PTSD nightmares: Prazosin and atypical antipsychotics

Rebecca L. Graham, PharmD, Susan G. Leckband, RPh, BCPP, and Rene A. Endow-Eyer, PharmD, BCPP

Mr. S, a 45-year-old veteran, was diagnosed with posttraumatic stress disorder (PTSD) 18 years ago after a tour of duty in the Persian Gulf. He had combat-related flashbacks triggered by the smell of gasoline or smoke from a fire, was easily startled, and began to isolate himself socially. However, his symptoms improved when he started volunteering at his local Veterans Affairs Medical Center. After he lost his job 3 years ago, Mr. S started experiencing flashbacks. He was irritable, easily startled, and avoided things that reminded him of his time in the Persian Gulf. His psychiatrist prescribed sertraline, titrated to 200 mg/d. The drug reduced the severity of his avoidance and hyperarousal symptoms and improved his mood.

During a clinic visit, Mr. S says he is doing well and can fall asleep at night but is having recurring nightmares about traumatic events that occurred during combat. These nightmares wake him up and have become more frequent, occurring once per night for the past month. Mr. S says he has been watching more news programs about conflicts in Afghanistan and Iraq since the nightmares began. His psychiatrist starts quetiapine, 50 mg at bedtime for 7 nights then 100 mg at bedtime, but after 6 weeks Mr. S says his nightmares continue.

Dr. Graham is a Second-Year Psychiatric Pharmacy Resident, Veterans Affairs San Diego Healthcare System (VASDHS); Ms. Leckband is a Clinical Psychiatric Pharmacist Specialist, VASDHS, and Assistant Clinical Professor through Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Psychiatry, University of California, San Diego; and Dr. Endow-Eyer is Psychiatric Clinical Pharmacy Specialist, VASDHS, and Assistant Clinical Professor through Skaggs School of Pharmacy and Pharmaceutical Sciences and Department of Psychiatry, University of California, San Diego, San Diego, CA.

PTSD occurs in approximately 19% of Vietnam war combat veterans[1] and 14% of service members returning from Iraq and Afghanistan.[2] PTSD symptoms are classified into clusters: intrusive/re-experiencing; avoidant/numbing; and hyperarousal.[3] Nightmares are part of the intrusive/re-experiencing cluster, which is Criterion B in DSM-IV-TR. See this article at CurrentPsychiatry.com for a description of DSM-IV-TR PTSD criteria. Among PTSD patients, 50% to 70% report PTSD-associated nightmares.[4] Despite adequate treatment targeted to improve PTSD's core symptoms, symptoms such as sleep disturbances or nightmares often persist.

Nightmares and other sleep disturbances are associated with significant distress and daytime impairment and can interfere with PTSD recovery[4-8] by disrupting sleep-dependent processing of emotional experiences and causing repeated resensitization to trauma cues (***Table 1, page 60***).[8]

Few randomized controlled medication trials specifically address PTSD-related

Practice Points

- Prazosin is recommended as a **first-line therapy for nighttime PTSD symptoms**, such as nightmares or sleep disturbances—especially among veterans—because of superior long-term effectiveness.
- **Risk of metabolic syndrome**, which has been reported with low-dose atypical antipsychotics used for treating insomnia, limits their use for PTSD-related nightmares.

Vicki L. Ellingrod, PharmD, BCPP, FCCP
Series Editor

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Table 1

Psychosocial consequences of sleep disruption in PTSD

Increased reactivity to emotional cues
Compromised ability to function in social and occupational roles
Negative psychiatric outcomes, including suicidal ideation or worsening of depression or psychosis
Interference of natural recovery from trauma exposure
Repeated resensitization to trauma cues
Neurocognitive deficits
Neuroendocrine abnormalities

PTSD: posttraumatic stress disorder
Source: Adapted from reference 8

Clinical Point

Prazosin reduced trauma nightmares and improved sleep quality and global clinical status more than placebo

nightmares. Most PTSD studies do not examine sleep outcomes as a primary measure, and comprehensive literature reviews could not offer evidence-based recommendations.[9,10] The American Academy of Sleep Medicine (AASM) also noted a paucity of PTSD studies that identified nightmares as a primary outcome measure.[11] See this article at CurrentPsychiatry.com for a list of recommended medication options for PTSD-associated nightmares.

CASE CONTINUED

Medication change, improvement

After reviewing AASM's treatment recommendations, we prescribe prazosin, 1 mg at bedtime for 7 nights, then increase by 1 mg at bedtime each week until Mr. S's nightmares improve. He reports a substantial improvement in nightmare severity and frequency after a few weeks of treatment with prazosin, 5 mg at bedtime.

Prazosin

Prazosin is an α1-adrenergic receptor antagonist with good CNS penetrability. The rationale for reducing adrenergic activity to address intrusive PTSD symptoms has been well documented.[12,13] In open-label trials,[14-18] a chart review,[19] and placebo-controlled trials,[20-22] prazosin reduced trauma nightmares and improved sleep quality and global clinical status more than placebo (***Table 2***). In these studies, prazosin doses ranged from 1 to 20 mg/d, with an average of 3 mg at bedtime and a starting dose of 1 mg. Prazosin is the only agent recommended in the AASM's Best Practice Guide for treating PTSD-related nightmares.[11]

Atypical antipsychotics

Atypical antipsychotics have been used to reduce nightmares in PTSD; however, most of the evidence from studies evaluated in the AASM's Best Practice Guide were considered to be low quality.[11] Quetiapine and ziprasidone were not included in the AASM review. Visit this article at CurrentPsychiatry.com for a table reviewing the evidence for atypical antipsychotics for treating PTSD nightmares.

Comparing prazosin and quetiapine. A historical prospective cohort study of 237 veterans with PTSD receiving prazosin or quetiapine for nighttime PTSD symptoms demonstrated that although the 2 drugs have similar efficacy (defined as symptomatic improvement) for short-term, 6-month treatment (61% vs 62%; $P = .54$), a higher percentage of patients continued prazosin long-term (3 to 6 years) than those taking quetiapine (48% vs 24%; $P < .001$).[23] Twenty-five percent of patients taking quetiapine switched to prazosin during the study, and approximately one-half of these patients remained on prazosin until the study's end. Only 8% of prazosin patients switched to quetiapine, and none continued this therapy until study end.[23] Patients in the quetiapine group were more likely to discontinue the drug because of lack of efficacy (13% vs 3%; $P = .03$) and adverse effects (35% vs 18%; $P = .008$), specifically sedation (21% vs 2%; $P < .001$) and metabolic effects (9% vs 0%; $P = .014$), compared with prazosin. Although this trial may be the only published comparison study of prazosin and quetiapine, its methodological quality has been questioned, which makes it difficult to draw definitive conclusions.

Metabolic syndrome—elevated diastolic blood pressure, increased waist circumference, and low high-density lipoprotein cholesterol—is common among PTSD patients treated with antipsychotics.[24] This

Visit this article at CurrentPsychiatry.com for a list of medication options for PTSD nightmares

Table 2

RCTs of prazosin for trauma-related nightmares

Study	Design	Patients	Results
Raskind et al, 2003[20]	20-week, double-blind, placebo-controlled, crossover study (mean dose 9.5 mg/d at bedtime)	10 Vietnam veterans with chronic PTSD and severe trauma-related nightmares	Prazosin was superior to placebo on scores on the recurrent distressing dreams item and difficulty falling/staying asleep item of the CAPS and change in PTSD severity and functional status on the CGI-C
Raskind et al, 2007[21]	8-week, placebo-controlled, parallel study (mean dose 13.3 ± 3 mg/d in the evening)	40 veterans with chronic PTSD, distressing trauma nightmares, and sleep disturbance	Prazosin was superior to placebo in reducing trauma nightmares and improving sleep quality and global clinical status; prazosin also shifted dream characteristics of trauma-related nightmares to those typical of normal dreams
Taylor et al, 2008[22]	7-week, randomized, placebo-controlled, crossover trial (mean dose 3.1 ± 1.3 mg)	13 outpatients with chronic civilian trauma PTSD, frequent nightmares, and sleep disturbance	Prazosin significantly increased total sleep time and REM sleep time; reduced trauma-related nightmares, distressed awakenings, and total PCL-C scores; improved CGI-I scores; and changed PDRS scores toward normal dreaming

CAPS: Clinician-Administered PTSD Scale; CGI-C: Clinical Global Impression of Change; CGI-I: Clinical Global Impression of Improvement; PCL-C: PTSD Checklist-Civilian; PDRS: PTSD Dream Rating Scale; PTSD: posttraumatic stress disorder; RCTs: randomized controlled trials; REM: rapid eye movement

syndrome may be caused by medications, lifestyle factors, or long-term overactivation of stress-response pathways. A retrospective chart review at a community mental health center revealed that patients taking even low doses of quetiapine for insomnia gained an average of 5 lbs (P = .037).[25] Another retrospective chart review at 2 military hospitals reported that patients receiving low-dose quetiapine (≤100 mg/d) gained an average of slightly less than 1 lb per month, which adds up to approximately 10 lbs per year (P < .001).[26] The benefit of using atypical antipsychotics may be outweighed by metabolic risks such as obesity, new-onset diabetes, and dyslipidemia.[27]

Prazosin is considered a first-line treatment for sleep disturbances and nightmares in PTSD because of its superior long-term efficacy and decreased adverse effects compared with quetiapine.

Clinical Point

Evidence supporting atypical antipsychotics to reduce nightmares in PTSD is considered to be low quality

Visit this article at CurrentPsychiatry.com for a summary of the evidence for atypical antipsychotics for PTSD nightmares

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Related Resources

- American Psychiatric Association. Practice guidelines for the treatment of patients with acute stress disorder and posttraumatic stress disorder. Arlington, VA: American Psychiatric Publishing, Inc.; 2004.
- Veterans Affairs/Department of Defense clinical practice guidelines. Management of traumatic stress disorder and acute stress reaction. www.healthquality.va.gov/Post_Traumatic_Stress_Disorder_PTSD.asp.

Drug Brand Names

Prazosin • Minipress
Quetiapine • Seroquel
Sertraline • Zoloft
Ziprasidone • Geodon

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

The benefits of using atypical antipsychotics for PTSD nightmares may be outweighed by metabolic issues

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Table 3

DSM-IV-TR diagnostic criteria for posttraumatic stress disorder

A. The person has been exposed to a traumatic event in which both of the following were present:
1) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
2) The person's response involved intense fear, helplessness, or horror
B. The traumatic event is persistently reexperienced in ≥1 of the following ways:
1) Recurrent and intrusive distressing recollections of the event
2) Recurrent distressing dreams of the event
3) Acting or feeling as if the traumatic event were recurring
4) Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
5) Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by ≥3 of the following:
1) Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2) Efforts to avoid activities, places, or people that arouse recollections of the trauma
3) Inability to recall an important aspect of the trauma
4) Markedly diminished interest or participation in significant activities
5) Feeling of detachment or estrangement from others
6) Restricted range of affect
7) Sense of a foreshortened future
D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by ≥2 of the following:
1) Difficulty falling or staying asleep
2) Irritability or outbursts of anger
3) Difficulty concentrating
4) Hypervigilance
5) Exaggerated startle response
E. Duration of disturbance (symptoms in Criteria B, C, and D) is >1 month
F. The disturbance causes clinically significant distress or impairment of social, occupational, or other important areas of functioning

Source: Diagnostic and statistical manual of mental disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000

Table 4

Recommended medication treatments for PTSD-associated nightmares

Evidence level	Medication	Evidence
Recommended for treating PTSD-associated nightmares		
1, 4	Prazosin	In 3 level 1 studies, adding prazosin (mean dose 3 mg/d) significantly decreased trauma-related nightmares according to the CAPS "recurrent distressing dreams" item after 3 to 9 weeks of treatment vs placebo in veteran and civilian patients (N = 57)
Not suggested for treating PTSD-associated nightmares		
1	Venlafaxine	No difference between extended-release venlafaxine (37.5 to 300 mg/d) and placebo in the CAPS-SX_{17} "distressing dreams" item at 12 weeks in 340 PTSD patients
May be considered for treating PTSD-associated nightmares		
4	Clonidine	Reduced the number of nightmares in 11 of 13 refugees for 2 weeks to 3 months (dose: 0.2 to 0.6 mg/d)
May be considered for treating PTSD-associated nightmares, but data are low grade and sparse		
4	Trazodone	Although trazodone (25 to 600 mg) significantly decreased nightmare frequency in veteran patients during an 8-week hospital stay (N = 60), 19% discontinued therapy because of side effects
4	Olanzapine	Adjunctive olanzapine (10 to 20 mg) rapidly improved sleep in a case series of combat-related PTSD patients resistant to SSRIs and benzodiazepines (N = 5)
4	Risperidone	In case series, risperidone (0.5 to 3 mg) significantly decreased CAPS scores for recurrent distressing dreams and proportion of traumatic dreams documented in diaries of combat veterans over 6 weeks (N = 17), and improved nightmares in adult burn patients taking pain medications after 1 to 2 days (N = 10)
4	Aripiprazole	In a case series, aripiprazole (15 to 30 mg at bedtime) with CBT or sertraline significantly improved nightmares in 4 of 5 combat-related PTSD patients
4	Topiramate	Topiramate reduced nightmares in 79% of civilians with PTSD and fully suppressed nightmares in 50% of patients in a case series (N = 35)
4	Low-dose cortisol	Significant decrease in frequency but not intensity of nightmares with low-dose cortisol (10 mg/d) in civilians with PTSD (N = 3)
4	Fluvoxamine	In 2 case series, fluvoxamine (up to 300 mg/d) significantly decreased the IES-R level of "dreams about combat trauma" but not the SRRS "bad dreams" rating at 10 weeks (N = 21). During 4 to 12 weeks of follow-up there was a qualitative decrease in reported nightmares in veteran patients (n = 12)
2	Triazolam/ nitrazepam	Limited data showed triazolam (0.5 mg) and nitrazepam (5 mg) provide equal efficacy in decreasing the number of patients who experience unpleasant dreams over 1 night
4	Phenelzine	One study showed phenelzine monotherapy (30 to 90 mg) resulted in elimination of nightmares within 1 month (N = 5); another reported "moderately reduced traumatic dreams" (N = 21) in veterans. Therapy was discontinued because of short-lived efficacy or plateau effect
4	Gabapentin	Adjunctive gabapentin (300 to 3,600 mg/d) improved insomnia and decreased nightmare frequency and/or intensity over 1 to 36 months in 30 veterans with PTSD
4	Cyproheptadine	Conflicting data ranges from eliminating nightmares to no changes in the presence or intensity of nightmares
4	TCAs	Among 10 Cambodian concentration camp survivors treated with TCAs, 4 reported their nightmares ceased and 4 reported improvement after 1-year follow-up
4	Nefazodone	Reduced nightmare occurrence in 3 open-label studies as monotherapy (386 to 600 mg/d). Not recommended first line because of hepatotoxicity risk

Recommended medication treatments for PTSD-associated nightmares (continued)

Evidence level	Medication	Evidence
No recommendation because of sparse data		
2	Clonazepam	Clonazepam (1 to 2 mg/d) was ineffective in decreasing frequency or intensity of combat-related PTSD nightmares in veterans (N = 6)

Evidence levels:

1. High-quality randomized clinical trials with narrow confidence intervals
2. Low-quality randomized clinical trials or high-quality cohort studies
3. Case-control studies
4. Case series; poor case-control studies; poor cohort studies; case reports

CAPS: Clinician-Administered PTSD Scale; CAPS-SX_{17}: 17-item Clinician-Administered PTSD Scale; CBT: cognitive-behavioral therapy; IES-R: Impact of Event Scale-Revised; PTSD: posttraumatic stress disorder; SRRS: Stress Response Rating Scale; SSRI: selective serotonin reuptake inhibitor; TCAs: tricyclic antidepressants

Source: Adapted from Aurora RN, Zak RS, Auerbach SH, et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389-401

Table 5

Combat-related nightmares: Evidence for atypical antipsychotics

Study	Design	Patients/dosage	Results
Aripiprazole			
Lambert, 2006[a]	Case report	4 veterans with combat-related PTSD (3 male, 1 female; age 22 to 24); dose: 15 to 30 mg; concurrent treatment sertraline or CBT	Decreased frequency of weekly nightmares and agitated sleep by at least 50%
Olanzapine			
Stein et al, 2002[b]	8-week, double-blind, placebo-controlled study	19 male veterans with combat-related PTSD (olanzapine group mean age: 55.2 ± 6.6; placebo group 51.1 ± 8.1); mean dose: 15 mg/d	Significantly greater reduction in sleep disturbances (PSQI: -3.29 vs 1.57; P = .01); significantly higher weight gain (13.2 lbs vs -3 lbs; P = .001)
Jakovljevic et al, 2003[c]	Case reports	5 veterans with combat-related PTSD for 6 to 7 years (age: 28 to 50); dose: 10 to 20 mg; adjunct treatment	Decreased frequency of nightmares within 3 days
Labbate et al, 2000[d]	Case report	1 male veteran (age: 58) with a 20-year history of combat-related PTSD; dose: 5 mg at bedtime; concurrent treatment with sertraline (200 mg/d), bupropion (150 mg/d), and diazepam (15 mg/d)	Eliminated nightmares after 1 week and improved sleep quality
Quetiapine			
Ahearn et al, 2006[e]	8-week, open-label trial	15 PTSD patients (8 male; 7 female; 5 with combat-related PTSD; mean age: 49); mean dose: 216 mg/d (100 to 400 mg/d)	Significantly improved re-experiencing (CAPS: 10 vs 23; P = .0012) and sleep (PSQI: 17.5 vs 30; P = .0044) at 8 weeks compared with baseline
Robert et al, 2005[f]	6-week, open-label trial	19 combat veterans; mean dose: 100 ± 70 mg/d (25 to 300 mg/d); adjunct treatment	Significantly improved sleep quality (PSQI: 1.67 vs 2.41; P = .006), latency (PSQI: 1.5 vs 2.65; P = .002), duration (PSQI: 1.31 vs 2.71; P < .001), and sleep disturbances (PSQI: 1.22 vs 1.71; P = .034) and decreased terror episodes (PSQI-A: 0.73 vs 0.91; P = .040) and acting out dreams (PSQI-A: 1.07 vs 1.35; P = .013); however, no difference in nightmares caused by trauma (PSQI-A: 1.53 vs 2.06)
Sokolski et al, 2003[g]	Retrospective chart review	68 male Vietnam War combat veterans (mean age: 55 ± 3.5); mean dose: 155 ± 130 mg (25 to 700 mg); adjunct treatment	Improved sleep disturbances in 62% and nightmares in 25% of patients
Ahearn et al, 2003[h]	Case report	2 male patients with combat-related PTSD (age 53, 72); dose: 25 to 50 mg; adjunct to SSRI therapy	Decreased frequency of nightmares with increased sleep duration
Risperidone			
David et al, 2006[i]	6-week, open-label trial	17 male veterans with combat-related PTSD (mean age: 53.7 ± 3.8); mean maximum dose: 2.3 ± 0.6 mg (range: 1 to 3 mg)	Improved recurrent distressing dreams (CAPS B-2: 3.8 vs 5.4; P = .04), but not with the PSQI subscale (PSQI bad dreams: 2.5 vs 2.7; NS). Decreased nighttime awakenings (1.9 vs 2.8; P = .003) and trauma dreams (19% vs 38%; P = .04)
Leyba et al, 1998[j]	Case reports	3 male patients (age 43 to 46); dose: 1 to 3 mg; adjunct therapy	Decreased occurrence of nightmares

Combat-related nightmares: Evidence for atypical antipsychotics (continued)

Study	Design	Patients/dosage	Results
Ziprasidone			
Siddiqui et al, 2005[k]	Case report	1 male veteran with chronic combat-related PTSD (age 55); dose: 80 to 120 mg/d; adjunct with trazodone (100 mg) and topiramate	Improved occurrence of nightmares up to 4 months

CAPS: Clinician-Administered PTSD Scale; CAPS B-2: Clinician-Administered PTSD Scale B-2 (recurrent distressing dreams of the event); CBT: cognitive-behavioral therapy; PSQI: Pittsburgh Sleep Quality Index; PSQI-A: Pittsburgh Sleep Quality Index Addendum for PTSD; NS: not significant; PTSD: posttraumatic stress disorder; SSRI: selective serotonin reuptake inhibitor

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