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Prazosin for treating sleep disturbances in adults with posttraumatic stress disorder: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) is a disorder with significant sleep morbidity and limited treatment options. Prazosin may constitute a novel management approach and has been tested recently in a number of trials. We conducted a meta-analysis to examine the effectiveness of prazosin for nightmares and other sleep disturbances in adults with PTSD.

Method: A systematic review of databases for randomized, double-blind, placebo-controlled trials of adults diagnosed with PTSD and reporting sleep disturbances that were treated with prazosin was conducted in January 2015. No limitations were placed on language or year of publication.

Results: Six randomized controlled trials of prazosin for sleep disturbances in patients with PTSD were included (sample $n=240$). We found that prazosin was statistically significantly more effective than placebo in improving sleep quality [$g=0.987$, 95% confidence interval (CI): 0.324–1.651] and in reducing overall PTSD symptoms ($g=0.699$, 95% CI: 0.139–1.260) and sleep disturbances in particular ($g=0.799$, 95% CI: 0.391–1.234).

Conclusions: Prazosin showed medium-to-large and statistically significant effects on PTSD symptoms in general and sleep disturbances in particular. While promising, results should be interpreted with caution given the limited total number of participants and the limitations induced by the majority of participants being male and noncivilian.

1. Introduction

Estimates of the lifetime prevalence of posttraumatic stress disorder (PTSD) vary substantially depending on the population studied (military, police, general adult population, etc.), but most population lifetime estimates are reported to be at around 10% (7.8% in the United States, 9.2% in Canada and 12.2% in Australia) [1–3]. PTSD can affect both the mental and physical functioning of individuals and is associated with the presence of comorbid psychiatric conditions and physical illnesses [4]. Despite significant advances in the treatment of PTSD, only 30%–50% of patients reach complete remission [5].

Sleep disturbances are extremely common in individuals with PTSD and are often considered a hallmark of the disorder [6]. Studies indicate that 70%–87% of patients diagnosed with PTSD experience sleep disruption [7,8]. Distressing dreams have been reported by 71% of patients with PTSD [7], and insomnia occurs in 60%–90% of PTSD patients [8]. Fragmented sleep, distressing dreams and insomnia reduce sleep quality and quantity and may lead to poor concentration, difficulty coping emotionally, and increased agitation and irritability [9]. Disordered sleep may also be an important link to psychiatric comorbidities including substance use disorders [10]. Patients with PTSD who experience frequent nightmares may also have a significantly increased risk for suicide attempts [11]. Recurrent distressing dreams may persist for up to 50 years following the traumatic experience in patients with chronic PTSD [12].

Two medications, sertraline (Zoloft) and paroxetine (Paxil), are currently approved by the Food and Drug Administration for the treatment of PTSD. Randomized controlled trials (RCTs) have shown that sertraline ameliorated PTSD symptom severity but did not help with nightmare frequency [13,14]. Paroxetine may be even associated with nightmare induction [15]. Thus, current treatment, while efficacious, seems to have limited effectiveness, specifically when sleep disturbances are the primary concern.

Over 25 years ago, adrenergic dysregulation was identified as a contributing mechanism in PTSD [16], and it has been postulated that

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altered reactivity of noradrenergic neurons is associated with symptoms of hyperarousal [17]. It has also been shown that in PTSD, increased central nervous system adrenergic activity results in greater release of norepinephrine and increased sensitivity to norepinephrine at receptor sites [17]. Patients with PTSD have been found to have elevated norepinephrine levels in the cerebrospinal fluid, indicating increased norepinephrine activity [18]. Increased responsiveness of the noradrenergic system is consistent with a sensitization model of PTSD where biochemical, physiological and behavioral responses to subsequent stressors increase over time [19]. Given the significant involvement of noradrenergic hyperactivity in PTSD and its link to intrusive and hyperarousal symptoms, it is consistent with available evidence and plausible that treatments targeting noradrenergic hyperactivity might be useful in addressing hyperarousal symptoms and sleep disturbances in particular.

Prazosin, a centrally acting α1-adrenergic receptor antagonist, has been hypothesized to counteract noradrenergic stimulation and, therefore, potentially reduce the startle response and primitive fear response and normalize sleep [20]. In addition, postsynaptic α-1 adrenergic receptor attenuation induced by prazosin has been shown to disrupt the reconsolidation of fear memories [21].

Prazosin was first introduced in 1970s and is now available as a generic medication that has been used safely for treatment of hypertension as well as urinary outflow obstruction caused by benign prostatic hypertrophy. The most significant adverse reaction to prazosin is the "initial dose or rapid dosage increase syncope" with sudden loss of consciousness in patients given an initial dose of 2 mg or greater. This can be minimized by limiting the initial dose of the drug to 1 mg and by a slow and careful increase in dosage. Some of the other common side effects of prazosin are dizziness (10%), headache (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%) and nausea (5%). The maximum recommended dose is 40 mg daily. In most cases, adverse effects disappear completely with continued therapy or remain at a level which can be well tolerated [22].

There have been number of case reports, open-label trails and more recently RCTs assessing the efficacy of prazosin in treating sleep disturbances in patients with PTSD. Reviews summarizing the results have been published [23–25]. Findings from these studies led to the update in the Veterans Administration/Department of Defense Clinical Practice Guideline (VA/DoD CPG) for Management of Post-Traumatic Stress. Recommendations for prazosin for nightmares have undergone a change in strength of evidence from level C to B [26]. In addition, the American Academy of Sleep Medicine gave prazosin a level-A recommendation for treatment of PTSD-associated nightmares [27].

Thus, the purpose of this study was to perform a meta-analysis of current RCTs to examine the effectiveness of prazosin for nightmares and other sleep disturbances in adults with PTSD.

2. Methods

2.1. Study selection

Only randomized, double-blind, placebo-controlled trials were included in this meta-analysis. Studies were limited to those using prazosin as the active intervention, enrolling adults (age 18 years and over) diagnosed with PTSD and reporting sleep disturbances. The following study designs were not included in the review: cohort, case–control, single case studies, case series and studies with no control groups. Reviews that summarized previous studies were also excluded. No limitation was placed on language or year of publication.

2.2. Search strategy

The databases MEDLINE, EMBASE, PsycINFO, CINAHL, AMED, Scopus, Web of Science and Cochrane CENTRAL (up to May 1, 2015) were searched. A separate, additional search of PubMed identified articles published electronically prior to print publication and not available through MEDLINE. The clinical trials registries clinicaltrials.gov and Current Controlled Trials (controlled-trials.com) were searched for unpublished data. Keywords included in the search were [(prazosin OR minipress) AND (dream* OR nightmare* OR night terror* OR dyssomnia* OR insomnia* OR parasomnia* OR PTSD OR posttraumatic stress disorder OR posttraumatic stress disorder OR sleep disorder* OR sleep disruption* OR sleep distress* OR fragmented sleep*)], with the asterisk specifying the plural and grammatical variations.

2.3. Quality assessment

Two authors (D.K. and D.G.) independently reviewed all titles and abstracts identified by the search. Articles were selected for full-text review if the inclusion criteria were met. Disagreements were resolved by discussion between the two reviewers, and a third author (C.S.) was available to determine eligibility if consensus could not be reached.

2.4. Data extraction and selection of outcome measures

Two authors (D.K and D.G) extracted data independently. In cases of missing information, attempts were made to contact the study authors to obtain additional information. Demographic information, moderating variables and outcome measures were abstracted from the included studies. Outcomes of interest were measures of nightmares and other sleep-related disorders. The most common were the Clinician-Administered PTSD Scale (CAPS) [28], PTSD checklist (PCL) [29] or PTSD score derived from Mini-International Neuropsychiatric Interview (MINI) [30]. Other outcome measures were Clinical Global Impression (CGI) [31] and Pittsburgh Sleep Quality Index (PSQI) [32] scales.

2.5. Publication bias and heterogeneity assessment

Analysis of publication bias was carried out using funnel plots, and quantitative measurement using Begg and Mazumdar's rank correlation test and Egger's test. For each global effect-size estimate, Q-statistic and I^2 were calculated using the Comprehensive Meta-Analysis (CMA) software to examine the presence and magnitude of heterogeneity, and inform on the degree of overlap between different studies' confidence intervals (CIs). It has been suggested that I^2 values of 25%, 50% and 75% are considered as low, moderate and high heterogeneity [33].

Potential moderator variables that might influence the effect of the medication such as age, gender, treatment dosage, quality of studies and duration of trials via single meta-regressions as a function of quality

Table 1
Quality of included studies.

	Adequate sequence generation	Blinding of participants and personnel	Blinding of assessors	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Raskind et al., 2003	Unclear	Yes	Yes	Yes	Yes	Yes
Raskind et al., 2007	Yes	Yes	Yes	No	Yes	Yes
Taylor et al., 2008	Unclear	Yes	Yes	Yes	Yes	Yes
Germain et al., 2012	Yes	Yes	Yes	No	No	Yes
Raskind et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes
Ahmadpanah et al., 2014	Yes	Yes	Yes	No	Yes	No