01	F(2,37.0)=0.83, p=0.44
<u>Sleep Diary</u>									
Sleep latency	37.98 (4.72)	-6.75 (6.55)	-6.24 (6.37)	-15.9 (5.94)	-5.84 (8.15)	3.68 (7.98)	F(2,30.0)=0.66, p=0.52	F(1,30.0)=26.09, p<.01	F(2,30.0)=0.77, p=0.47
Wake time after sleep onset ¹	5.17 (0.58)	-0.42 (0.80)	-0.07 (0.78)	-1.14 (0.77)	-0.71 (1.05)	-0.51 (1.03)	F(2,29.0)=0.17, p=0.85	F(1,29.0)=13.84, p<.01	F(2,29.0)=0.24, p=0.79
Total sleep time	366.0 (20.51)	27.38 (28.04)	0.29 (27.28)	-3.27 (21.74)	31.91 (29.42)	51.33 (28.82)	F(2,29.0)=0.68, p=0.52	F(1,29.0)=4.41, p=0.04	F(2,29.0)=1.59, p=0.22
Sleep efficiency ²	85.62 (2.25)	-0.22 (3.07)	-1.10 (2.99)	3.73 (2.96)	6.11 (4.01)	4.02 (3.93)	F(2,29.0)=0.08, p=0.92	F(1,29.0)=19.93, p<.01	F(2,29.0)=1.18, p=0.32
<u>PSG Measures</u>									
Sleep latency ³	2.70 (0.20)	0.44 (0.28)	0.29 (0.27)	-0.11 (0.21)	-0.41 (0.30)	-0.25 (0.29)	F(2,34.0)=1.28, p=0.29	F(1,34.0)=7.74, p<.01	F(2,34.0)=0.99, p=0.38
Wake time after sleep onset ⁴	5.30 (0.60)	2.16 (0.82)	0.92 (0.81)	0.30 (0.65)	-1.34 (0.91)	-1.15 (0.90)	F(2,34.0)=3.53, p=0.04	F(1,34.0)=2.03, p=0.16	F(2,34.0)=1.25, p=0.30
Total sleep time	365.1 (18.70)	-24.2 (25.66)	-9.33 (25.32)	14.74 (13.73)	5.60 (19.37)	38.23 (19.00)	F(2,34.0)=0.46, p=0.64	F(1,34.0)=14.15, p<.01	F(2,34.0)=2.40, p=0.11
Sleep Efficiency ²	2.41 (0.15)	0.46 (0.20)	0.30 (0.20)	-0.03 (0.15)	-0.24 (0.20)	-0.44 (0.20)	F(2,34.0)=2.57, p=0.09§	F(1,34.0)=9.81, p<.01	F(2,34.0)=2.39, p=0.11
% REM	24.01 (1.32)	-0.62 (1.81)	1.07 (1.78)	0.55 (1.57)	-0.02 (2.20)	0.45 (2.16)	F(2,34.0)=0.49, p=0.62	F(1,34.0)=0.62, p=0.44	F(2,34.0)=0.03, p=0.97
% Slow wave sleep	4.49 (1.48)	1.90 (2.03)	-0.55 (2.00)	0.26 (1.04)	0.66 (1.47)	1.08 (1.44)	F(2,34.0)=0.87, p=0.43	F(1,34.0)=2.03, p=0.16	F(2,34.0)=0.28, p=0.75
REM Density* 4	2.81 (0.22)	0.40 (0.30)	0.39 (0.30)	-0.26 (0.14)	0.15 (0.20)	0.27 (0.20)	F(2,34.0)=1.16, p=0.33	F(1,34.0)=1.96, p=0.17	F(2,34.0)=0.94, p=0.40
<u>Symptom Measures</u>									
PCL 4	5.83 (0.30)	0.12 (0.41)	0.68 (0.40)	-0.07 (0.21)	-0.65 (0.30)	-0.58 (0.28)	F(2,37.0)=1.68, p=0.20	F(1,37.0)=17.01, p<.01	F(2,37.0)=3.01, p=0.06

Variables	Beta (standard error)					Type 3 Tests of Fixed Effects				
	Intercept	Group (BSD)	Group (DRUG)	Time	Group*Time (BSD)	Group*Time (DRUG)	Group	Time	Group*Time	
BDI ¹	2.86 (0.30)	0.10 (0.41)	0.75 (0.41)	-0.10 (0.22)	-0.48 (0.32)	-0.47 (0.30)	F(2,37.0)=2.09, p=0.14	F(1,37.0)=10.90, p=<.01	F(2,37.0)=1.57, p=0.22	
BAI ¹	2.54 (0.30)	-0.16 (0.40)	0.47 (0.40)	-0.10 (0.16)	0.01 (0.23)	-0.34 (0.22)	F(2,35.0)=1.43, p=0.25	F(1,35.0)=5.35, p=0.03	F(2,35.0)=1.64, p=0.21	
SDS ⁵	1.48 (0.29)	-0.07 (0.40)	0.10 (0.40)	-0.20 (0.25)	-0.24 (0.36)	-0.07 (0.35)	F(2,37.0)=0.09, p=0.91	F(1,37.0)=4.43, p=0.04	F(2,37.0)=0.23, p=0.80	

ISI = Insomnia Severity Index; PSQI = Pittsburgh Sleep Quality Index; PSQI-A: PSQI Addendum for PTSD; PSG = polysomnography; REM = Rapid eye movement; PCL = PTSD Checklist; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SDS = Sheehan Disability Scale.

¹ Transformation of raw data for analyses using $\sqrt{x + 1}$

² Transformation of raw data for analyses using $\ln(100-x)$

³ Transformation of raw data for analyses using $\ln(x)$

⁴ Transformation of raw data for analyses using $\sqrt{x}$

⁵ Transformation of raw data for analyses using $\ln(x+1)$

⁸ Main effect of Group became significant when controlling for age ($p = 0.02$). The main effect of Time or the Group by Time interaction remained unchanged.