Prazosin for treatment of nightmares related to posttraumatic stress disorder

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Purpose. The efficacy of prazosin for the treatment of posttraumatic stress disorder (PTSD)-related nightmares is reviewed.

Summary. PTSD is an anxiety disorder that can occur after experiencing or witnessing a life-threatening event, such as military combat, natural disasters, terrorist attacks, serious accidents, or violent personal assaults. The event that induced PTSD is often relived through nightmares or flashbacks. Sleep disturbances affect approximately 70% of patients with PTSD. Several medications have been evaluated for reducing PTSD-related nightmares, with limited success. Prazosin is a centrally and peripherally acting α_1-adrenergic antagonist whose mechanism of action, favorable adverse-effect profile, and low cost make it a promising agent for the treatment of PTSD. To date, two case reports, two chart reviews, three open-label trials, and two placebo-controlled trials have been published documenting the efficacy and safety of prazosin in the treatment of PTSD-related nightmares. Therapy with prazosin resulted in a reduction in nightmares in patients with both combat- and noncombat-related trauma. A therapeutic benefit occurred with prazosin dosages as low as 1 mg daily, and suppression of nightmare symptoms occurred within one week of prazosin initiation. The most frequently reported adverse event was orthostatic hypotension. The variability in the populations studied (e.g., combat, noncombat, recent traumatic experiences) leaves additional unanswered questions that must be addressed in large, randomized, controlled trials.

Conclusion. Prazosin appears to be a promising and well-tolerated agent for the management of PTSD-related nightmares. Further well-designed trials are warranted to establish its place in the treatment of PTSD.

Index terms: Dosage; Dreams; Hypotensive agents; Mechanism of action; Prazosin; Stress disorders; Toxicity

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Posttraumatic stress disorder (PTSD) is an anxiety disorder that can occur after experiencing or witnessing a life-threatening event, such as military combat, natural disasters, terrorist attacks, serious accidents, or violent personal assaults.[1,2] Persistent avoidance of stimuli associated with the trauma and numbing of responsiveness (e.g., feelings of detachment, loss of interest in activities), reexperiencing the trauma (e.g., intrusive recollections, daydreams, nightmares), and increased autonomic arousal (e.g., hyperactivity, irritability, sleep abnormalities) may develop shortly after the traumatic event. In the United States, PTSD occurs in 10% of women and 5% of men.[2] In addition, nonwhite and younger patients with a lower socioeconomic status have an increased risk of developing PTSD.[3]

The event that induced PTSD is often relived through nightmares or flashbacks. Nightmares are intrusive recollections of the traumatic event that cause high levels of anxiety or terror.[1,4] PTSD-related nightmares recollect circumstances that were involved during the original traumatic event.[4] Sleep disturbances affect approximately 70% of patients with PTSD.[5,6] Nightmare frequency may be affected by PTSD severity, exposure to combat or other forms of aggression, and comorbid psychiatric diagnoses.[6] Several medications have been evaluated for reducing PTSD-related nightmares, including nefazodone, trazodone, cyproheptadine, olanzapine, quetiapine, mirtazapine, gabapentin, and topiramate, with limited success.[5-7]

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PTSD may occur as a result of increased central nervous system (CNS) adrenergic activity,[3,8-10] which causes an increased release of norepinephrine and hyperresponsiveness of postsynaptic receptors to norepinephrine. Studies of patients with PTSD have demonstrated that the increase in CNS adrenergic activity occurs primarily at night, and the hyperresponsiveness of the postsynaptic α_1-adrenergic receptors disrupts the sleep cycle and increases feelings of fear.[8-11]

The α_1-receptors are located in the hippocampus (involved with memory), amygdala (part of the limbic system that plays a role in emotions, especially fear responses), and other areas of the brain.[10] Prazosin is a centrally and peripherally acting α_1-receptor antagonist.[12] Blocking the α_1-receptors in the brain may help ameliorate PTSD-induced nightmares. Several investigators have evaluated the efficacy of prazosin in the management of PTSD-induced nightmares.[8-10,13-16] Prazosin's mechanism of action, favorable adverse-effect profile, and low cost make it a promising agent for the treatment of PTSD. This article reviews the literature regarding the efficacy of prazosin in the treatment of nightmares in patients with PTSD.

Literature review

The published medical literature was searched via PubMed, International Pharmaceutical Abstracts, and PsychInfo using the terms "prazosin" and "posttraumatic stress disorder." Reference citations from the publications identified were also reviewed. The English-language articles identified were evaluated. Of these, two case reports, two chart reviews, three open-label trials, and two placebo-controlled trials documented the efficacy and safety of prazosin and are summarized in this review. One trial was excluded because it focused on the effect of prazosin on PTSD daytime symptoms.[17]

Case reports. Two case reports were published in which patients received prazosin for PTSD-induced nightmares. In the first case report, a 38-year-old man complained of nightmares and irritability as a result of the September 11, 2001, terrorist attacks despite trials of selective serotonin-reuptake inhibitors (SSRIs), a mood stabilizer, and an atypical antipsychotic.[14] A trial of prazosin 1 mg before bedtime was initiated. The patient reported no nightmares after taking the medication for three weeks. No dosage increase was required. He described lightheadedness and morning grogginess after beginning prazosin therapy.

The second case report involved a 15-year-old girl who was admitted to a long-term psychiatric care facility for self-harm and aggression.[15] At admission, she met the diagnostic criteria for chronic PTSD secondary to sexual and physical abuse and was receiving nefazodone, trazodone, and zolpidem. After three months of hospitalization, she reported having nightmares. Prazosin 1 mg was initiated and was gradually increased in 1-mg increments to 4 mg at bedtime. The patient reported improvement when evaluated after four weeks of therapy. Nightmare remission continued over the subsequent two months.

Retrospective chart reviews. The efficacy of prazosin in the treatment of combat-related nightmares was reported in a chart review conducted at the Madigan Army Medical Center Behavioral Health Clinic.[8] A total of 28 soldiers (27 men and 1 woman) age 20–41 years who reported combat-related nightmares received prazosin. Two patients reported previous psychiatric or substance abuse issues, and 10 were receiving no psychotropic medications before prazosin was initiated. Eighteen patients described nightmares despite treatment with at least one psychotropic drug (paroxetine, sertraline, escitalopram, venlafaxine, bupropion, mirtazapine, and amitriptyline).

Prazosin 1 mg was initiated at bedtime, and the dosage was increased by 1 mg weekly if nightmares persisted. The highest dosage associated with nightmare reduction was 5 mg daily. Combat-related nightmares were assessed weekly using the Clinical Global Impressions—Change (CGI-C) scale, with a score of 1 indicating very much improved and 7 indicating very much worse.[18] Results were available for only 20 patients (5 were lost to follow-up and 3 were not assessed). Twenty soldiers reported marked improvement in nightmare severity, 2 reported moderate improvement, and 1 reported no change, even after the dosage was increased to 6 mg at bedtime.

A retrospective chart review was conducted at the Department of Veterans Affairs in Seattle, Washington, to determine the effects of prazosin on PTSD-related nightmares.[16] Prazosin was prescribed to male, Vietnam and Gulf War veterans ($n = 59$) with chronic, severe, combat-related nightmares, defined by a score of ≥5 on the Recurrent Distressing Dreams item of the Clinician Administered PTSD Scale (CAPS) despite treatment with at least one psychoactive medication (e.g., SSRI, trazodone, sedating antihistamine, valproic acid, benzodiazepine). The CAPS measures the core symptoms of PTSD. Scores range from 0 to 8 for each of the 17 items and from 0 to 136 for all 17 symptoms.[19] Patients' current medications were continued during the study. Prazosin 1 mg was initiated at bedtime. Several days later, the dosage was increased to 2 mg, and it was gradually increased until nightmares were improved, adverse effects prohibited use, or a maximum daily dose of 20 mg was achieved. If >10 mg was required, the additional prazosin dose was given as a separate dose in the early evening.

A total of 51 patients began treatment. Patients who did not have the prazosin prescription filled were designated the treatment com-

parison group (n = 8). The CAPS was administered at baseline and after eight weeks of stable prazosin therapy. Of the 51 patients who received prazosin and remained in the primary analysis, 36 completed at least eight weeks of further prazosin treatment.[16] The mean ± S.D. prazosin dosage was 6.3 ± 0.8 mg daily, and the 36 patients who completed prazosin therapy received a mean ± S.D. maximum dosage of 9.6 ± 0.9 mg daily.

The scores for the CAPS Recurrent Distressing Dreams item were substantially decreased from baseline (7.1 ± 0.2) to posttreatment (4.2 ± 0.3) for the 51 patients who received prazosin ($p < 0.0001$). A statistically significant decrease in CAPS score from baseline (7.0 ± 0.2) to posttreatment (3.5 ± 0.3) was achieved by the 36 patients who completed prazosin therapy ($p < 0.0001$). In the treatment comparison group, no significant change in mean ± S.D. scores from baseline (6.8 ± 0.5) to study end (6.7 ± 0.4) was noted. Scores in the treatment group were significantly greater than in the treatment comparison group ($p < 0.01$).

Approximately 78% of prazosin-treated patients had improved CAPS scores for overall PTSD severity. Mean ± S.D. CGI-C scores were improved in the 51 patients in the primary analysis when compared with the 8 patients in the nontreatment group (2.9 ± 0.1 versus 3.9 ± 0.1, respectively; $p < 0.01$). Twenty-nine percent of patients (n = 15) discontinued prazosin therapy; however, mean ± S.D. CAPS scores were significantly reduced from baseline in these patients (from 7.0 ± 0.3 to 5.7 ± 0.5, $p < 0.01$). The most reported adverse effects were orthostatic dizziness and headache (n = 3) and nausea (n = 2). Patients frequently reported improved sleep quality and normal dream patterns.

Open-label trials. Peskind et al.[9] conducted an open-label clinical trial to determine the efficacy of prazosin in elderly patients (mean ± S.D. age, 76 ± 2 years) with PTSD. A total of nine patients met the following criteria for chronic PTSD: symptoms present since the traumatic experience, recurrent trauma-related nightmares that had not improved with the use of other psychotropic medications, a score of ≥5 on the CAPS Recurrent Distressing Dreams item, and the absence of orthostatic hypotension. The patients also had multiple medical comorbidities and were maintained on numerous general and psychotropic medications, including SSRIs and other antidepressants. Psychotropic and other medications remained unchanged throughout the study. Eight patients were combat veterans; one patient, a Nazi Holocaust survivor, resided in a nursing home. A Mini-Mental State Exam[20] was administered to all patients; the eight veterans had a mean ± S.D. score of 27 ± 3 and the nursing home patient scored 24. The nursing home patient met the criteria for mild cognitive impairment.

Nightmares were assessed via the Recurrent Distressing Dreams item of the CAPS, and the effect of prazosin on overall severity and functional impairment was estimated using the CGI-C at eight weeks. Prazosin 1 mg was initiated at bedtime for one week, and the dosage was increased weekly by 1 mg before bedtime to a maximum dosage of 4 mg one hour before bedtime. Two patients were admitted to the hospital for prazosin dosage adjustment due to serious cardiovascular and other medical comorbidities; two had prazosin initiated during psychiatric inpatient admissions to a specialized PTSD unit, one patient remained in the nursing home facility, and the remaining four were treated as outpatients.

Eight patients experienced considerable (>50%) reduction in nightmares after eight weeks of prazosin treatment ($p < 0.001$) and had markedly or moderately improved CGI-C scores in overall functioning and PTSD severity. Nightmare suppression persisted as long as the patients continued to take prazosin regularly. Two patients had a partial recurrence of nightmares, which resolved after a dosage increase (3–4 mg at bedtime). Three patients who temporarily discontinued prazosin for unknown reasons experienced nightmare recurrence within two nights of terminating therapy. After therapy was resumed, the nightmares were suppressed. One patient developed orthostatic dizziness that later resolved, and treatment was continued without further episodes.[9]

Taylor and Raskind[11] conducted an open-label trial with five civilian patients (age 35–58 years) who met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*) criteria for PTSD, scored at least 80 on the CAPS, were seeking treatment for PTSD symptoms, had no alcohol or substance abuse problems, and scored at least 4 on the nightmare item of the CAPS One Week Symptom Version (CAPS-SX). CGI-C and Clinical Impression of Change—Nightmares (CIC-Nightmares)[21] scores were measured at baseline, week 2, and week 6 of prazosin therapy. Prazosin 1 mg was initiated at bedtime, and the dosage was increased to 2 mg at bedtime. If needed, a morning dose was added to control daytime PTSD symptoms. The mean dosage of prazosin was 1.8 mg daily.

At week 6, all five patients reported moderate improvement, three of whom had marked improvement of PTSD symptoms per CGI-C scores. All patients reported moderate improvement on the CIC-Nightmares scale. Patients had a mean ± S.D. CAPS total score of 103 ± 3.9 at baseline and 73.4 ± 19.4 at week 6. Patients' mean ± S.D. score on the nightmare item of the CAPS also decreased from baseline (6.8 ± 0.8) to week 6 (1.8 ± 1.3).

An open-label, eight-week feasibility study of prazosin was con-

ducted in four veterans with PTSD and severe, chronic, combat-trauma-related nightmares.[10] All patients had undergone previous treatment with psychotherapy and psychotropic medications that gave no relief of the nightmares. Patients were included in the trial if they were a combat veteran who met the *DSM-IV* criteria for PTSD; were seeking treatment for PTSD-related, chronic, severe nightmares; had no alcohol or substance abuse problems for at least six months; and had a score of ≥6 on the nightmare item of the CAPS-SX. All patients had mild-to-moderate hypertension despite treatment with antihypertensive medications.

Prazosin 1 mg was initiated at bedtime during week 1, and the dosage was increased to 2 mg at bedtime during week 2. If nightmares persisted and no adverse effects were observed, the dosage was increased to 5 mg at bedtime during weeks 3 and 4. The dosage could be increased to 10 mg in divided doses of 5 mg in the afternoon and 5 mg at bedtime during weeks 5–8. All four patients were maintained on prazosin dosages of 2–10 mg, with one patient receiving 5 mg twice daily and another receiving 5 mg every day in combination with propranolol (due to increased cardiac symptoms). Although propranolol has been associated with intensified nightmares,[22] it was thought that it would decrease the patient's cardiovascular symptoms (sinus tachycardia) without increasing the nightmares when used in combination with prazosin. Two days after concomitant propranolol and prazosin administration, the patient reported that he was no longer having nightmares, and the cardiac symptoms had subsided. All four patients had decreased nightmare severity while taking prazosin according to the CAPS-SX nightmare severity score (7.5 ± 0.57 versus 1.75 ± 2.06).[10]

All four patients tolerated therapy well; however, two patients developed lethargy and mild orthostatic dizziness, which resolved without discontinuation of prazosin. One patient discontinued therapy because he ran out of medication; during those two weeks, his nightmare severity increased to pretreatment levels. When prazosin was reintroduced, the severity of the nightmares rapidly declined.

Placebo-controlled studies. Two placebo-controlled clinical trials have been published evaluating the use of prazosin in the treatment of PTSD-induced nightmares.[13,23] Forty military veterans participated in a placebo-controlled, randomized clinical trial evaluating the effect of prazosin taken at bedtime on distressing trauma nightmares and sleep disturbance over eight weeks.[23] Patients included in the trial met *DSM-IV* criteria for combat-related PTSD or other life-threatening, war-zone trauma. In addition, patients had to have a CAPS score of ≥5 on both the CAPS Recurrent Distressing Dreams item and Difficulty Falling Asleep or Staying Asleep item and been experiencing symptoms for at least three months. Patients were excluded if they had a history of schizophrenia, bipolar disorder, other psychotic disorder, or depression with active suicidal ideation.

Prazosin 1 mg or placebo was initiated at bedtime for three days. The prazosin dosage was increased to 2 mg at bedtime through day 7. If patients continued to have nightmares, the dosage was increased to 4 mg at bedtime through day 14. The dosage could be increased to 6 mg at bedtime through day 21 and to 10 mg at bedtime through day 28. The maximum daily dose was 15 mg at bedtime. The primary outcomes were the CAPS Recurrent Distressing Dreams item, Pittsburgh Sleep Quality Index (PSQI),[24] and CGI-C scores. The PSQI scale assesses sleep quality during the previous month, with each of its seven components generating a score ranging from 0 (no difficulty) to 3 (severe difficulty). Total scores greater than 5 indicate a significant sleep disturbance.

A total of 40 patients (38 men and 2 women) were included in the study. Patients had a baseline mean ± S.D. CAPS score of 70 ± 20 and a Combat Exposure Scale[25] score of 9 ± 3. All patients' chronic nighttime PTSD symptoms were unresponsive or partially responsive to treatment. Most patients (n = 27) had been receiving psychotherapy for two months before study initiation, and 20 patients were receiving psychotropic medications that remained unchanged during the study period. The mean ± S.D. daily dose of prazosin was 13 ± 3 mg. Of the 40 patients who participated in the study, 6 did not complete outcome assessments due to protocol discontinuations: 4 patients discontinued the study due to adverse effects (3 treated with prazosin and 1 received placebo), and 2 (randomized to placebo) were lost to follow-up for unknown reasons.

Of the 34 evaluable patients, 33 completed the trial. Statistically significant improvements were observed between prazosin and placebo in mean ± S.D. CAPS Recurrent Distressing Dreams item scores (3.2 ± 2.6 versus 5.2 ± 2.2, p = 0.02), PSQI scores (9.7 ± 3.9 versus 12.6 ± 4.1, p = 0.008), and CGI-C scores (2.41 ± 1.1 versus 3.65 ± 1.2, p = 0.002). Recurrent distressing dreams in prazosin-treated patients decreased by 50% compared with a reduction of 15% in patients receiving placebo (p = 0.02). Statistically significant improvements between prazosin and placebo were also observed for the Nightmare Frequency Questionnaire[26] for the subscale of nights with military trauma-related nightmares (0.9 ± 1.8 versus 2.3 ± 2.1, p = 0.02). No significant differences in the number of nights with nightmares and unpleasant dreams of any kind were observed for the same subscale. Fifteen patients reported transient dizziness (prazosin [n =

9] and placebo [n = 6]); however, no significant differences in systolic or diastolic blood pressure were reported between groups. The authors concluded that prazosin was effective for the treatment of PTSD in combat veterans with traumatic nightmares and sleep disturbance.[23]

Ten Vietnam veterans with chronic, severe, combat-related PTSD (as measured by the *DSM-IV* criteria) participated in a placebo-controlled, 20-week, crossover trial.[13] All patients had been diagnosed with PTSD since returning from the Vietnam war (at least for 25 years). Although five patients met the criteria for alcohol abuse in the past, all had been free from alcohol or other substance abuse for at least six months. In addition, all patients had frequent and severe combat-trauma-related nightmares (defined by a score of ≥6 on the CAPS Recurrent Distressing Dreams item). The primary efficacy measures were the change in CAPS score on the Recurrent Distressing Dreams item and Difficulty Falling and Staying Asleep item. The change in overall severity and functional status on the CGI-C was also measured.

Patients included in the study completed a three-week prazosin dosage adjustment period, followed by six weeks of maintenance therapy. Patients were randomly assigned to prazosin (n = 5) or placebo (n = 5) first. Patients were initiated on placebo or prazosin 1 mg at bedtime for three days, followed by 2 mg nightly for four days. If nightmares continued, the dosage was increased to 4 mg nightly for seven days. The dosage could be increased to a total of 10 mg (6 mg at bedtime and 4 mg during the day). At the end of week 9, patients entered a two-week washout period. The second treatment was initiated at week 11, and the prazosin dosage was again adjusted over three weeks. At week 20, maintenance treatment was terminated.

The mean age of patients included in the trial was 53 years. Seven of the 10 patients were receiving other psychotropic medications that were maintained during the study. The mean ± S.D. prazosin dosage was 9.5 ± 0.5 mg per day. A statistically significant difference was observed in the CAPS score between prazosin and placebo at week 20 ($p < 0.001$). In addition, a statistically significant reduction in the mean ± S.D. number of recurrent distressing dreams was observed between prazosin and placebo (6.9 ± 0.9 versus 3.6 ± 2.8, $p < 0.01$), and CGI-C scores (overall PTSD severity and function) also differed significantly between prazosin and placebo (2.0 ± 0.5 versus 4.5 ± 1.8, respectively; $p < 0.01$). Two patients experienced mild orthostatic hypotension and dizziness, which quickly resolved after adjusting the dosage. Mean ± S.D. systolic and diastolic blood pressures were within normal limits at study endpoint (mean systolic pressure, 135 ± 12 mm Hg [supine] and 129 ± 12 mm Hg [standing]; mean diastolic pressure, 89 ± 8 mm Hg [supine] and 84 ± 15 mm Hg [standing]). Patients randomized to the second treatment period experienced a return of nightmare symptoms during the prazosin washout period that prompted them to ask for open-label prazosin therapy. The investigators concluded that prazosin was efficacious in the treatment of PTSD-induced nightmares, sleep disturbance, and other related symptoms.[13]

Discussion

The reviewed literature included two case reports that documented the efficacy of low-dose prazosin in patients with noncombat-related PTSD. Because follow-up was not maintained longer than four months and no objective measures of nightmares were included in the assessments, it is difficult to determine the clinical benefit from prazosin from those reports.

Most patients included in the reviewed studies were male (149 versus 8 females).[8-11,13,14,16,22] This may have important implications, considering that PTSD is more prevalent in female patients.[3] In addition, the types of experiences that precipitate PTSD symptoms between men and women differ.[3,27,28] Men are more likely to witness someone being badly injured or killed or be involved in a fire, natural disaster, or life-threatening accident. Women are more likely to be victims of sexual molestation, childhood parental neglect, and childhood physical abuse.[3,27,28] Although the severity of PTSD directly affects the occurrence of nightmares,[6] it is unknown which experiences produce the greatest PTSD symptoms. As a result, it is unknown if prazosin acts the same in the resolution of PTSD symptoms in women and men. In addition, the majority of patients in the literature reviewed experienced some combat-related trauma (n = 148),[8-10,13,16,23] and combat-related trauma is associated with more severe PTSD; therefore, it is unknown which type of trauma responds greater to prazosin therapy.[6]

Significant improvements were observed in CGI-C scores in the double-blind, placebo-controlled trials with prazosin.[13,23] However, when the frequency of nightmares was compared in the clinical trials, conflicting results were found. Although significant improvements with respect to the CAPS Recurrent Distressing Dreams item score, PSQI score, and Nightmare Frequency Questionnaire were observed,[23] clinical significance was unlikely due to the overlap in the scores between prazosin and placebo-treated patients. Likewise, in a separate trial, significant improvements were found in CGI-C scores, recurrent distressing dreams, total CAPS score, difficulty falling or staying asleep, reexperiencing or intrusion, and avoidance or numbing; however, clinically significant differences were observed only in CGI-C scores and the number of recurrent or distressing dreams (in-

dicated by no overlap in scores for these outcome measures).

The optimal dosage of prazosin for the treatment of PTSD-related nightmares has not been elucidated. The mean ± S.D. daily dose for combat veterans and elderly patients ranges from 2.3 ± 0.7 mg[9] to 13.3 ± 3 mg.[23] Patients with noncombat-related trauma have received between 1[14] and 4 mg[15] of prazosin daily. Since combat-related trauma is associated with more severe PTSD, higher doses of prazosin are anticipated to control PTSD symptoms. It is unknown if the dosage required is related to the duration of PTSD symptoms.

In the double-blind study by Raskind et al.,[10] combat veterans who received a mean ± S.D. prazosin daily dose of 13 ± 3 mg had significant improvements in the endpoint; however, the mean dose of prazosin in the other double-blind study with combat veterans was not reported.[13] No mean doses were reported in studies with younger patients who did not have other comorbid illnesses.[11,16] In addition, the study by Raskind et al.[10] included a control group of individuals who did not get the prescription filled for prazosin. This control group is subject to bias because the patients were not randomized to treatment and may not have been interested in their care, which could have adversely affected the outcome of the study.

The onset of action of prazosin has varied in clinical trials. The majority of the trials were conducted over six to eight weeks [10,11,23]; however, patients were assessed at predetermined time periods during the trials to determine response. In the retrospective chart review by Daly et al.,[8] patients were monitored weekly, and beneficial response was observed in as few as five days. Other investigators assessed response to therapy between one[9,13,22] and two weeks.[10,11]

The appropriate length of prazosin therapy has not been determined. The longest length of prazosin therapy for PTSD-related nightmares reported in the literature was 20 weeks.[13] The return of nightmares after discontinuation of prazosin therapy was relatively sudden in patients receiving the medication for prazosin-related PTSD[9-11]; nightmares returned two days after discontinuing prazosin and resolved when prazosin was reinstituted.[9] A diminished therapeutic response is anticipated in this time frame, as the half-life of prazosin is two to four hours.[22]

The adverse effects most commonly seen in clinical trials with prazosin for PTSD-related nightmares were orthostatic hypotension, nausea, and headache.[13,16,23] As evidenced by the results of the double-blind, placebo-controlled clinical trials, orthostatic hypertension was not significant because of the dosage adjustment schedule during prazosin administration.[13,21]

Role in therapy

Clinical trials indicate that prazosin therapy is beneficial for the treatment of PTSD-related nightmares; however, several unanswered questions remain related to prazosin therapy. Additional randomized, controlled clinical trials should focus on the approximate duration of prazosin therapy, optimal dose, differences in dosages based on severity, frequency and duration of PTSD symptoms, differences in responses between military and civilian patients, and differences in responses between male and female patients. Likewise, objective measures of improvement need to be used to manage therapy in these patients.

Ongoing clinical trials evaluating prazosin in the treatment of PTSD-related nightmares (combat-related [including patients returning from Operation Iraqi Freedom] and noncombat-related) are being conducted.[29] In the meantime, practitioners should reserve prazosin for those patients with at least a moderate degree of intensity or severity of nightmares and with no orthostasis. Prazosin may be an option for those patients with concomitant hypertension or benign prostatic hypertrophy. In addition, prazosin should be initiated at low dosages and gradually increased (1 mg per week) until the patient's condition improves (one-to two-week trial period) or adverse events occur that limit dosage increases.

Conclusion

Prazosin appears to be a promising and well-tolerated agent for the management of PTSD-related nightmares. Further well-designed trials are warranted to establish its place in the treatment of PTSD.

References

1. Anxiety disorders: post traumatic stress disorder. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 1994:424-9.
2. National Center for Post Traumatic Stress Disorder. What is PTSD? www.ncptsd.va.gov/ncmain/ncdocs/fact_shts/fs_faqs_on_ptsd.html (accessed 2008 Jan 10).
3. Schnurr PP, Friedman MJ, Bernardy NC. Research on posttraumatic stress disorder: epidemiology, pathophysiology, and assessment. *J Clin Psychol.* 2002; 58:877-89.
4. Anxiety disorders: post traumatic stress disorder. In: Hales RE, Yudofsky SC, eds. The American Psychiatric Publishing textbook of clinical psychiatry. 4th ed. Arlington, VA: The American Psychiatric Publishing; 2002:595-607.
5. Van Lieempt S, Vermetten E, Geuze E et al. Pharmacotherapeutic treatment of nightmares and insomnia in posttraumatic stress disorder: an overview of the literature. *Ann N Y Acad Sci.* 2006; 1071:502-7.
6. Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact, and approaches to management. *CNS Drugs.* 2006; 20:567-90.
7. American Psychiatric Association. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. www.psych.org/psych_pract/treatg/pg/ASD_PTSD_05-15-06.pdf (accessed 2007 Mar 2).
8. Daly CM, Doyle ME, Radkind M et al. Clinical case series: the use of prazosin for combat-related recurrent nightmares among Operation Iraqi Freedom combat veterans. *Mil Med.* 2005; 170:513-5.

9. Peskind ER, Bonner LT, Hoff DJ et al. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. *J Geriatr Psychiatry Neurol.* 2003; 16:165-71.
10. Raskind MA, Dobie DJ, Kanter ED et al. The alpha-1 adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of four cases. *J Clin Psychiatry.* 2000; 61:129-33.
11. Taylor FT, Raskind MA. The alpha-1 adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol.* 2002; 22:82-5.
12. Mosby's drug consult. St. Louis: Mosby; 2006:II-2371-3.
13. Raskind MA, Peskind ER, Kanter ED et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry.* 2003; 160:371-3.
14. Griffith LJ. Case report: use of prazosin for treatment of posttraumatic stress disorder. *Am Fam Physician.* 2005; 72:758, 761. Letter.
15. Brkanac Z, Pastor JF, Storck M. Prazosin in PTSD. *J Am Acad Child Adolesc Psychiatry.* 2003; 42:384-5. Letter.
16. Raskind MA, Thompson C, Petrie EC et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry.* 2002; 63:565-8.
17. Taylor FB, Lowe K, Thompson C et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry.* 2006; 59:577-81.
18. Guy W. Clinical Global Impressions (CGI) scale. In: Rush AJ, Pincus HA, First MB et al., eds. Handbook of psychiatric measures. 1st ed. Washington, DC: American Psychiatric Association; 2000:100-2.
19. Blake DD, Weathers FW, Nagy LN et al. The development of a clinician administered PTSD scale. *J Trauma Stress.* 1995; 8:75-80.
20. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189-98.
21. Lehman E. Practicable and valid approach to evaluate the efficacy of drugs by means of rating scales. *Pharmacopsychiatry.* 1984; 17:71-85.
22. Micromedex Healthcare Series. Drugdex evaluations: prazosin. www.thomsonhc.com.ezproxy.samford.edu/home/dispatch (accessed 2007 Mar 2).
23. Raskind MA, Peskind ER, Hoff DJ et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. *Biol Psychiatry.* 2007; 61:928-34.
24. Buysse DJ, Reynolds CF III, Monk TH et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989; 28:193-213.
25. Laufer RS, Yager T, Frey-Wouters E et al. Legacies of Vietnam: comparing adjustment of veterans and their peers. Vol. 3. Washington, DC: U.S. Government Printing Office; 1981.
26. Krakow B, Schrader R, Tandberg D et al. Nightmare frequency in sexual assault survivors with PTSD. *J Anxiety Disord.* 2002; 16:175-90.
27. Lecrubier Y. Posttraumatic stress disorder in primary care: a hidden diagnosis. *J Clin Psychiatry.* 2004; 65(suppl 1):49-54.
28. Grinage BD. Diagnosis and management of post-traumatic stress disorder. *Am Fam Physician.* 2003; 68:2401-8.
29. Clinicaltrials.gov. www.clinicaltrials.gov (accessed 2007 Feb 21).