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# Treatment of Nightmares With Prazosin: A Systematic Review

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## Abstract

Nightmares, frequently associated with posttraumatic stress disorder and clinically relevant in today's world of violence, are difficult to treat, with few pharmacologic options. We performed a systematic review to evaluate the evidence for the use of prazosin in the treatment of nightmares. A comprehensive search was performed using the databases EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systematic Reviews, from their inception to March 9, 2012, using keywords *prazosin* and *nightmares/PTSD* or associated terms (see text). Two authors independently reviewed titles and abstracts and selected relevant studies. Descriptive data and outcomes of interest from eligible studies were extracted by 1 author, and checked by 2 others. The risk of bias of randomized controlled trials (RCTs) was assessed independently by 2 reviewers. Articles met criteria for inclusion if prazosin was used to treat nightmares, and outcome measures included nightmares or related symptoms of sleep disorders. Our search yielded 21 studies, consisting of 4 RCTs, 4 open-label studies, 4 retrospective chart reviews, and 9 single case reports. The prazosin dose ranged from 1 to 16 mg/d. Results were mixed for the 4 RCTs: 3 reported significant improvement in the number of nightmares, and 1 found no reduction in the number of nightmares. Reduced nightmare severity with use of prazosin was consistently reported in the open-label trials, retrospective chart reviews, and single case reports.


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Extremely distressing and disturbing, nightmares can have a profound negative effect on more than just an individual's sleep; they also affect mental health, physical health, and quality of life. These "repeated awakenings from the major sleep period or naps with detailed recall of extended and extremely frightening dreams, usually involving threats to survival, security, or self-esteem" are most frequently associated with posttraumatic stress disorder (PTSD) but can also be associated with other conditions.[1-3] They can be a contributing factor to alcohol and substance abuse, suicidal ideation, or completed suicide.[4] Trauma-related nightmares in PTSD are more severe than non–trauma-related nightmares in terms of increased frequency and association with more frequent awakenings and worse sleep maintenance.[5,6] In the National Comorbidity Survey Replication of American adults, the lifetime prevalence of PTSD was 6.8%.[7] With an increasing number of veterans of military deployments being reintegrated into civilian life, physicians can expect to see more patients with symptoms of PTSD, including nightmares and reduced sleep quality.

Norepinephrine has a role in the pathophysiology of PTSD. Higher norepinephrine cerebrospinal fluid concentrations have been found in patients with PTSD and are associated with greater severity of PTSD symptoms.[8] This increased central nervous system noradrenergic state contributes to the disruption of normal rapid eye movement sleep, in turn contributing to nightmares.[9] Thus, blocking postsynaptic adrenergic receptors is a possible pharmacologic approach to the treatment of PTSD-associated nightmares.

Prazosin is a lipid-soluble $\alpha_1$-adrenergic receptor antagonist that crosses the blood-brain barrier and decreases the sympathetic outflow in the brain. It has been approved by the US Food and Drug Administration for treatment of hypertension but is seldom used today as an antihypertension medication because of the numerous other preferred antihypertension drugs available. However, prazosin has been studied off-label for treatment of trauma-associated nightmares. It has been recommended for treatment of PTSD-associated nightmares, with a level A recommendation supported by a substantial amount of high-quality evidence.[2] The 2010 Veterans Administration (VA)/Department of Defense *Clinical Practice Guideline for Management of Post-Traumatic Stress* recommends that clinicians provide prazosin to treat sleep disorders and nightmares with a level B strength of recommendation, on the basis of at least fair evidence that the intervention improves health outcomes and that benefits outweigh harm.[10]

On the basis of VA-associated studies and diffusion of knowledge, awareness of prazosin for treatment of PTSD-associated nightmares is increasing.[11] The objective of the present systematic review was to evaluate and update the evidence for the use of prazosin in the treatment of nightmares, regardless of PTSD diagnosis. Other pharmacologic and psychological treatments of nightmares exist but are not in the scope of this focused review.[2]



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## METHODS

An expert medical librarian designed and conducted an electronic search strategy with input from investigators for articles on the treatment of nightmares with prazosin using the EMBASE, Ovid MEDLINE, PubMed, Scopus, Web of Science, and Cochrane Database of Systematic Reviews databases from their inception to March 9, 2012. Key words were [(*prazosin*) AND (*dream** OR *nightmare** OR *night terror** OR *dyssomnia** OR *insomnia** OR *parasomnia** OR *PTSD* OR *posttraumatic stress disorder* OR *post-traumatic stress disorder* OR *sleep disorder** OR *sleep disruption** OR *sleep distress*)], with the asterisk specifying the plural and grammatical variations and with no search limits. Inclusion criteria consisted of any clinical trial, retrospective review, or case report of treatment with prazosin for nightmares. Except for case reports, we searched for studies that used an outcome measure to describe the reduction in nightmares and other symptoms of sleep disorders. Reviews that summarized previous studies were excluded. The abstracts from these articles were reviewed independently by 2 of us (S.K., Z.E.) to determine whether they met the inclusion criteria. Disagreements were resolved by consensus. For the randomized, double-blind, controlled trials (RCTs), 2 reviewers (S.K., M.I.L.) independently assessed risk of bias using the Cochrane Collaboration Risk of Bias Tool.[12]

The most common primary outcome measures were the Clinician-Administered PTSD Scale (CAPS) items B2 ("recurrent distressing dreams of the event") and D1 ("difficulty falling or staying asleep") and the Clinical Global Impression of Change Scale (CGI-C).[13,14] CAPS item B2 quantifies the frequency of upsetting dreams (0 = never, 1 = once or twice, 2 = once or twice a week, 3 = several times a week, and 4 = daily or almost every day) and the intensity of distress and being awakened by these dreams (0 = none, 1 = mild distress without necessarily awakening, 2 = moderate with awakening in distress but readily returning to sleep, 3 = severe with considerable distress and difficulty returning to sleep, and 4 = extreme with incapacitating distress and not returning to sleep). A modified form of the B2 item was sometimes used in which the term *distressing dreams* was replaced by *nonnightmare distressed awakenings*. CAPS item D1 quantifies the difficulty of falling or staying asleep with the frequency (scoring identically as the B2 frequency item) and intensity (0 = none; 1 = mild, with up to 30 minutes of loss of sleep; 2 = moderate, with 30 to 90 minutes of loss of sleep; 3 = severe, with 90 minutes to 3 hours of loss of sleep; and 4 = extreme, with >3 hours of loss of sleep). For both items, the final score is the summation of frequency and intensity, with a maximum score of 8. Some studies used the CAPS-SX, which asks the same questions as CAPS except with a 1-week symptom time course. The 7-item CGI-C scale estimates the change in clinical status in terms of function and well-being. A score of 1 = markedly improved, 2 = moderately improved, 3 = minimally improved, 4 = unchanged, 5 = minimally worse, 6 = moderately worse, and 7 = markedly worse. The CGI-C is also known as the CGI-I (CGI-Improvement).

### ARTICLE HIGHLIGHTS

- Prazosin can reduce the severity and frequency of nightmares associated with posttraumatic stress disorder.
- The evidence base is small (only 4 randomized controlled trials comprising 96 patients, 4 open-label trials with 31 patients, and 4 retrospective chart reviews with 132 patients) but positive.
- Prazosin is well tolerated, with doses ranging from 1 to 16 mg/d.
- Most studies were from a common Veterans Administration research group, and 2 newer studies reported less impressive results.
- More studies will be needed to confirm and replicate these findings in other settings and patient populations.

## RESULTS

Of 172 articles identified, 21 met our inclusion criteria. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram is shown in the Figure.[15] Twelve were clinical studies consisting of 4 randomized placebo-controlled trials, 4 open-label case series, and 4 retrospective chart reviews (Table 1). Nine were case reports (Table 2). We discussed 2 additional studies of interest because of their use of prazosin but did not formally include them in our synthesis because they did not use a formal measurement outcome such as a rating scale or did not measure sleep symptoms as a primary outcome.

### Randomized Placebo-Controlled Trials

Of the 4 randomized, double-blind, placebo-controlled trials, 3 used similar methods.[4,16,17] Patients in these 3 studies had a diagnosis of PTSD, with a CAPS minimum severity score for item B2, and active substance use within 3 to 6 months was excluded. Concurrent psychotropic medications were continued unchanged. Statistically significant improvement was found in the active vs placebo groups for CAPS-B2 and CGI-C; however, improvement in sleep quality measured using CAPS-D1 was mixed. Changes in blood pressure by the end of the studies were not statistically significant. Dizziness was a common adverse effect. There were reports of patients experiencing a return of distressing nightmares when prazosin therapy was discontinued.

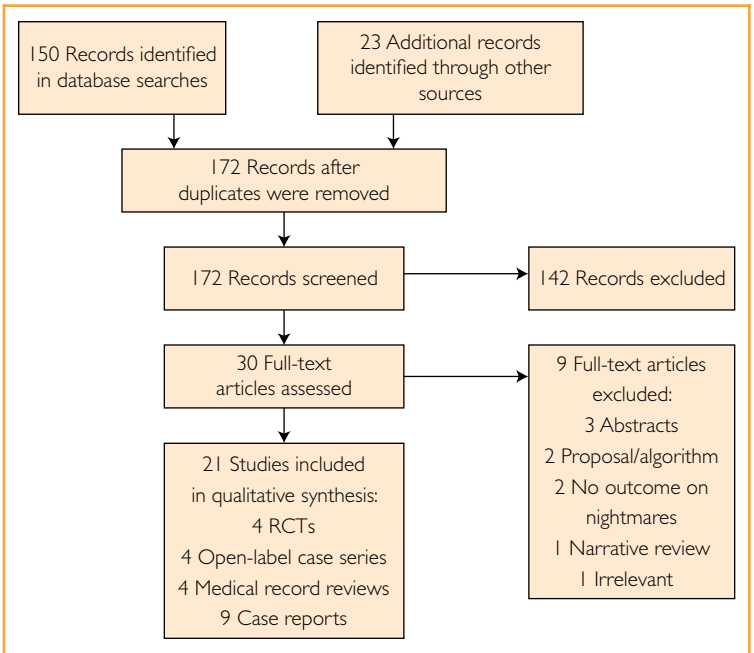


**FIGURE.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. RCT = randomized controlled trial.

The fourth RCT was a more recent study that randomized 50 veterans with sleep disturbances to receive 8 weeks of prazosin therapy (n=18), behavioral sleep intervention (n=17), or placebo (n=15).[18] Fifty-eight percent met criteria for PTSD, and the remaining 42% endorsed subthreshold PTSD symptoms. Concurrent medications were also continued unchanged. Primary outcome measures included a sleep diary and the number of distressing dreams or nightmares recalled on wakening. Although prazosin and behavioral sleep intervention were found to be more effective than placebo, the frequency of nightmares was not reduced. The authors noted the low baseline frequency of nightmares, the use of prospective sleep and dream diaries, and the number of patients with only subthreshold PTSD symptoms as possible factors to explain the negative finding of nightmare reduction. The baseline frequency of nightmares ranged from a mean of 0.09 to 1.0 per night in the 3 groups, and nightmare intensity was not measured. The baseline nightmare frequency in this study cannot be compared with that of the previous 3 RCTs because those studies used the CAPS-B2, which combines a nightmare frequency range with nightmare intensity.

The risk of bias of these 4 randomized studies was assessed using the Cochrane Collaboration Risk of Bias Tool and agreed on by 2 of us (S.K., M.I.L.) (Table 3).[12] For the randomization categories, only 2 studies mentioned the method of sequence generation.[4,18] None of the studies described the details of the allocation concealment sufficient for assessment. All of the studies seemed to use adequate blinding techniques, eg, with how the placebos were provided. Insofar as incomplete data, 1 study of 40 patients reported 6 discontinuations (3 prazosin and 1 placebo assignments because of adverse effects, and 2 placebo assignments for unknown reasons), which were not evenly spread between the prazosin and placebo groups.[4] In addition, 5 of the remaining 34 patients could not accurately recall their nightmares to provide acceptable rating scales and were not included in the data analysis for the B2 item. These factors led to a designation of high risk of bias of the results. In the most recent study, the fate of all randomized patients was described, and discontinuations were spread similarly between the prazosin and placebo groups.[18] However, there still seemed to be missing data in the analysis, which was not explained, leading to concern about potential bias of the results. Also, the primary outcomes of clinician- and patient-reported CGI-I were not reported numerically, and the text commented only on the lack of a statistically significant difference between the active treatment groups vs the placebo group using the CGI-I, without specifying clinician- vs patient-reported CGI-I. Not clearly reporting the primary outcome led to a designation of high risk of bias of the results.

### Open-Label Trials

Four open-label case series described 31 patients (25 military personnel and 6 civilians).[19-22] In the 3 older studies from 2000 to 2003, including 18 patients, participants had a diagnosis of PTSD with a minimum CAPS-B2 score, and active substance use within 3 to 6 months was excluded.[19-21] Seventeen of 18 patients (94.4%) experienced at least 50% reduction in occurrence of nightmares. Nightmare severity was reduced, in general, from a score of 6 to 8 to 0 to 3, and CGI-C showed markedly and moderate improvement in 17 of 18 patients. Adverse effects included dizziness, light-headedness, dry mouth, micturition syncope, and urinary incontinence. There were also reports of patients experiencing a return of nightmares when prazosin therapy was discontinued.

In the more recent 2010 study involving combat soldiers on active duty with acute stress disorder or PTSD, results were less impressive.[22] Of 13 patients, CGI-C showed markedly and moderate improvement in 8 (61.5%) patients, minimal improvement in 4 patients, and no improvement in 1 patient, who also reported adverse effects of headache and nausea. However, 9 patients (69.2%) still experienced at least 50% reduction in occurrence of nightmares, with 5 experiencing complete remission.


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**TABLE 1. Summary of Randomized Controlled Trials, Open-Label Trials, and Medical Record Reviews on Use of Prazosin to Treat Nightmares in Adults[a]**

| Reference | Study design | Patient demographic data[b] | Primary outcome measures | Dose (mg/d)[c] | Adverse effects | Results | Comments |
|---|---|---|---|---|---|---|---|
| Raskind et al,[16] 2003 | Randomized, double-blind, placebo-controlled; 20 wk with crossover at wk 10 | 10 male Vietnam war veterans, age (y), 53±3 | CAPS, CGI-C | 9.5<br>Titration schedule (d):<br>1 mg × 3<br>2 mg × 4<br>4 mg × 7<br>6 mg × 7<br>10 mg max | 2 patients experienced decreased blood pressure and dizziness, which resolved during titration | CAPS-B2: improvement of 3.3 vs placebo 0.4; $P<.001$<br>CAPS-D1: improvement of 3.4 vs placebo 0.2; $P<.01$<br>CGI-C: 2.0±0.5 vs placebo 4.5±1.8 (unchanged to minimally worse); $P<.01$ | Patients with PTSD and initial CAPS-B2 ≥6<br>7 patients were receiving concurrent psychotropic medications<br>5 patients experienced rapid return of distressing nightmares during post-prazosin washout, with 4 discontinuing the study for open-label prazosin therapy |
| Raskind et al,[4] 2007 | Randomized, double-blind, placebo-controlled; 8 wk | 40 veterans (38 men), age (y), 56±9 | CAPS, CGI-C, PSQI | 13±3<br>Titration schedule (d):<br>1 mg × 3<br>2 mg × 4<br>4 mg × 7<br>6 mg × 7<br>10 mg × 7<br>15 mg max | 15 patients (9, prazosin; 6, placebo) reported transient dizziness, with 2 patients withdrawing from the study | CAPS-B2: improvement of 3.3 vs placebo 0.9; $P=.02$<br>PSQI: improvement of 3.8 vs placebo 0.8; $P=.008$<br>CGI-C: 2.41±1.1 vs placebo 3.65±1.2; $P=.002$ | Patients with PTSD and initial CAPS-B2 ≥5 and CAPS-D1 ≥5<br>20 patients were receiving concurrent psychotropic medications<br>34 evaluable patients (prazosin, 17; placebo, 17)<br>4 patients discontinued because of adverse effects, and 2 patients were lost to follow-up<br>Statistically significant improvement noted at wk 8 but not at wk 4 |
| Taylor et al,[17] 2008 | Randomized, double-blind, placebo-controlled; 7 wk with washout/crossover after 3 wk | 13 civilians (2 men), age (y), 49±10 | CAPS, CGI-I, NNDA, PCL-C, PDRS | 3.1±3<br>Titration schedule (d):<br>1 mg initial dose, then increase by 1 mg every 2-3d<br>6 mg max | Dizziness occurred 3 times under both placebo and prazosin conditions | CAPS-B2: improvement of 1.5 vs placebo 0; $P=.04$<br>CAPS-D1: improvement of 1.2 vs placebo 0.5; $P=.35$, not significant<br>NNDA: improvement of 2.8 vs placebo 0.1; $P=.05$<br>PTSD PDRS indicated significant change toward normal dream content with prazosin<br>CGI-I: 2.6±0.9 vs placebo 4.1±1.1; $P=.002$ | Patients with PTSD and initial CAPS-B2 ≥4 and CAPS-D1 ≥4<br>11 patients were receiving concurrent psychotropic medications<br>NNDA is a modification of CAPS-B2, replacing "distressing dreams" with "non-nightmare distressed awakenings"<br>CGI-I (improvement) is equivalent to CGI-C<br>Sleep parameters during last 3 nights of treatments were measured using the REMView device, which found that prazosin improved total sleep time by 94 minutes, and increased REM sleep time, REM latency, and mean REM duration |

(continued)

**TABLE 1. Continued**

| Reference | Study design | Patient demographic data[b] | Primary outcome measures | Dose (mg/d)[c] | Adverse effects | Results | Comments |
|---|---|---|---|---|---|---|---|
| Germain et al,[18] 2012 | Randomized, placebo comparison; 8 wk | 50 veterans (45 men), age (y), 40.9±13.2 | CGI-I<br>ISI, PSQI, PSQI addendum for PTSD<br>Pittsburgh Sleep Diary | 8.9±5.7<br>Titration schedule (d):<br>1 mg x 7<br>2 mg x 7<br>4 mg x 7<br>6 mg x 7<br>10 mg x 7<br>15 mg max | Sporadic mild orthostatic symptoms across active and placebo conditions<br>1 patient randomized to receive prazosin withdrew because of morning cataplexy like symptoms | No reduction in nightmare frequency across all 3 groups<br>CGI-I response rates (defined as 1 or 2 of 7) not statistically different across all 3 groups; however, sleep-specific criteria favored active treatment over placebo<br>Sleep improvement in 61.9% of those who completed active treatment vs 25% assigned to receive placebo | Patients with PTSD (n=29) and subsyndromal PTSD (n=21), initial CAPS-B2 ≥3 and PSQI >5<br>17 patients receiving concurrent medications<br>BSI (n=17) vs prazosin (n=18) vs placebo (n=15)<br>Secondary outcomes included laboratory polysomnography |
| Raskind et al,[19] 2000 | Open-label case series; 8 wk | 4 African American veterans (men), age (y), 50-75 | CAPS-SX (1-wk symptom version)<br>CGI-C | 4.75 | 2 patients reported transient lethargy, and 1 reported transient dizziness | CAPS-SX-B2: reduction from 8 to 0, 7 to 0, 8 to 4, 7 to 3, by end of wk 8 (mean reduction from 7.5 to 1.75)<br>CGI-C: markedly improved in 2 patients, and moderately improved in 2 | Patients with PTSD and initial CAPS-SX-B2 ≥6<br>All patients experienced at least 50% improvement in nightmares, with remission in 2 who tolerated at least 5 mg<br>After trial completion, 1 patient who "ran out" of prazosin for 2 wk experienced return of combat trauma nightmares to pretreatment levels, with nightmare intensity improving after reinstitution of prazosin therapy |
| Taylor and Raskind,[20] 2002 | Open-label case series; 6 wk | 5 civilians (1 man), age (y), 35-58 | CAPS-SX<br>CGI-C | 1.8 | 1 patient each reported an episode of nocturnal micturition syncope, transient morning sedation, and transient dry mouth. | CAPS-SX nightmare: reduction from 6 to 2, 7 to 0, 6 to 1, 8 to 3, 7 to 3 (mean improvement from 6.8 to 1.8)<br>CGI-C: markedly improved in 3 patients, and moderately improved in 2 patients | Patients with PTSD and initial CAPS-SX-B2 ≥4<br>All patients experienced at least 50% improvement in nightmares<br>Benefits from continuing prazosin were still noted after 4, 8, 9, and 13 mo after study conclusion; 1 patient discontinued prazosin after 2 mo and still experienced benefit at 6 mo; 1 patient reported return of symptoms when prazosin dose was missed |

(continued)

**TABLE 1. Continued**

| Reference | Study design | Patient demographic data[b] | Primary outcome measures | Dose (mg/d)[c] | Adverse effects | Results | Comments |
|---|---|---|---|---|---|---|---|
| Peskind et al,[21] 2003 | Open-label case series; 8 wk | 9 male patients, including 8 veterans and 1 civilian, age (y), 76±2 | CAPS, CGI-C | 2.3±0.7 | 1 patient each reported episodic nocturnal urinary incontinence, transient light-headedness, and dizziness | CAPS-B2: improvement from 6.6±1.1 to 0.9±1.5; $P<.001$<br>CGI-C: mean improvement 1.8+0.7; markedly improved in 3 patients, moderately improved in 5, and minimally improved in 1 | Patients with PTSD and initial CAPS-SX-B2 ≥5<br>8 of 9 patients experienced at least 50% improvement in nightmares, with remission in 6<br>7 patients were already receiving anti-hypertensive medications; pretreatment BP, 144/74±19/4 vs posttreatment BP, 134/72±16/4<br>1 patient had mild cognitive impairment; no others had evidence of cognitive decline |
| Calohan et al,[22] 2010 | Open-label case series | 13 active combat soldiers (11 men), age (y), 26.7±3.2 | CAPS, CGI-C | 4.1±2.2 | 1 patient reported nausea and headaches | CAPS-B2: improvement from 7.0±0.7 to 2.9±3.0; $P<.001$<br>CAPS-D1: improvement from 6.7±0.9 to 3.7±2.2; $P<.001$<br>CGI-C: mean improvement 1.9±1.0; markedly improved in 6 patients, moderately improved in 3, minimally improved in 3, and unchanged in 1 | Patients with PTSD or acute stress disorder<br>9 of 13 patients experienced at least 50% improvement in nightmares, with complete remission in 5<br>Follow-up duration and comorbidity exclusions were unspecified |
| Raskind et al,[23] 2002 | Retrospective medical records review; 8 wk | 59 male veterans, age (y), 51±1.2 | CAPS, CGI-C | 6.3±0.8 (9.6±0.9 in completers) | 15 patients (29%) reported adverse effects including dizziness in 3, headache in 3, and nausea in 2 | CAPS-B2: improvement of 7.1±0.2 to 4.2±0.3 in primary 51 patients; $P<.001$; improvement of 7.0+0.2 to 3.5±0.3 in 36 completers $P<.001$<br>CGI-C: markedly improved in 2 patients, moderately improved in 14, minimally improved in 24, and unchanged in 11 | Patients with PTSD and initial CAPS-B2 ≥5<br>36 patients completed the prazosin titration and 8 wk; 15 patients started prazosin therapy but did not complete; 8 patients did not start prazosin therapy<br>CGI-C exclusive of nightmares and at least moderately improved in 16 of 51 patients (31%) |

(continued)

**TABLE 1. Continued**

| Reference | Study design | Patient demographic data[b] | Primary outcome measures | Dose (mg/d)[c] | Adverse effects | Results | Comments |
|---|---|---|---|---|---|---|---|
| Daly et al,[24] 2005 | Retrospective medical records review, variable follow-up rarely >3 mo, case examples were typically at 2 wk | 28 veterans (27 men), age (y), 20-41 | CGI-C | 1-5 | No significant adverse effects | CGI-C: markedly improved in 20 patients, moderately improved in 2, and unchanged in 1 | PTSD diagnosis not formally established<br>23 patients had complete follow-up data<br>1 patient experienced recurrence of nightmares when stopping prazosin therapy and cessation of nightmares when resuming prazosin therapy<br>CGI-C at least moderately improved in 22 of 23 patients (96%) |
| Thompson et al,[25] 2008 | Retrospective medical records review at 1 wk after stable dosage of prazosin | 22 male veterans, ages unspecified | CAPS, CGI-C, NNDA | 9.6±6 | Adverse effects not reported | CAPS-B2: improvement of 1.4; $P<.05$<br>CAPS-D1: improvement of 3.1; $P<.001$<br>CGI-C: mean improvement 2.7±1.0<br>NNDA: improvement of 3.1; $P<.001$ | Patients with PTSD<br>Individual CGI-C scores not reported |
| Boynton et al,[26] 2009 | Retrospective medical records review; 8 wk | 23 refugees (8 men), age (y), 49.8±15.3 | CAPS, CGI-C | 2.3±1.4 | Most common adverse effect was dizziness | CAPS-B2: improvement of 6.91±0.85; $P<.005$<br>CGI-C: markedly improved in 6 patients, moderately improved in 11, and minimally improved in 6 | Patients with PTSD<br>CGI-C exclusive of nightmares, and at least moderately improved in 17 of 23 patients (74%) |

[a] BP = blood pressure; BSI = behavioral sleep intervention; CAPS = Clinician-Administered PTSD Scale; CAPS-SX = CAPS 1-wk symptoms version; CGI-C = Clinical Global Impression of Change. CGI-I = Clinical Global Impression of Improvement; ISI = Insomnia Severity Index; max = maximum; NNDA = non-nightmare distressed awakenings; PCL-C = PTSD Checklist–Civilian; PDRS = PTSD Dream Rating Scale; PSQI = Pittsburg Sleep Quality Index; PTSD = posttraumatic stress disorder; REM = rapid eye movement.

[b] Age is given as mean ± SD or as range.

[c] Dose is given as mean ± SD or as range.

**TABLE 2. Summary of Case Reports for Use of Prazosin to Treat Nightmares**

| Reference | Age (y)/sex/source of trauma | Dose (mg/d) | Duration | Nightmare and sleep improvement | Comments |
|---|---|---|---|---|---|
| | | | Adults | | |
| Gehrman and Harb,[27] 2010 | 50/F/sexual abuse | 9 | 3 mo | Yes, initially | Nightmares returned after 3 mo, then treated with imagery rehearsal |
| Coupland,[28] 2009 | 42/M/firefighter responder | 6 | 3 wk | Yes | Some weeks without trauma-related nightmares<br>Adverse effects of initial light-headedness and fatigue; tolerable dry mouth |
| Nuzhat and Osser,[29] 2009 | 25/M/veteran | 1 | 3 d | No | Discontinued because of chest pain, dizziness, and muscle twitching<br>Adverse effects resolved 1 wk after discontinuation of medication |
| Reardon and Factor,[30] 2008 | 42/M/veteran | 1 | 1 wk | No | Medical comorbidities included type 2 diabetes, receiving insulin; and arthritis, receiving hydroxychloroquine and oxycodone therapy<br>Discontinued because of "blurred awareness of the line between dreaming and reality," bizarre behaviors, erratic driving, uncharacteristic tardiness, and suicidal and homicidal ideations<br>Behavioral adverse effects resolved 30 h after discontinuation of medication |
| Griffith,[31] 2005 | 38/M/emergency relief worker | 1 | 3 wk | Yes | One minor spell of lightheadedness and morning grogginess |
| | | | Children/Adolescents | | |
| Strawn and Keeshin,[32] 2011 | 7/M/sexual assault | 1 | 10 mo | Yes<br>CGI improved | Comorbid ADHD<br>During a lapse in medication, intrusive and hyperarousal symptoms returned and resolved again after resuming medication<br>No significant adverse effects; no change in BP or heart rate; weight gain |
| Fraleigh et al,[33] 2009 | 16/M/witnessed friend's violent death | 1.5 | 1.5 mo | Yes | Nightmares remitted but recurred when medication was discontinued<br>On resuming prazosin, nightmares remitted again |
| Strawn et al,[34] 2009 | 16/F/robbery victim | 2 | 1 mo | Yes | No adverse effects |
| Brkanac et al,[35] 2003 | 15/F/childhood abuse | 4 | 4 wk | Yes | Continued improvement at 2-mo follow-up |

ADHD = attention-deficit/hyperactivity disorder; BP = blood pressure; CGI = Clinical Global Impression; F = female; M = male.

In combining these 4 studies, response to nightmare symptoms, as defined by at least 50% reduction in the nightmare item B2, would be 83.9% (26 of 31 patients). Treatment response, as measured using a CGI-C rating of 1 (markedly improved) or 2 (moderately improved), would be 80.6% (25 of 31 patients).

### Retrospective Chart Reviews

Four retrospective reviews of medical records for 132 patients (109 veterans and 23 refugees) were identified.[23-26] Of these 4 reviews, the 3 that measured CAPS-B2 all reported statistically significant improvement by the end of the studies. In combining the 3 studies that reported individual CGI-C scores, the treatment response rate was 56.7% (55 of 97 patients). In one review, PTSD was not necessarily formally diagnosed; however, all patients reported symptoms consistent with PTSD.[24]

### Case Reports

There were 9 case reports of 5 adults and 4 children/adolescents (Table 2). Three of the 5 adults reported improvement in symptoms, and 2 veterans experi-

**TABLE 3. Cochrane Risk of Bias Tool Ratings for Prazosin Randomized Placebo-Controlled Trials**

| Reference | Adequate sequence generation | Allocation concealment | Blinding | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---|---|---|---|---|---|---|
| Raskind et al,[16] 2003 | ? | ? | + | + | + | + |
| Raskind et al,[4] 2007 | + | ? | + | – | + | + |
| Taylor et al,[17] 2008 | ? | ? | + | + | + | + |
| Germain et al,[18] 2012 | + | ? | + | – | – | + |

+ = low risk of bias; – = high risk of bias; ? = unclear.

enced adverse effects resulting in medication discontinuation. All 4 of the children/adolescents experienced benefit from prazosin therapy for nightmares and quality of sleep and had no significant adverse effects.

### Other Studies

Two other studies that assessed prazosin were not included in our summary because they did not incorporate formal rating scale outcome measurements of nightmare improvement. In a comparison of the effectiveness of prazosin vs quetiapine for nighttime PTSD symptoms in veterans, outcomes consisted of 6-month short-term effectiveness, as measured by whether there was a notation in the patient's medical record that the symptoms improved, and long-term effectiveness, as measured by whether the patient continued taking the medication for up to 3 to 6 years.[36] Of 237 patients, 62 were prescribed prazosin and 175 were prescribed quetiapine. After 6 months, the average prazosin dose was 3.2 mg/d, and by the study end date, the average dose was 6.3 mg/d. Short-term effectiveness was similar for prazosin and quetiapine (61.3% vs 61.7%; $P=.54$). Long-term effectiveness was significantly greater in the prazosin group than in the quetiapine group (48.4% vs 24%; $P=.001$). More adverse effects, such as sedation and metabolic effects, were observed in the quetiapine group than in the prazosin group (34.9% vs 17.7%; $P=.008$). The resolution of symptoms that led to discontinuation was more frequently observed in patients who received prazosin than in those who received quetiapine.

Another study of prazosin measured sleep outcomes according to a subjective sense of sleep impairment and feeling rested and the Epworth Sleepiness Scale. This observational study of 74 Iraq War veterans with mild traumatic brain injury and comorbid headaches (71 had PTSD, and only 5 had restful sleep) assessed changes in headache pain, cognition, and sleep.[37] Sleep hygiene counseling and prazosin improved sleep symptoms and Epworth Sleepiness Scale scores in the 60 patients who completed the 9-week intervention of prazosin therapy, up to 7 mg nightly.

## DISCUSSION

This systematic review found a small but positive evidence base to support the efficacy of prazosin therapy for nightmares. Twelve studies comprising 259 patients were identified, in addition to 9 case reports. Four of the studies were randomized placebo-controlled trials of good quality but were limited by small sample sizes (total of 96 patients, not including patients randomized to receive behavioral intervention). The first 3 trials of similar design reported superiority of prazosin over placebo, but the most recent study did not.[18] The 4 open-label trials, also described as case series, reported that 26 of 31 patients (83.9%) experienced greater than 50% reduction in nightmares. The remaining medical record reviews also found statistically significant improvement in the nightmare scores, with the exclusion of one study that measured only CGI-C and not a nightmare score.

Common prazosin usage patterns and results were observed throughout these studies. Initial prazosin dose was 1 mg before bedtime to test for first-dose hypotension, and subsequent increases varied from 1 mg every 2 to 3 days earlier in the titration to 2 to 5 mg every week later in the titration. The final doses ranged from 1 to 16 mg/d, with patients at both age extremes (7-83 years) successfully treated with lower doses of up to 4 mg/d. Civilian patients, most of whom were female, also only needed lower mean ± SD doses of less than 3.1±3 mg/d. Symptom improvement occurred within a few days to a few weeks, and duration of therapy continued for several months. Regularly, nightmares returned rapidly when prazosin therapy was discontinued and resolved when reintroduced. Prazosin was well tolerated, and common adverse effects consisted of transient dizziness and orthostatic hypotension.

One of the objectives of this systematic review was to identify evidence for the use of prazosin to treat non–PTSD-related nightmares. We did not find any such evidence. Patients in these studies all

had a diagnosis of PTSD (or were presumed to meet the criteria for PTSD), subsyndromal PTSD, or acute stress disorder, which can be considered a precursor of PTSD. It seems logical to extend the use of prazosin therapy to non–PTSD-related nightmares, especially if the nature of recurrent nightmares suggests an underlying PTSD diagnosis. However, there are likely differences in the severity and nature of PTSD- vs non–PTSD-related nightmares that affect the efficacy of prazosin. Given the relative lack of significant adverse effects when used for PTSD-related nightmares, research should be conducted for its use in recurrent non–PTSD-related nightmares.

Our systematic review agrees with other recent narrative reviews of the use of prazosin to treat PTSD-related nightmares.[38-42] We used a method that would be reproducible for future updates, and we assessed the risk of bias for the randomized studies. Already, our review includes 2 recent studies from 2010 and 2012 that other recent reviews were unable to include, and the significance is that one of these studies reported a negative finding and the other study reported less impressive results than the earlier studies.[18,22] With the continued traumas of today's world, both from civilian and military causes, further prazosin trials can help clarify its efficacy compared with that reported in the older studies and whether continued optimism insofar as its efficacy is justified. Upcoming results from 2 large clinical trials of use of prazosin to treat PTSD symptoms (a 13-site VA study of 320 veterans and a single-site study of 120 soldiers on active duty), expected to be completed in late 2012, will add greatly to our knowledge.[38]

There are several limitations to the present literature review. One is the relatively small number of studies and total number of patients. There is also heterogeneity of the studies, including the variability of inclusion criteria, psychiatric comorbidities, follow-up periods, outcome measures, and allowance for concurrent medications. A formal meta-analysis would be difficult because of the heterogeneity. Another potential bias is related to the commonality of the research groups, with all but 1 of the 12 studies originating from or including the senior author(s) from the VA Puget Sound Health Care System. Of interest, a study that examined the diffusion of knowledge about prazosin for treatment of PTSD concluded that it diffused quickly in the local Puget Sound area but not so fast in farther geographic areas.[11] Of the 1 study not from that group, the finding of decreased nightmares was not replicated, although there were other possible reasons for that finding, including lower baseline severity of nightmares.[18] Nightmares are difficult to treat, and further positive results using prazosin would be welcome but would have to be replicated by different research groups and in other patient populations.

## CONCLUSIONS

Prazosin is a well-tolerated generically available medication that has a small but positive evidence base for the treatment of PTSD-associated nightmares. Given the difficulty of treating nightmares, combined with the continued presence of patients with nightmares, prazosin can be an important pharmacologic treatment option. Further clinical trials to expand our knowledge about prazosin in different patient populations are recommended.

**Abbreviations and Acronyms:** **CAPS** = Clinician-Administered PTSD Scale; **CGI-C** = Clinical Global Impression of Change [Scale]; **PTSD** = posttraumatic stress disorder; **RCT** = randomized controlled trial; **VA** = Veterans Administration

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