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Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

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ABSTRACT

BACKGROUND

In randomized trials, prazosin, an α_1-adrenoreceptor antagonist, has been effective in alleviating nightmares associated with post-traumatic stress disorder (PTSD) in military veterans.

METHODS

We recruited veterans from 13 Department of Veterans Affairs medical centers who had chronic PTSD and reported frequent nightmares. Participants were randomly assigned to receive prazosin or placebo for 26 weeks; the drug or placebo was administered in escalating divided doses over the course of 5 weeks to a daily maximum of 20 mg in men and 12 mg in women. After week 10, participants continued to receive prazosin or placebo in a double-blind fashion for an additional 16 weeks. The three primary outcome measures were the change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 ("recurrent distressing dreams"; scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams); the change in score from baseline to 10 weeks on the Pittsburgh Sleep Quality Index (PSQI; scores range from 0 to 21, with higher scores indicating worse sleep quality); and the Clinical Global Impression of Change (CGIC) score at 10 weeks (scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change).

RESULTS

A total of 304 participants underwent randomization; 152 were assigned to prazosin, and 152 to placebo. At 10 weeks, there were no significant differences between the prazosin group and the placebo group in the mean change from baseline in the CAPS item B2 score (between-group difference, 0.2; 95% confidence interval [CI], −0.3 to 0.8; P=0.38), in the mean change in PSQI score (between-group difference, 0.1; 95% CI, −0.9 to 1.1; P=0.80), or in the CGIC score (between-group difference, 0; 95% CI, −0.3 to 0.3; P=0.96). There were no significant differences in these measures at 26 weeks (a secondary outcome) or in other secondary outcomes. At 10 weeks, the mean difference between the prazosin group and the placebo group in the change from baseline in supine systolic blood pressure was a decrease of 6.7 mm Hg. The adverse event of new or worsening suicidal ideation occurred in 8% of the participants assigned to prazosin versus 15% of those assigned to placebo.

CONCLUSIONS

In this trial involving military veterans who had chronic PTSD, prazosin did not alleviate distressing dreams or improve sleep quality. (Funded by the Department of Veterans Affairs Cooperative Studies Program; PACT ClinicalTrials.gov number, NCT00532493.)

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Trauma-related nightmares and sleep disturbance are common symptoms of post-traumatic stress disorder (PTSD).[1,2] Enhanced central nervous system adrenergic activity and its persistence during sleep provide a rationale for the use of antiadrenergic medications to ameliorate these symptoms.[3-6] Animal models support antagonism of the postsynaptic α_1-adrenergic receptor of the central nervous system as a target for PTSD treatment.[7,8] Of the clinically available α_1-adrenergic antagonists, prazosin most readily enters the central nervous system.[9]

Six randomized, placebo-controlled clinical trials, in which the number of participants ranged from 10 to 100, showed moderate to large effects of prazosin in alleviating chronic nighttime PTSD symptoms and in improving overall clinical status.[10-15] Four trials involved U.S. military veterans or active-duty service members, one involved U.S. civilians, and one involved both Iranian military veterans and Iranian civilians. Three trials showed benefits with respect to trauma-related nightmares, change in overall clinical status, and total PTSD symptoms[12,14,15]; two showed benefits with respect to trauma-related nightmares, sleep quality, and change in overall clinical status[10,11]; and one showed benefits with respect to sleep quality and daytime PTSD symptoms.[13] These effects of the drug were observed in some, but not in other, measures of sleep quality and PTSD symptoms. However, the duration of these positive trials was shorter than 15 weeks, and the trials were of moderate size. There are limited data on the ability of prazosin to have sustained efficacy for chronic PTSD symptoms over longer periods. We conducted the Prazosin and Combat Trauma PTSD (PACT) trial to determine the efficacy of prazosin in patients with chronic combat-related PTSD who had frequent nightmares. We hypothesized that veterans randomly assigned to prazosin would have less frequent and less intense trauma-related nightmares, greater improvement in sleep quality, and greater improvement in overall clinical status (the three primary outcome measures) than veterans assigned to placebo after short-term treatment (10 weeks) and improvement in at least one of the three primary outcome measures after longer-term treatment (26 weeks).

Methods

Trial Design and Oversight

The PACT trial was a 26-week, multicenter, double-blind, randomized, controlled trial that was conducted at 13 Veterans Affairs (VA) medical centers. Primary outcomes were determined at 10 weeks. After the primary outcomes were assessed, prazosin or placebo was continued in a double-blind fashion for an additional 16 weeks, but other treatments could be added if judged necessary by the patients' clinicians, who were unaware of the trial-group assignments.

This trial was approved by the human rights committee at the Palo Alto Cooperative Studies Program Coordinating Center, by the VA central institutional review board, and by the local VA research and development committees at the participating sites. Before enrollment, all participants provided written informed consent. The responsibilities of the authors and the sponsor are detailed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol, available at NEJM.org. There was no industry support of or involvement in the trial.

Trial Participants

Participants from 12 VA medical centers underwent randomization and were followed for 26 weeks. Data from a 13th site were excluded because of persistent protocol deviations and issues with data quality at that site. The site was first suspended and was then terminated during the trial; all persons at this site remained unaware of the group assignments (see the Study Sites section in the Supplementary Appendix).

Participants were eligible if they met the criteria for PTSD according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), and had a total score of at least 50 on the 17-item Clinician-Administered PTSD Scale (CAPS; scores range from 0 to 136, with higher scores indicating greater frequency and intensity of symptoms)[16]; if they had been exposed to one or more traumatic, life-threatening events in a war zone that preceded the onset of recurrent nightmares; if they reported and could recall combat-related nightmares; if they had a frequen-

cy score of at least 2 and a cumulative score of at least 5 on CAPS item B2 ("recurrent distressing dreams"; cumulative scores range from 0 to 8 [with a range of 0 to 4 for frequency and 0 to 4 for intensity], with higher scores indicating more frequent and more distressing dreams); and if, for at least 4 weeks before randomization, they were receiving a stable dose of non-excluded medications or had been receiving supportive psychotherapy.

Exclusion criteria were acute or unstable medical illness; a systolic blood pressure of less than 110 mm Hg while the patient was in the supine position, a decrease in systolic blood pressure of more than 20 mm Hg after 2 minutes of standing, or any decrease in blood pressure accompanied by dizziness; the presence of a psychotic or cognitive disorder; substance dependence within the previous 3 months; current cocaine or stimulant use; active suicidal or homicidal ideation with plan or intent; and psychosocial instability (defined as a short-term or long-term situational life crisis). Sleep apnea was not a criterion for exclusion, nor was it screened for except by means of history taking and chart review. However, veterans with a diagnosis of sleep apnea on their medical record who did not adhere to treatment for the condition were excluded.

Participants were also excluded if they were receiving prazosin or another α_1-adrenergic antagonist at the time of recruitment or if they had participated in a previous trial of prazosin for PTSD; if they had received prolonged exposure therapy, eye-movement desensitization and reprogramming, or cognitive processing therapy within 4 weeks before randomization; or if they had taken trazodone within 2 weeks before randomization. Women were excluded if they were pregnant or nursing or if they declined to use an effective birth-control method.

TRIAL TREATMENT

During the first 10 weeks, patients maintained the pharmacotherapy and psychotherapy that they had been receiving before randomization, and no new treatment could be added. During the next 16 weeks, participants continued to receive prazosin or placebo in a double-blind manner, but other pharmacologic therapies (except prazosin, trazodone, or psychostimulants) or psychotherapeutic treatments could be added, discontinued, or modified according to the judgment of the treating clinicians.

Eligible participants were randomly assigned, in 1:1 ratio, to receive prazosin or placebo (in identical 1-mg, 2-mg, and 5-mg capsules) in escalating doses. Adaptive randomization[17] was used to achieve balance in the following stratification factors within each site: current antidepressant use (yes vs. no) and a traumatic experience before versus on or after October 7, 2001 (the date of the U.S. invasion of Afghanistan).

Flexible-dose adjustment was used to achieve the maximal alleviation of nightmares with acceptable adverse effects (Table S5 in the Supplementary Appendix). The maximum allowed dose was 5 mg at midmorning and 15 mg at bedtime for men and 2 mg at midmorning and 10 mg at bedtime for women. Additional information on escalating dose schedules, the timing of escalation, the criteria for halting escalation, and the differences in maximum dose between men and women is provided in the Supplementary Appendix. The maximum achieved daily dose of prazosin was continued as the maintenance dose.

OUTCOME MEASURES

Interview-based assessments were performed by trained clinician raters at weeks 6, 10, 14, 18, 22, and 26. The primary outcomes were the change from baseline to 10 weeks in the score on the CAPS "recurrent distressing dreams" item B2[16] and on the Pittsburgh Sleep Quality Index (PSQI; scores range from 0 to 21, with higher scores indicating worse sleep quality),[18] and the score at 10 weeks on the Clinical Global Impression of Change (CGIC) scale (scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change from baseline).[19] The CGIC assessed the participant's ability to function in daily activities and the participant's sense of well-being, as determined on the basis of interviews with participants.

Secondary outcomes were repeated measures over 26 weeks of the CAPS item B2 score,[16] PSQI score,[18] CGIC score,[19] total CAPS score,[16] score on the PTSD Checklist–Military Version (PCL-M; scores range from 17 to 85, with higher scores indicating greater PTSD symptoms),[20] score on the Patient Health Questionnaire 9-item depression scale (PHQ-9; scores range from 0 to 27, with higher scores indicating greater depressive

symptoms),[21] score on the Quality of Life Inventory (QOLI; scores range from −6 to 6, with higher scores indicating greater life satisfaction),[22] score on the Veterans 12-Item Short-Form General Health Survey (SF-12; scores are assessed on the basis of the physical component summary [scores range from 10 to 30] and the mental component summary [scores range from 6 to 72], with higher scores indicating greater health-related quality of life),[23] and score on the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C; scores range from 0 to 12, with higher scores indicating greater alcohol use).[24] Systolic and diastolic blood pressure and heart rate were measured after the participant was in the supine position for 10 minutes and again after the participant was standing for 2 minutes. All adverse events commonly associated with prazosin and instances of suicidal ideation were specifically queried at baseline and at each trial visit as part of the prespecified safety analysis plan.

Trial office personnel, site personnel, and participants were unaware of the group assignments. Clinician raters were unaware of assignments as well as participants' vital signs, adverse events, and dose of the trial drug or placebo.

STATISTICAL ANALYSIS

We calculated that with a target sample size of 326, the trial would have at least 90% power to detect a mean between-group difference in the change from baseline to 10 weeks of 0.45 on the CAPS "recurrent distressing dreams" item B2 and of 0.50 on the PSQI scale and a mean difference between the groups of 0.65 on the CGIC scale at 10 weeks, at a two-sided alpha level of 0.05, assuming a 20% anticipated dropout rate. Analyses were conducted according to a modified intention-to-treat principle. All participants who underwent randomization were included in the analyses of baseline characteristics. Participants for whom 10-week outcome assessments were missing were not included in the primary analyses of the primary outcomes. Details of missing data and post hoc sensitivity analyses are provided in the Supplementary Appendix. Adjustment for multiple comparisons was not needed in this intersection–union test design, which requires that significant differences be detected on all three primary outcome measures to consider the findings positive.

An independent data and safety monitoring committee reviewed the unblinded data every 6 months. Results of the interim analyses are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Participants were recruited during the period from January 2010 through August 2012, and all trial procedures were completed in February 2013. The number of participants and the disposition of participants at each stage of the trial are shown in Figure S1 in the Supplementary Appendix. Of the 413 persons who were screened at the 12 trial sites, 304 (74%) underwent randomization, and 152 were assigned to each group. A total of 271 participants (90% in the prazosin group and 89% in the placebo group) completed the 10-week primary outcome assessments, and 284 (94% in the prazosin group and 93% in the placebo group) completed one or more of the 10-week primary outcome assessments; 59 participants (20% in the prazosin group and 19% in the placebo group) withdrew from the trial before the 26-week visit. The pattern of missing data did not differ significantly between the groups at either 10 weeks or 26 weeks.

The two groups did not differ significantly at baseline with respect to age; race; the experience of war-zone trauma before versus on or after October 7, 2001; behavioral ratings; coexisting psychiatric disorders; or disability status (Table 1). Four of the 304 participants met DSM-IV criteria for alcohol abuse, and 2 met DSM-IV criteria for cannabis abuse.

TRIAL REGIMEN AND OTHER TREATMENTS

The maintenance dose of the trial regimen was reached at a mean (±SD) of 30.1±19.3 days in the prazosin group and 28.2±10.5 days in the placebo group. A total of 187 male participants (54% in the prazosin group vs. 70% in the placebo group, P=0.003) reached the maximum dose of 20 mg; the mean maintenance dose reached for both men and women was 14.8±6.1 mg in the prazosin group as compared with 16.4±5.9 mg in the placebo group (P=0.009). A total of 33 participants (11% in each group) permanently discontinued the trial regimen; 24 of these partici-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Prazosin (N=152)	Placebo (N=152)
Age — yr	52.3±13.8	51.4±13.8
Male sex — no. (%)	146 (96.1)	151 (99.3)
Race — no. (%)†		
White	98 (64.5)	105 (69.1)
Black	41 (27.0)	38 (25.0)
Hispanic ethnic group — no. (%)†	25 (16.4)	27 (17.8)
Marital status — no. (%)		
Single, divorced, separated, or widowed	65 (42.8)	57 (37.5)
Married or cohabitating	85 (55.9)	93 (61.2)
Highest educational level — no. (%)		
Some high school, high school graduate, or GED	119 (78.3)	111 (73.0)
College graduate or postgraduate degree	29 (19.1)	38 (25.0)
Major depression — no. (%)	51 (33.6)	64 (42.1)
Anxiety disorder other than PTSD — no. (%)	36 (23.7)	33 (21.7)
Receiving a maintenance dose of any antidepressant — no. (%)‡	119 (78.3)	117 (77.0)
Receiving a maintenance dose of any benzodiazepine — no. (%)	18 (11.8)	20 (13.2)
Alcohol abuse — no. (%)	2 (1.0)	2 (1.0)
Cannabis abuse — no. (%)	1 (1.0)	1 (1.0)
Experienced war-zone trauma on or after October 7, 2001 — no. (%)‡	43 (28.3)	45 (29.6)
Receiving or will receive VA disability for PTSD — no. (%)	130 (85.5)	123 (80.9)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the prazosin group and the placebo group. GED denotes General Equivalency Diploma, PTSD post-traumatic stress disorder, and VA Veterans Affairs.
† Race and ethnic group were reported by the participants.
‡ Current antidepressant use (yes vs. no) and a traumatic experience before versus on or after October 7, 2001, were stratification factors at randomization.

pants (9% in the prazosin group and 7% in the placebo group) underwent outcome assessments.

A total of 11 participants (4% in the prazosin group and 3% in the placebo group) received maintenance individual or group psychotherapy from randomization through week 10; at 26 weeks, 43 participants (12% in the prazosin group and 16% in the placebo group) had received individual or group psychotherapy. Concomitant use of prescribed psychotropic medications was similar in the two groups at baseline and over 26 weeks. At 10 weeks, the most frequently used medications in addition to the trial drug or placebo were antidepressants (95% in the prazosin group and 89% in the placebo group), nonopioid analgesics (59% and 57%, respectively), and antiepileptic medications (31% and 30%, respectively). At 10 weeks, benzodiazepines were prescribed for 13% of the participants assigned to prazosin as compared with 17% of the participants assigned to placebo, and antipsychotic medications were prescribed for 14% and 19%, respectively. At 26 weeks, benzodiazepine use had increased by 1% in the prazosin group and 2% in the placebo group, and antipsychotic use had increased by 4% and 0%, respectively.

PRIMARY OUTCOMES

Changes from baseline in the three primary outcome measures did not differ significantly between the groups at 10 weeks (Table 2) or at 26 weeks (Fig. 1). At 10 weeks, the mean change in the CAPS "recurrent distressing dreams" item

Table 2. Primary and Secondary Outcomes at 10 Weeks.*

Outcome	Prazosin		Placebo		Mean Difference in Change from Baseline Between Groups (95% CI)	P Value
	Baseline (N=152)†	Week 10 (N=135)‡	Baseline (N=152)†	Week 10 (N=136)‡		
Primary outcomes						
CAPS item B2 score§	6.3±0.9	4.4±2.1	6.3±0.9	4.6±2.3	0.2 (–0.3 to 0.8)	0.38
PSQI score¶	14.4±3.3	12.1±4.4	14.7±3.5	12.3±4.3	0.1 (–0.9 to 1.1)	0.80
CGIC score‖		3.3±1.4		3.3±1.4	0 (–0.3 to 0.3)	0.96
10-Week secondary outcomes						
CAPS total score§	80.7±15.5	68.9±19.9	81.9±17.1	68.8±23.9	–0.8 (–5.2 to 3.6)	0.73
PHQ-9 score**	13.7±5.9	11.6±6.0	14.6±5.9	12.2±6.7	–0.3 (–1.5 to 0.9)	0.63
PCL-M score††	62.5±11.1	55.1±14.4	64.3±12.2	57.7±15.0	1.3 (–1.7 to 4.2)	0.40
Veterans SF-12 MCS score‡‡	38.2±9.1	37.2±9.3	39.4±8.4	38.2±9.7	–0.1 (–2.3 to 2.0)	0.92
Veterans SF-12 PCS score‡‡	35.4±14.5	35.3±14.4	34.2±12.2	34.9±14.4	0 (–2.5 to 2.5)	1.00
QOLI score§§	0.1±1.9	0.1±1.6	0±1.9	0.1±1.8	0.1 (–0.3 to 0.4)	0.68
AUDIT-C score¶¶	2.0±2.8	1.4±2.2	2.2±2.6	1.8±2.6	0.2 (–0.2 to 0.6)	0.33

* Plus–minus values are means ±SD.
† The behavioral ratings did not differ significantly by group at baseline.
‡ Analyses were conducted according to a modified intention-to-treat principle. All participants who underwent randomization were included in the analyses of baseline characteristics. Participants for whom 10-week outcome assessments were missing were not included in the primary analyses of the primary outcomes.
§ Clinician-Administered PTSD Scale (CAPS) "recurrent distressing dreams" item B2 scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams. CAPS total scores range from 0 to 136, with higher scores indicating greater frequency and intensity of symptoms.
¶ Pittsburgh Sleep Quality Index (PSQI) scores range from 0 to 21, with higher scores indicating worse sleep quality.
‖ Clinical Global Impression of Change (CGIC) scores range from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change from baseline. The CGIC assessed the participant's ability to function in daily activities and the participant's sense of well-being.
** Patient Health Questionnaire 9-item depression scale (PHQ-9) scores range from 0 to 27, with higher scores indicating greater depressive symptoms.
†† PTSD Checklist–Military Version (PCL-M) scores range from 17 to 85, with higher scores indicating greater PTSD symptoms.
‡‡ Veterans 12-Item Short-Form General Health Survey (SF-12) mental component summary (MCS) scores range from 6 to 72 and physical component summary (PCS) scores range from 10 to 70, with higher scores indicating greater health-related quality of life.
§§ Quality of Life Inventory (QOLI) scores range from –6 to 6, with higher scores indicating greater life satisfaction.
¶¶ Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) scores range from 0 to 12, with higher scores indicating greater alcohol use.

B2 score was –1.9 in the prazosin group and –1.7 in the placebo group, a difference of 0.2 (95% confidence interval [CI], –0.3 to 0.8; P=0.38); the mean change in the PSQI score was –2.3 and –2.4, respectively, a difference of 0.1 (95% CI, –0.9 to 1.1; P=0.80); and the CGIC score was 3.3±1.4 and 3.3±1.4, respectively, a difference of 0 (95% CI, –0.3 to 0.3; P=0.96) (Table 2). Linear mixed models were used to analyze the change in scores from baseline to 10 weeks, with adjustment for the two stratification variables (antidepressant use [yes vs. no] and war-zone trauma before vs. on or after October 7, 2001) and for site; these analyses showed consistent nonsignificant differences between the groups.

SECONDARY OUTCOMES

No significant differences between the prazosin group and the placebo group were found for the change from baseline in secondary outcomes at 10 weeks (Table 2) or at 26 weeks (Fig. S2 and

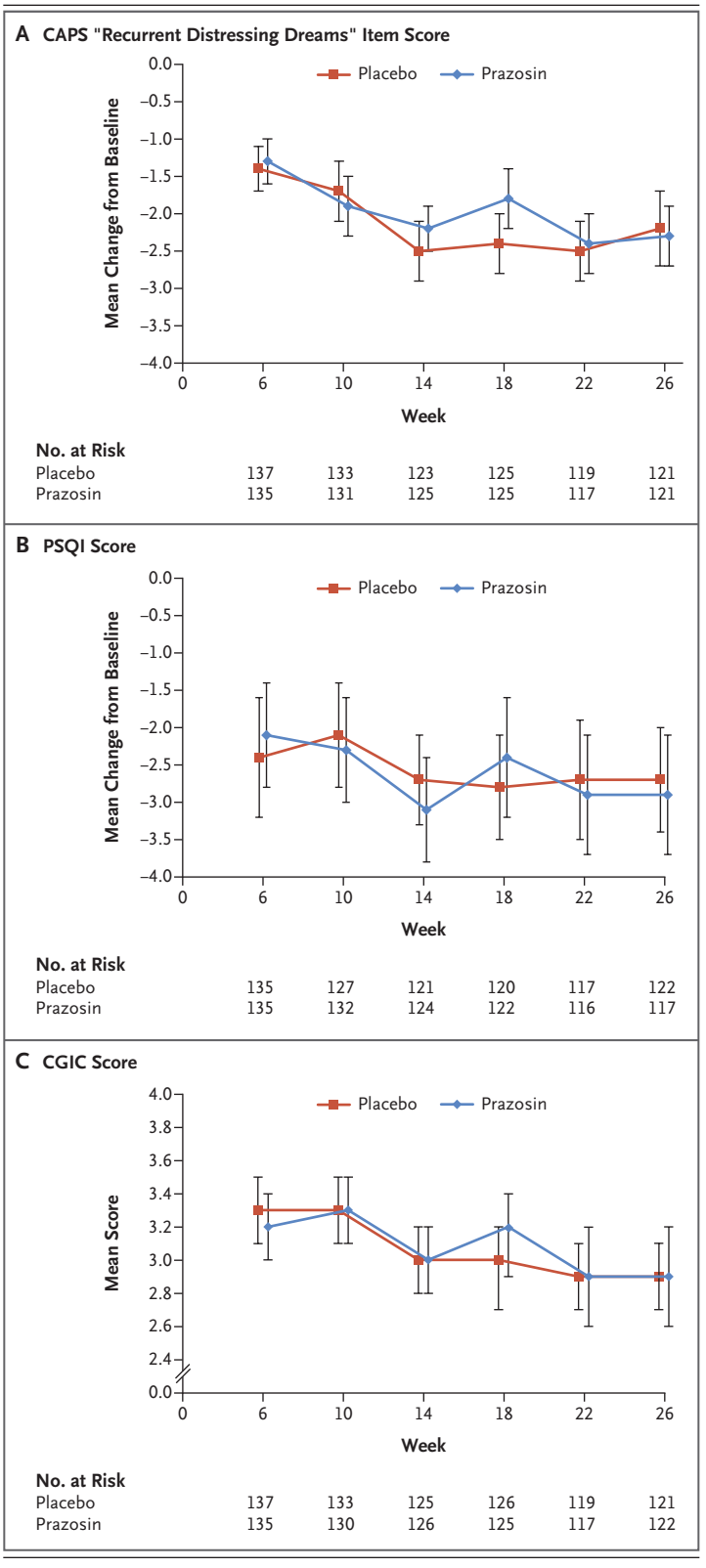

Figure 1. Change in Scores of Primary Outcome Measures from Baseline.

The three primary outcome measures were the change in score from baseline to 10 weeks on the Clinician-Administered PTSD Scale (CAPS) item B2 (scores range from 0 to 8, with higher scores indicating more frequent and more distressing dreams) (Panel A), the change in Pittsburgh Sleep Quality Index (PSQI) score from baseline to 10 weeks (scores range from 0 to 21, with higher scores indicating worse sleep quality) (Panel B), and the Clinical Global Impression of Change (CGIC) score at 10 weeks (range, 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change from baseline; the CGIC assessed the participant's ability to function in daily activities and the participant's sense of well-being) (Panel C). Over the entire 26 weeks, the mean change from baseline on the CAPS item B2 was −2.0 (95% confidence interval [CI], −2.1 to −1.8) with prazosin and −2.1 (95% CI, −2.2 to −1.9) with placebo (P=0.56); the mean change from baseline on the PSQI was −2.6 (95% CI, −2.9 to −2.3) with prazosin and −2.6 (95% CI, −2.9 to −2.3) with placebo (P=0.99); and the mean CGIC score was 3.1 (95% CI, 3.0 to 3.2) with prazosin and 3.1 (95% CI, 3.0 to 3.2) with placebo (P=0.86). I bars indicate 95% confidence intervals.

Table S2 in the Supplementary Appendix). Over the entire 26 weeks, the least-squares mean (±SE) change in total CAPS score was −12.0±1.4 in the prazosin group versus −13.5±1.4 in the placebo group (P=0.48); for the change in PHQ-9 score, −7.5±0.9 versus −7.8±0.9 (P=0.84); for the change in PCL-M score, −2.0±0.4 versus −2.6±0.4 (P=0.29); for the change in the physical component summary score of the Veterans SF-12, 0.9±0.8 versus 0.1±0.8 (P=0.51), and for the change in the mental component summary score, −1.1±0.7 versus −1.0±0.6 (P=0.95); for the change in the QOLI score, 0.2±0.1 vs. 0.1±0.1 (P=0.73); and for the change in the AUDIT-C score, −0.3±0.1 versus −0.2±0.1 (P=0.75). Repeated-measure analyses, with or without adjustment for the two stratification variables and for site, showed no significant difference in the mean change from baseline between the prazosin group and the placebo group over 26 weeks (Fig. 1) (CAPS "recurrent distressing dreams" item B2 score, −2.0±0.2 vs. −2.1±0.2, P=0.56; PSQI score, −2.6±0.3 vs. −2.6±0.3, P=0.99; and CGIC score, 3.1±0.1 vs. 3.1±0.1, P=0.86).

Table 3. Blood Pressure at Baseline and 10 Weeks, and Between-Group Differences in Change from Baseline at 10 Weeks.*

Blood Pressure	Prazosin		Placebo		Mean Difference in Change from Baseline Between Groups (95% CI)	P Value
	Baseline (N=150)†	Week 10 (N=132)‡	Baseline (N=151)†	Week 10 (N=133)‡		
	millimeters of mercury					
Supine systolic	130±13.3	126±12.4	129±14.8	131±16.1	6.7 (3.2–10.1)	<0.001
Supine diastolic	81±9.2	78±9.1	80±9.8	80±10.8	3.3 (1.1–5.5)	0.003
Standing systolic	130±14.1	123±13.7	129±16.5	131±16.7	9.6 (5.9–13.3)	<0.001
Standing diastolic	83±10.5	79±10.5	83±10.7	83±11.2	4.7 (2.2–7.2)	<0.001

* Plus–minus values are means ±SD. Systolic and diastolic blood-pressure measurements did not differ significantly between the prazosin and placebo groups at baseline.
† All participants who had a blood-pressure measurement were included at baseline (150 in the prazosin group and 151 in the placebo group).
‡ At 10 weeks, only participants who completed the 10-week assessment and had a blood-pressure measurement were included (132 in the prazosin group and 133 in the placebo group).

EFFECTS ON BLOOD PRESSURE

The prazosin group had significantly greater decreases in supine and standing systolic and diastolic blood pressure than the placebo group at 10 weeks (P<0.005 for all comparisons). See Table 3 for details.

ADVERSE EVENTS

The number of serious adverse events did not differ significantly by group (19 events among 152 participants in the prazosin group and 18 events among 152 participants in the placebo group, P=0.72) (Table S3 in the Supplementary Appendix). There was one death in each group; both deaths involved a combination of an accident and a medical event and were considered by the data and safety monitoring committee to be unrelated to trial participation. Details about adverse events are provided in Table S4 in the Supplementary Appendix. Of the adverse events, dizziness, lightheadedness, and urinary incontinence were significantly more common in the prazosin group than in the placebo group (34% vs. 21%, P=0.02; 34% vs. 20%, P=0.01; and 12% vs. 4%, P=0.02, respectively). However, new or worsening suicidal ideation was significantly less common among participants assigned to prazosin than among those assigned to placebo (8% vs. 15%, P=0.048). There were two instances of suicidal ideation in the placebo group that led to hospitalization and none in the prazosin group.

DISCUSSION

This 26-week trial involving military veterans with chronic PTSD failed to show a benefit of prazosin over placebo in reducing the frequency and intensity of trauma-related nightmares. These results contrast with previous smaller randomized trials of prazosin involving a total of 283 active-duty service members, veterans, and civilian participants, which showed efficacy of prazosin with respect to PTSD-related nightmares, sleep disturbance, and overall clinical function.[10-15] The failure of the current trial to show benefits does not appear to be attributable to the dose of prazosin, which was higher than in all but one of the previous trials.

A possible explanation for these negative results is selection bias resulting from recruitment of patients who were mainly in clinically stable condition, since symptoms in such patients were less likely to be ameliorated with antiadrenergic treatment. Concern about the increasing incidence of suicide and of violent behavior among veterans led the planning committee to make psychosocial instability an exclusion criterion for participation in the trial. None of the previous smaller randomized trials of prazosin for PTSD[10-15] had such an exclusion criterion. Similarly, the concern that the condition of potential participants would deteriorate clinically during 6 months of receiving placebo could have motivated pro-

viders to use available open-label prazosin rather than refer patients for trial participation. Furthermore, the exclusion of participants who were unwilling or unable to discontinue trazodone, an antidepressant with α_1-adrenoreceptor antagonist activity, may have eliminated potential participants who would have had a response to prazosin. It is also possible that the high threshold for frequency and intensity of nightmares in the inclusion criteria selected for patients who would be less likely to have a response.

The clinical characteristics of patients recruited in this trial suggest that participants had clinically stable PTSD. For example, the lower-than-expected baseline mean blood-pressure levels in this cohort of veterans (among whom the average age was approximately 50 years and who reported high levels of PTSD symptoms) suggest low baseline adrenergic activity, which makes unstable PTSD unlikely. Furthermore, VA clinicians frequently prescribe benzodiazepines for PTSD in patients with distressing anxiety and agitation.[25] Only 13% of trial participants were receiving benzodiazepine at the time of recruitment; by comparison, nationwide surveys have shown that more than 30% of veterans with a diagnosis of PTSD have received a prescription for a benzodiazepine.[25] Another supporting factor for the chronic nature of PTSD in the trial cohort is that heavy alcohol use as self-medication for the temporary relief of PTSD symptoms is common among combat veterans.[26] However, alcohol consumption as measured by the AUDIT-C score of 2.1, reflecting one to two drinks two to four times per month, was relatively low. The high retention of participants may also suggest that even though the levels of reported PTSD symptoms were high, they were not unacceptable to most participants. The low use of the option to add additional treatments after week 10 may also have been consistent with the chronicity of PTSD.

A further limitation of this trial was that participants were not screened for sleep apnea or sleep-disordered breathing except by means of history taking and chart review. There is a high prevalence of previously undiagnosed sleep apnea among veterans with PTSD.[27,28] It is therefore possible that many participants had undiagnosed sleep apnea, which may have interfered with the mechanism of prazosin or masked its possible beneficial effects. Another limitation is that the screening measure for nightmares was derived from the CAPS, which was also an outcome measure.

The current trial is not the first instance in which a multicenter, randomized trial involving male military veterans with psychiatric disorders has failed to show efficacy for a treatment that had been effective in initial studies and that was available within the VA health care system. Other examples include a negative randomized trial of sertraline for PTSD,[29] despite Food and Drug Administration (FDA) approval of the drug for PTSD and recommendations in VA practice guidelines that it be used as first-line pharmacotherapy for PTSD[30]; a negative trial of trauma-focused psychotherapy for PTSD,[31] despite its promotion within the VA system as first-line evidence-based psychotherapy; a negative trial of naltrexone for alcoholism, despite FDA approval of the drug for this purpose[32]; a negative trial of risperidone for PTSD[33]; and a negative trial of depot risperidone (vs. oral risperidone) for schizophrenia[34] — all in solely VA populations. As with prazosin, each treatment studied in these multicenter, randomized trials was already available throughout the VA health care system.

Regarding adverse events in this trial, despite the FDA black-box warning regarding hypotension occurring after receipt of the first dose of prazosin (and other α_1-adrenoreceptor antagonists) and a moderate decrease in standing and supine blood pressure between baseline and 10 weeks, symptomatic hypotension occurred infrequently, even at the high doses achieved. Given the concern about suicide among veterans, it is noteworthy that the specifically solicited adverse event of new or worsening suicidal ideation was less common in the prazosin group than in the placebo group, but the absolute number of events was small; this issue warrants further study.

The current results notwithstanding, previous single-site trials of prazosin have shown that there may be veterans with PTSD of many years' duration who derive a benefit from prazosin with respect to trauma-related nightmares, sleep disruption, and daytime hyperarousal symptoms.[10,11,13] Further studies with more refined characterization of autonomic nervous system activity and nocturnal behaviors are needed to determine whether there might be subgroups of veterans with PTSD who can benefit from prazosin.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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