Iran J Psychiatry Behav Sci. 2016 September; 10(3):e2603. doi: 10.17795/ijpbs-2603.

Published online 2016 August 6. **Original Article**

Prazosin for Trauma Nightmares and Sleep Disturbances in Combat Veterans with Post-Traumatic Stress Disorder

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Received 2015 June 10; **Revised** 2015 November 04; **Accepted** 2016 July 18.

Abstract

Background: Prazosin is significantly effective to reduce sleep disturbance and trauma nightmare in patients with post-traumatic stress disorder (PTSD); however, results of different studies were evaluated.
Objectives: The current randomized clinical trial aimed to assess the effects of prazosin on sleep parameters and nightmares among veterans with chronic PTSD.
Materials and Methods: Thirty-two veterans with chronic war-induced PTSD and distressing nightmares were randomized into prazosin and placebo groups for eight weeks. The main symptoms were qualified using the recurrent distressing dreams item of the clinician administered PTSD scale (CAPS) and the daytime symptom severity was measured by PTSD checklist (PCL) and the objective sleep quality assessment by actigraphy.
Results: Compared with placebo, prazosin had no significant effects on reduction of daytime symptoms ($P = 0.69$) and frequency and intensity of trauma-related nightmares. Also, there were no significant differences between pre- and post-treatment actigraphy measurements ($P > 0.05$).
Conclusions: The study findings showed that prazosin had no significant effect on reduction of PTSD symptoms as well as nightmares among veterans with chronic PTSD. Further clinical trials are needed to define the effect of prazosin on sleep physiology and whether such effects regarding the therapeutic response.

Keywords: Nightmare, Post-Traumatic Stress Disorder, Prazosin, Sleep Disturbance

1. Background

Post-traumatic stress disorder (PTSD) is a pathological response to a traumatic event affecting many combat veterans. Sleep disturbance, nightmares and insomnia are distressing and often treatment-resistant symptoms of PTSD (1, 2) and are also the criteria to diagnose PTSD in the diagnostic and statistical manual of mental disorders, 4th edition, text revision (DSM-VI-TR). Although, sleep disturbances are often viewed as a secondary symptom of PTSD that resolve into treating the underlying disease, but recently it is suggested that disturbed sleep may be a core feature of PTSD (3). Sleep disturbances and insomnia are common residual complaints after successful PTSD treatment (4). In contrast, sleep target intervention improves both sleep disturbances and PTSD symptom severity (3).

Previous studies suggest that increased central nervous system (CNS) noradrenergic activity might contribute to the pathophysiology of PTSD (5, 6). Mellman et al., showed a relationship between nighttime central noradrenergic activity and sleep disturbance in chronic PTSD (7). Elevated levels of norepinephrine disturb normal rapid eye movement (REM) sleep and increase non-rapid eye movement (NREM) sleep in patients with PTSD (3). Also, specific involvement of the postsynaptic alpha 1-adrenoceptor in this pathophysiologic process is suggested in some clinical studies (6, 8).

Prazosin is a generic alpha 1-adrenoceptor antagonist used to treat hypertension and the urinary symptoms of benign prostatic hypertrophy (9). Prazosin crosses the blood–brain barrier and particularly blocks central nervous system responses to adrenergic stimulation (9, 10). Prazosin is significantly more effective than placebo to reduce sleep disturbance and PTSD trauma nightmares and to improve global clinical status in both civilian and military veteran in several relatively small placebo-controlled trials (10-12); however, results of randomized controlled trials (RCTs) were mixed, since recent RCT reported no reduction in the nightmare frequency (12).

Although, the department of veterans affairs (VA)/department of defense clinical practice guideline for the management of post-traumatic stress recom-

mends that clinicians provide prazosin to treat sleep disorders and nightmares with a level B strength (13), the effectiveness of prazosin for nightmares and insomnia is not directly assessed among veterans, and on the other hand, the current clinical experiments showed no significant improvements in sleep disturbance and nightmares among veterans with PTSD.

2. Objectives

The current RCT aimed to assess the effects of prazosin on sleep, nightmares and daytime psychiatric symptoms among veterans with chronic PTSD.

3. Materials and Methods

The current study was approved by the ethical committee of Kermanshah University of Medical Sciences (KUMS) and conducted in Kermanshah, West of Iran, from March 2013 to November 2014. Informed contest was obtained from all participants and the project was registered under the code: IRCT2013022512596N1 at the Iranian center of clinical trials (IRCT.ir). Study participants included 32 veterans of Iran-Iraq war (1980 to 1988) with chronic PTSD. All subjects met DSM-IV-TR criteria for PTSD related to combat exposure and the diagnosis of PTSD was made by a psychiatrist based on the results of the clinician administered PTSD scale (CAPS) interview. The CAPS is a structured clinical interview aimed to uncover core and associated symptoms of PTSD. The combat traumatic event (the index event) reported by the participant was evaluated at the beginning of the interview to determine whether it met the diagnostic criteria for criterion A (traumatic event). If the index event met the criteria, frequency and intensity of 17 PTSD symptoms were rated on 5-point scales ranging from 0 (never [frequency], not at all [intensity]) to 4 (daily or almost daily, [extremely]). When the participant reported at least the frequency rating of 1 and the intensity rating of 2 for the symptom, the symptom was considered as positive (14, 15).

Also, a self-report measure of PTSD checklist (PCL) was used to assess daytime symptom severity. The PCL is a 17-item self-report checklist of PTSD symptoms based closely on the DSM-IV criteria. Respondents rate each item from 1 (not at all) to 5 (extremely) to indicate the degree to which they were bothered by that particular symptom over the past month. Previously, Goodarzi validated the Persian version of PCL with alpha Cronbach's as 0.93 (16).

Subjects had scores of at least 4 (of a maximum of 8) on CAPS recurrent distressing dreams item, and at least 4 on the CAPS difficulty falling asleep/staying asleep item. Medical history and examination revealed that all participants were in good general health and without restless legs syndrome, narcolepsy and other substance abuse for at least three months. Exclusion criteria were schizophrenia, bipolar or other psychotic disorders and active suicidal ideation. Patients with a diagnosis of depression were not excluded, since combat veterans with PTSD usually have concurrent depression. No subject started a new psychotropic medication after enrolment in the study. Persian version of CAPS was validated by Firoozabadi et al., with alpha Cronbach's as 0.92 (17).

Objective sleep was evaluated by two consecutive overnight actigraphic assessments before intervention and two consecutive overnight actigraphy after intervention. The actigraph is a portable device (similar to a wrist watch) that records patient movements to evaluate sleep parameters such as total sleep time (TST), sleep-onset latency, total wake time, number of awakenings (NWAK) and sleep efficiency (SE) (18-21).

Participants wore an ambulatory monitoring actigraph (Somnomedics, Germany) on the wrist of their non-dominant hand. Participants followed their habitual sleeping habits as closely as possible. Data recorded by the actigraph were then transferred to a computer and the average of variables over two nights was used for analysis.

Eligible subjects were assigned to receive prazosin. Prazosin was initiated at 1 mg one hour before bedtime for three nights; then increased to 2 mg before bedtime. If trauma-related nightmares were not at least moderately reduced by participant report after the night seven and there were no clinically significant adverse effects, prazosin was then increased by weekly 2 mg increments to a possible dose of 10 mg at bedtime. Dose increase was stopped and the dose was maintained at a dose that the participant reported at least moderately reduced trauma-related nightmares. An additional increase by 5 mg to a maximum 15 mg prazosin at bedtime could be prescribed if nightmares had not moderately improved and adverse effects were not problematic at one week after achieving the 10 mg dose. This is a common prazosin usage pattern employed throughout several studies (10-12, 22, 23). Trauma-related nightmares were again rated by a psychologist in a visit at least one week after maintenance of prazosin dose. Phone contact for adverse effect query was made in the morning after drug initiation and after each dose increase through the titration phases.

If a medication was stopped because of an adverse effect(s), the specific symptom(s) experienced by the patient was noted. If no reason for discontinuation was documented by a provider and refill history revealed non-adherence, then the patient's non-adherence was indicated. Additional reasons to distinguish the study drug

included treatment failure, resolution of PTSD nighttime symptoms and paradoxical worsening of symptoms. If a provider documented that the study medication was to be discontinued, but did not describe the reason, the case was categorized as other reasons for discontinuation.

Main outcome measures were the CAPS recurrent distressing dreams item, daytime symptom severity measured by PCL and the objective sleep quality assessment using actigraphy. The CAPS recurrent distressing dreams item is computed by summing frequency and intensity of trauma-related distressing dreams. Scores ranged from 0 to a maximum score of 8 (frequency of "daily or almost every day" and intensity of "extreme, incapacitating distress, could not return to sleep"). Sleep quality parameters included TST, sleep latency (SL), SE and NWAK.

Based on the pilot study, to detect a decrease of 1.4 in the nightmare frequency, a minimum sample size of 32 patients was required, with an alpha of 0.05, an expected standard deviation of less than 3 and a power of 0.80. The data before and after treatment were compared using Chi 2 (or the Fisher exact test) for categorical variables and paired T-test for continuous variables. Differences were considered significant if P values were less than 0.05.

4. Results

Of the 36 subjects, four failed to complete scheduled outcome assessment because of protocol discontinuation. Two discontinued because of adverse effects (dizziness) and two were lost to follow-up for unknown reasons. Thirty-two subjects completed the full trial through the end. Table 1 summarized the demographic characteristics of the study subjects.

At the end of the treatment phase, the final mean dose of prazosin was 8.9 ± 2.8 mg (ranging from 1 to 15 mg). Analysis of PCL revealed that prazosin had no significant effects on reduction of daytime symptoms (pre-PCL score= 56.2 ± 16 vs. post-PCL score= 51.4 ± 17.3; P = 0.69). Prazosin produced no significant improvement in each of the outcome measures addressing frequency and intensity of trauma-related nightmares (the CAPS recurrent distressing dreams item). Before intervention, mean frequency and intensity of trauma-related nightmares were 2.84 ± 1.2 and 3.2 ± 0.9, respectively. After eight weeks of intervention, frequency and intensity of nightmare were 2.56 ± 1.4 and 2.88 ± 1.2, respectively (Table 2).

Pre- to post-treatment changes on mean frequency and intensity nightmare did not reach the statistically significant level (P > 0.05). Also, Table 2 presents means and standard deviations of TST, SL, SE and NWAK measured by actigraphy for the study subjects before and after the intervention.

Table 1. Demographic Characteristics of the Study Subjects[a]

	Subjects, n = 32
Age, y	50.4 ± 6.5
Body mass index, kg/m²	25.7 ± 5.7
Current smoker	15 (46)
Substance abuser	6 (18)
Drugs	
Antihypertension	14 (43)
SSRI	16 (50)
TCA	9 (28)
Benzodiazepine	18 (56)
Antipsychotics	12 (37)

Abbreviations: SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.
[a]Data presented as mean ± SD or No. (%).

Average TST before intervention ranged from 5.3 to 8.6 hours (mean 7.62 ± 1.2 hour). Actigraphy measures demonstrated that TST ranged from 4.8 to 8.5 hours (mean 7.06 ± 2 hour) after the treatment. Comparison of the average TST ratings measures across the two assessment time showed no significant differences between pre- and post-treatment actigraphy measurements (P = 0.472). Similar results were observed for SL, SE and NWAK during bedtime (P > 0.05) (Table 2).

5. Discussion

The current study assessed the efficacy of prazosin in reduction of PTSD symptoms and distressing nightmare in veterans with chronic PTSD. The findings demonstrated that although the reduction in the total CAPS score was observed during prazosin use in the study subjects, differences between pre- and post-treatment scores were not statistically significant. Furthermore, there was no significant reduction in trauma nightmares. Findings of the current study were opposite to the previous findings (10, 11, 22, 23) showing that the administration of prazosin in the veteran samples were associated with clinically significant improvements in PTSD symptoms, nightmares and sleep complaints.

The lack of a significant effect of prazosin administration on total CAPS score may be due to the short half-life and action duration of prazosin. The mean elimination half-life of prazosin is about 2.5 hours and its duration of action is six to eight hours (24, 25). Due to prazosin short half-life, it is administrated two or three times per day in general medicine to treat symptoms of benign prostatic

Table 2. Summary of the Study Measured Outcomes[a]

	Pre-Treatment	Post-Treatment	P Value
Total CAPS score	70 ± 27	59 ± 25	0.182
PCL	56.2 ± 16	51.4 ± 17.3	0.69
Frequency of trauma-related nightmares	2.84 ± 1.2	2.56 ± 1.4	0.148
Intensity of trauma-related nightmares	3.2 ± 0.9	2.88 ± 1.2	0.56
TST, h	7.1 ± 1.2	6.6 ± 2	0.472
SL, min	20.3 ± 19.8	27.3 ± 23.1	0.589
SE, %	81.2 ± 10.6	75.6 ± 17.9	0.441
NWAK, n	10 ± 7.4	9.8±6.7	0.252

Abbreviations: CAPS, the clinician administered post-traumatic stress disorder scale; PCL, PTSD checklist; TST, total sleep time; SL, sleep latency; SE, sleep efficiency; NWAK, number of awakenings.
[a] Data presented as mean ± SD.

hypertrophy and hypertension (10). It seems that a single dose at bedtime cannot provide adequate concentrations of prazosin to affect PTSD symptoms during the following daytime hours. Consistent with this opinion, Taylor et al. suggested that adding two daytime prazosin doses (midmorning and evening) can reduce PTSD symptoms in persons with civilian trauma PTSD (26). Based on prazosin pharmacokinetic considerations, it is difficult to explain why bedtime or evening doses of prazosin had significant effects on nightmare and PTSD symptoms. There are controversies about the equal effects of prazosin on PTSD symptoms and total CAPS scores. Previously, in a crossover study by Raskind et al., evening prazosin (mean = 9.5 mg/day) compared to placebo significantly reduced both nighttime PTSD symptoms and total CAPS score in Vietnam combat veterans (11). However, the second randomized clinical trial by Raskind suggested that compared to placebo, prazosin (mean = 13 mg/day) had significant improvement in the frequency of trauma-related nightmares (based on the recurrent distressing dreams item of the CAPS) and sleep quality (based on Pittsburgh sleep quality Index (PSQI), but did not have a significant effect on total CAPS score (10). On the other hand, the study by Germain et al. showed greater reductions in insomnia severity and daytime PTSD symptom severity in the prazosin group rather than placebo; however, prazosin was not associated with reductions in nightmare frequency (12). It should be noted that Raskind et al., selected patients based on persistent nightmares; therefore, sampling factors may be for the cause of difference between the results of Raskind studies (10, 11, 22) and those of the others. Furthermore, this difference may be ascribed to the use of prospective nightmare diaries and the participation of veterans with low nightmare frequency.

In the current study, treatment response to sleep was defined as the improvement of objective insomnia and sleep quality measured by the actigraphy. The use of actigraphy has greater sensitivity for recording insomnia and sleep quality compared to that of a subjective sleep quality assessment (18, 19, 27). Actigraphic measurements did not differ between pre- and post-treatment time.

Due to the lack of enough evidence and discrepancy in studies conducted on the effects of prazosin on PTSD symptoms and nightmares in patients with PTSD, any argument on the mechanisms of prazosin action in nightmares in PTSD is difficult. Nightmares are mainly presented during light sleep and disrupted REM sleep, and are mostly attended by motor activity (28, 29). The effects of block of alpha-1 adrenergic receptor pathway on REM sleep in humans are unclear and those of the animal studies are not consistent. Some animal studies reported that prazosin decreased REM in rats (30, 31); others reported increased REM in rats (32) and cats (33, 34) by administration of prazosin. On the other hand, the conditions which lead to the advent of trauma nightmares are uncertain, and there is no evidence to affirm that PTSD trauma nightmares differ from non-trauma nightmares or normal dreams (35). While motor activity during REM is observed in patients with PTSD, there is no evidence that motor activity during REM is a characteristic of PTSD or related to nightmares (36, 37). Although few animal studies conducted in this regard, it is important to consider the idea that prazosin can regulate REM sleep in PTSD.

5.1. Conclusions

The current study findings showed that prazosin had no significant effect on reduction of PTSD symptoms and nightmares among veterans with chronic PTSD. However,

since there are conflicting study results on the effectiveness of prazosin, further clinical trials with larger sample sizes, based on polysomnographic assessments, are needed to define the effect of prazosin on sleep physiology and whether such effects relate to the therapeutic response.

Footnotes

Authors' Contribution: Habibolah Khazaie conceived and designed the study. Habibolah Khazaie and Marzie Nasouri collected the clinical data. Habibolah Khazaie, Marzie Nasouri and Mohammad Rasoul Ghadami interpreted the clinical data. Mohammad Rasoul Ghadami performed the statistical analysis. Habibolah Khazaie and Mohammad Rasoul Ghadami drafted the manuscript. Habibolah Khazaie and Mohammad Rasoul Ghadami revised the manuscript according to the reviewers' comments. All authors read and approved the final manuscript.

Funding/Support: There was no financial support.

Declaration of Interest: None declared.

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