A Parallel Group Placebo Controlled Study of Prazosin for Trauma Nightmares and Sleep Disturbance in Combat Veterans with Post-Traumatic Stress Disorder

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Background: Excessive brain responsiveness to norepinephrine appears to contribute to post-traumatic stress disorder (PTSD), particularly at night. Prazosin, a brain active alpha-1 adrenergic receptor antagonist, significantly reduced trauma nightmares and sleep disturbance in 10 Vietnam War combat veterans in a previous placebo-controlled crossover study. The current parallel group trial in a larger sample of veterans evaluated prazosin effects on trauma nightmares, sleep quality, global clinical status, dream characteristics, and comorbid depression.

Methods: Forty veterans (mean age 56 ± 9) with chronic PTSD and distressing trauma nightmares and sleep disturbance were randomized to evening prazosin (13.3 ± 3 mg/day) or placebo for 8 weeks.

Results: In the evaluable sample (n = 34), primary outcome measures demonstrated that prazosin was significantly superior to placebo for reducing trauma nightmares and improving sleep quality and global clinical status with large effect sizes. Prazosin shifted dream characteristics from those typical of trauma-related nightmares toward those typical of normal dreams. Blood pressure changes from baseline to end study did not differ significantly between prazosin and placebo.

Conclusions: Prazosin is an effective and well-tolerated treatment for trauma nightmares, sleep disturbance and global clinical status in veterans with chronic PTSD.

Key Words: Adrenergic antagonist, military, nightmare, post-traumatic stress disorder, prazosin, sleep

Trauma nightmares and sleep disturbance are among the most treatment resistant and distressing symptoms of post-traumatic stress disorder (PTSD) (Neylan *et al.* 1998). These nighttime PTSD symptoms likely contribute to alcohol and drug abuse (Chilcoat and Breslau 1998; McFall *et al.* 1992; Saladin *et al.* 1995), suicidal ideation (Krakow *et al.* 2000), and can precipitate completed suicide (Lewis 2005). Psychopharmacologic approaches to treating PTSD rarely have been effective for these nighttime PTSD symptoms (Friedman 2002; Jacobs-Rebhun *et al.* 2000; Obendorfer *et al.* 2000).

Clinical studies suggest that enhanced postsynaptic adrenergic receptor responsiveness to central nervous system (CNS) norepinephrine contributes to the pathophysiology of PTSD (Southwick *et al.* 1993), particularly at night (Mellman *et al.* 1995). Preclinical studies provide rationale for specific involvement of the postsynaptic alpha-1 adrenoreceptor in this pathophysiologic process. Specifically, CNS alpha-1 adrenergic receptor stimulation disrupts sleep physiology and enhances sleep stage phenomena associated with emergence of trauma nightmares (Pickworth *et al.* 1997), increases release of the anxiogenic neuropeptide corticotropin releasing factor (CRF) (Day *et al.* 1999; Feldman *et al.* 1996; Koob, 1999; Vythilingam *et al.* 2000), and favors emergence of primitive alarm-related cognitive processing (Birnbaum *et al.* 1999). These neurobiologic considerations suggest that pharmacologic blockade of brain postsynaptic alpha-1 receptors could provide symptomatic relief from trauma nightmares, sleep disturbance and perhaps other PTSD symptoms.

Prazosin is the alpha-1 adrenergic receptor antagonist that most easily enters the brain (Hardman *et al.* 1996) and prazosin has been demonstrated active at brain alpha-1 adrenergic receptors when administered peripherally (Menkes *et al.* 1981). Prazosin has been used safely for many years in general medicine for hypertension and urinary outflow obstruction caused by benign prostatic hypertrophy (Hieble and Ruffolo 1996; Lund-Johansen *et al.* 1993). Prazosin is usually nonsedating and has long been clinically available as an inexpensive generic drug.

We previously demonstrated in a small (n = 10) placebo-controlled crossover study in Vietnam combat veterans that prazosin substantially reduced PTSD trauma nightmares and sleep disturbance, and improved global clinical status (Raskind et al 2003). Many of these subjects reported anecdotally that long absent "normal" dreams returned when trauma nightmares were reduced or eliminated during prazosin treatment and that symptoms of depression had decreased. Here we report results of a larger parallel group placebo-controlled trial of prazosin in combat veterans with chronic PTSD, intractable trauma nightmares and sleep disturbance. It was hypothesized that prazosin would be more effective than placebo for reducing trauma nightmares, improving sleep quality, and improving global clinical status. It also was hypothesized that characteristics of recalled dreams in the prazosin condition would shift from those typical of trauma nightmares toward those typical of normal dreams, and that comorbid depressive symptoms would decrease.

Methods and Materials

Subjects (n = 40) were United States military veterans who gave written informed consent for participation in this study, which was approved by the University of Washington Human Subjects Review Committee. Randomized subjects included 38

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men and 2 women. Mean (± SD) age was 56 ± 9 years. Subjects included 26 whites, 11 African-Americans, 1 Asian-American, 1 Hispanic and 1 Native American. Thirty-two subjects were veterans of the Vietnam War. Two were veterans of World War II, 3 of the Korean War, 1 of the Panama invasion, and 2 of the first Gulf War. All subjects met DSM-IV criteria for PTSD related to combat exposure (n = 31) or other life-threatening war zone trauma. The diagnosis of PTSD was made by consensus of the senior investigators (MAR and ERP) based on results of the Clinician Administered PTSD Scale (CAPS) (Blake *et al.* 1995) interview. CAPS score at study entry averaged 70 ± 20, and Combat Exposure Scale (Laufer *et al.* 1981) was 9 ± 3. All subjects had frequent and severe trauma-related nightmares and disturbed sleep. These nighttime PTSD symptoms had been chronic and unresponsive or only partially responsive to treatment administered prior to entry into the study. At screening examination, scores of ≥ 5 (of a maximum score of 8) on both the CAPS "recurrent distressing dreams" item and the CAPS "difficulty falling asleep or staying asleep" item were required for inclusion. All subjects had been free of alcohol or other substance abuse for at least three months. Persons with a history of schizophrenia, bipolar disorder, other psychotic disorder or depression with active suicidal ideation were excluded.

Most subjects (n = 14 prazosin, 13 placebo) had been receiving group and/or individual psychotherapy for at least two months prior to entering the study. They maintained ongoing psychotherapy unaltered through the trial. Subjects who had not been receiving psychotherapy (n = 6 prazosin, 7 placebo) did not initiate psychotherapy during the trial. Twenty subjects had been receiving one or more maintenance psychotropic medications at study entry. These medications were continued unchanged during the trial. The most commonly prescribed (n = 13 subjects) were selective serotonin reuptake inhibitors (SSRIs) (the prazosin arm = 6 and the placebo arm = 7). Other psychotropic medications included the serotonin and norepinephrine reuptake inhibitor venlafaxine (n = 2), a tricyclic antidepressant (n = 2), nefazodone (n = 2), buproprion (n = 2), a benzodiazepine (n = 4), the sedating antihistamine hydroxyzine (n = 5), zolpidem (n = 3), perphenazine (n = 1), quetiapine (n = 1) and divalproex (n = 1). No subjects were started on a new psychotropic medication after they were randomized. Thirteen of the 40 randomized subjects were receiving one or more maintenance antihypertensive medications at study entry. Seven of these subjects were randomized to prazosin and 6 to placebo.

Randomization and Drug Titration

Eligible subjects were assigned to prazosin or indistinguishable placebo capsules using a stratified permuted block randomization procedure. On the day of drug initiation, a clinician rater administered the baseline behavioral evaluation (see below). A separate clinician prescriber initiated study drug at 1 mg before bedtime. This low initiation dose is recommended in the FDA-approved package insert to avoid the "first dose hypotension" that occasionally occurs if an alpha-1 adrenergic antagonist is initiated at a higher dose. The clinician rater, the clinician prescriber, and the subjects all were blind to treatment condition. The clinician rater also was blind to the number of capsules/day prescribed, vital signs measurements, and any adverse effects. Prazosin (or placebo) capsules were titrated upward by the clinician prescriber based on clinical response with a therapeutic goal of complete absence of trauma nightmares. Prazosin or equivalent placebo was initiated at 1 mg at bedtime for three days and then increased to 2 mg at bedtime through day 7. If the clinician prescriber ascertained that trauma nightmares still were present and adverse effects absent or mild, the dose was increased to 4 mg at bedtime through day 14. Using the same clinical guidelines, dose could be increased to 6 mg at bedtime through day 21 and to 10 mg at bedtime through day 28. At the day 28 visit a final increase of 5 mg at bedtime could be added for a maximum maintenance daily dose of 15 mg at bedtime. The mean achieved daily dose of prazosin (13 ± 3 mg) or placebo capsules (equivalent to 14 ± 2 mg) was continued as the maintenance dose for 8 weeks. Length of titration period did not differ significantly between groups. Behavioral ratings were obtained by the clinician rater at baseline (the day of the first 1 mg evening dose) and week 4 and week 8 of the maintenance dose phase.

Systolic and diastolic blood pressure after five minutes in the supine position and again after two minutes standing were measured at baseline, each titration visit and at maintenance dose weeks 4 and 8. Adverse events were monitored at baseline and at each subsequent visit by asking patients if they had experienced any problems or symptoms since the previous visit.

The three prospectively designated primary outcome measures were the CAPS "recurrent distressing dreams" item, the Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al.* 1989; Backhaus *et al.* 2002) and the Clinical Global Impression of Change (CGIC) (Guy 1976). The CAPS "recurrent distressing dreams" item is computed by summing frequency and intensity of trauma-related distressing dreams. Scores range from 0 to a maximum score of 8 (frequency of "daily or almost every day" and intensity of "extreme, incapacitating distress, did not return to sleep"). The PSQI is a self-report scale assessing sleep quality and sleep disturbance. Scores range from 0 to 21. The CGIC is an investigator rated assessment of change in global clinical status, which was defined in this study as sense of well-being and ability to function in daily activities. The CGIC is a 7-point scale in which 1 is "markedly improved," 2 is "moderately improved," 3 is "minimally improved," 4 is "unchanged," 5 is "minimally worse," 6 is "moderately worse," and 7 is "markedly worse."

Secondary outcome measures included the total 17-item CAPS score, the Nightmare Frequency Questionnaire-Revised (NFQ) (Krakow *et al.* 2002), the PTSD Dream Rating Scale (PDRS) (Esposito *et al.* 1999), and the Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960). The 17-item CAPS uses a structured interview to rate all the symptoms of PTSD described in the DSM-IV on both frequency and intensity dimensions. The NFQ is an interviewer administered instrument that uses four scales differentially to quantify those nightmares and unpleasant dreams specifically with military trauma content as well as total nightmares and unpleasant dreams regardless of content. The PDRS is an interviewer administered instrument assessing pathologic content of dreams associated with combat-related trauma. It assesses constructs and characteristics derived from empirically based dream content analyses. Characteristics consistent with combat trauma-related dreams such as settings, characters and objects similar to traumatic experience, high threat, low contemporaneity and low distortion are given higher scores. The HAM-D is a 17-item interviewer rated scale for depression that assesses somatic symptoms, insomnia, mood, working capacity and interests, psychomotor retardation, agitation and anxiety.

Differences in outcome measures between prazosin and placebo groups were analyzed using regression models. Differences were considered significant if p values were ≤ .05. To test the hypothesis that changes in behavioral outcome scale measures over time differed by treatment, week 4 and week 8

Table 1. Prazosin Effects on Primary Outcome Measures

Outcome Measure	Prazosin (n = 17)	Placebo (n = 17)	Change Score Differences (p Value)	Effect Size (Cohen's d)
CAPS Distressing Dreams[a]				
Baseline	6.5 ± 1.0	6.1 ± 1.0		
Week 4	3.8 ± 2.1	5.1 ± 2.5	.09	
Week 8	3.2 ± 2.6	5.2 ± 2.2	.02	.94
Pittsburgh Sleep Quality Index				
Baseline	13.5 ± 4.2	13.4 ± 2.7		
Week 4	10.4 ± 4.3	11.3 ± 5.4	.5	
Week 8	9.7 ± 3.9	12.6 ± 4.1	.008	1.00
CGIC scores				
Week 4	2.47 ± .8	3.44 ± 1.2	.02	.95
Week 8	2.41 ± 1.1	3.65 ± 1.2	.002	1.08
CGIC − percentage moderately or markedly improved at end study	71%	12%	.002	18.0 (3.0, 110)[b]

[a]n = 14 prazosin subjects and 15 placebo subjects with quantifiable recalled trauma nightmares.
[b]Odds ratio and confidence intervals.

measures were used as dependent variables in linear regressions on treatment (prazosin versus placebo) adjusting for baseline scale value. Effect sizes for these analyses were calculated using the adjusted difference between groups over the mean squared error. Logistic regression was used to test for differences in the percent of subjects considered clinically improved by the CGIC scale (outcome of 2 "moderately improved" or 1 "markedly improved"). All models were also adjusted for age, gender, ethnicity and combat exposure. To estimate if outcomes were affected by the 6 subjects who were randomized but discontinued study participation prior to the four week outcome rating, an intent to treat analysis using last observation carried forward was performed on CAPS nightmare item scores. Such scores were available from the titration phase for 4 of these 6 discontinued subjects. Baseline values were carried forward for the other 2 discontinued subjects.

Results

Subject Disposition

Of 40 randomized subjects, 6 failed to complete any scheduled outcome assessment because of protocol discontinuation. Four discontinued because of adverse effects, (3 randomized to prazosin and 1 to placebo) and 2 (randomized to placebo) were lost to follow-up for reasons unknown. Thirty-three of the 34 evaluable subjects completed the full trial through the end study week 8 rating. One evaluable subject (randomized to prazosin) completed the baseline and the 4 week outcome behavioral rating only. This one subject's week 4 CGIC rating was treated as an end study CGIC rating in the efficacy analysis of the 34 evaluable subjects.

Five of the 34 evaluable subjects had met the CAPS recurrent distressing dreams item criterion (score of ≥ 5) at screening, but at the subsequent baseline evaluation (prior to receiving study drug) could not recall accurately the frequency and severity of their trauma-related nightmares. Each continued to experience frequent and intense sleep disturbance (CAPS sleep difficulty item score ≥ 5) at this baseline rating and each attributed sleep difficulty to poorly recalled and therefore not accurately quantifiable nightmare phenomena. It was elected to continue these 5 subjects in the study (3 on prazosin and 2 on placebo), but not to assign them scores on the CAPS recurrent distressing dreams item, the NFQ or the PDRS.

Efficacy Outcomes

Prazosin produced significantly and substantially greater improvement than placebo in each of the three primary outcome measures addressing frequency and intensity of trauma-related nightmares (the CAPS recurrent distressing dreams item), sleep quality (the PSQI), and global clinical status (the CGIC) (Table 1). Differences between study conditions on nightmares and sleep quality were not statistically significant at week 4, but by the week 8 follow-up, prazosin was significantly improved over placebo on all primary outcome measures. Recurrent distressing dreams in the prazosin condition decreased over 50% compared to a decrease of only 15% for placebo at the 8-week assessment p (2.9 ± 2.6 versus 1.1 ± 1.8, $p = .02$). Differences were similarly significant between decrease in prazosin vs. placebo subjects in the 40 subjects' intent to treat analysis. Mean CGIC rating of overall change in global clinical status (defined as sense of well-being and ability to function) was 2.4 ± 1.1 ("minimally to moderately improved") in the prazosin subjects versus 3.7 ± 1.2 ("unchanged to minimally improved") in the placebo subjects ($p = .002$).

Changes in secondary outcome measures demonstrated that prazosin specifically reduced military trauma-related nightmares compared to nightmares of any kind (per the NFQ) and shifted dream characteristics from those typical of trauma nightmares toward those of typical normal dreams (per the PDRS) (Table 2). There also was a trend toward greater reduction from baseline to week 8 of depression signs and symptoms in the prazosin compared to placebo group as quantified by HAM-D scores ($p = 0.08$). Because the HAM-D contains three items measuring sleep disturbance, we examined changes in HAM-D scores between groups with these three sleep items removed. Reduction in depression signs and symptoms continued numerically to favor prazosin vs. placebo (3.6 versus 0.7) although this difference was not significant ($p = .13$). Although reduction of the total 17-item CAPS score was numerically greater in the prazosin group, differences between groups were not significant.

To estimate if prazosin responses differed between subjects receiving or not receiving other psychotropic medications, CGIC and CAPS recurrent distressing dreams score changes from baseline to week 8 were compared between these groups by unpaired *t* tests. There were no significant differences between those on psychotropics and those not on psychotropics in CGIC scores (2.8 ± 1.2 versus 2.1 ± .9, $p =$

Table 2. Prazosin Effects on Secondary Outcome Measures

Outcome Measures	Prazosin	Placebo	Significance of Change Score Differences (p Value)
Nightmare Frequency Questionnaire past week (n = 14 prazosin, 15 placebo with quantifiable nightmares)			
Scale A (nights with nightmares and unpleasant dreams of any kind)			
Baseline	3.6 ± 2.0	3.3 ± 1.5	
Week 8	2.3 ± 2.6	2.8 ± 2.1	.4
Scale B (nights with military trauma-related nightmares)			
Baseline	3.1 ± 2.0	3.2 ± 1.8	
Week 8	.9 ± 1.8	2.3 ± 2.1	.02
Scale C (total number of nightmares and unpleasant dreams of any kind)			
Baseline	7.6 ± 8.1	4.2 ± 2.3	
Week 8	2.9 ± 3.8	3.1 ± 2.5	.12
Scale D (total number of military trauma-related nightmares)			
Baseline	4.5 ± 3.6	3.8 ± 2.5	
Week 8	1.0 ± 1.9	2.6 ± 2.6	.01
PTSD Dream Rating Scale[a] (n = 11 prazosin subjects and 11 placebo subjects)			
Baseline	20.9 ± 3.8	20.3 ± 2.5	
Week 8	16.7 ± 8.9	22.4 ± 2.0	<0.001
Total CAPS[b]			
Baseline	76 ± 22	78 ± 18	.4
Week 8	63 ± 20	71 ± 22	.3
Hamilton Depression Rating Scale			
Baseline	18.3 ± 8.8	15.3 ± 7.8	
Week 8	12.7 ± 7.7	14.7 ± 7.1	.08

[a] Scale added at mid-study.
[b] No significant prazosin vs. placebo effects on CAPS reexperiencing, avoidance or hyperarousal cluster subscales.

0.24) or reductions in CAPS recurrent distressing dreams item (2.7 ± 3.3 versus 3.8 ± 2.4, $p = .51$).

Adverse Effects

Transient dizziness upon standing was reported by 15 subjects (9 prazosin and 6 placebo). There were no episodes of fall or syncope. Of the 9 prazosin subjects reporting dizziness, 1 was receiving other concurrent antihypertensive medications (hydrochlothiazide and lisinopril) and 3 were receiving a concurrent psychotropic medication with alpha-1 adrenergic receptor antagonist activity (1 each on nefazodone, nortriptyline or quetiapine). There were no significant differences in changes from baseline to end study between prazosin and placebo groups in supine or standing blood pressure (Table 3). Four of the 13 subjects receiving concurrent antihypertensive medications were among those reporting transient dizziness upon standing. Of these, 3 were receiving placebo and only 1 was receiving prazosin. This latter subject's orthostatic dizziness accompanied by a 25 mmHg orthostatic drop of systolic blood pressure occurred with increase of prazosin from 2 mg to 4 mg during the second titration week. Orthostatic dizziness and systolic blood pressure reduction resolved when his lisinopril dose was decreased by 50%, and he went on to tolerate further prazosin dose increases without recurrence of orthostatic dizziness or any systolic blood pressure drop greater than 10 mmHg.

Table 3. Blood Pressure (Supine and After Two Minutes Standing) in Prazosin and Placebo Subjects

	Baseline		8 Weeks	
	Supine	Standing	Supine	Standing
Prazosin				
Systolic mmHg	129 ± 10.7	126 ± 12.0	128 ± 17.0	125 ± 18.3
Diastolic mmHg	82 ± 6.8	83 ± 9.2	81 ± 10.1	83 ± 11.8
Placebo				
Systolic mmHg	130 ± 12.0	125 ± 11.2	129 ± 14.8	129 ± 15.1
Diastolic mmHg	81 ± 7.6	84 ± 6.8	81 ± 7.8	85 ± 7.7

n = 14 prazosin subjects and 15 placebo subjects with quantifiable recalled trauma nightmares. Total CAPS B score to account for missing subjects.

Nasal or sinus congestion was reported by 7 subjects (6 prazosin and 1 placebo). Headache was reported by 4 subjects (3 prazosin and 1 placebo); initial insomnia was reported by 2 subjects (1 prazosin and 1 placebo); dry mouth was reported by 2 prazosin subjects; and sweating, depression and lower extremity edema each were reported by 1 placebo subject.

Adverse effects in the subgroup of subjects randomized but discontinuing the study before receiving the first (week 4) outcome evaluation were as follows: One subject randomized to prazosin had a self-limited episode of upper gastrointestinal bleeding prior to the 4 week rating that was considered not related to study drug. This subject's trauma nightmares subsequently responded positively to open-label prazosin with no recurrence of gastrointestinal bleeding. One subject had a manic episode after randomization but prior to ingesting any study drug. Two subjects (randomized to prazosin) withdrew consent because of transient but subjectively uncomfortable orthostatic dizziness during drug titration. Neither experienced syncope or fall. Two subjects (both randomized to placebo) failed to return for scheduled appointments.

Discussion

This parallel group study is the second placebo-controlled study to demonstrate that evening prazosin substantially re-

duces distressing nighttime PTSD symptoms in veterans with chronic PTSD. That these reductions of trauma nightmares and sleep disturbance were clinically meaningful was supported by the large treatment effect sizes and the CGIC scores. The latter indicated greater improvement in overall sense of well-being and ability to function in the prazosin subjects compared to the placebo subjects. These findings replicate the results of our smaller placebo-controlled crossover study in Vietnam combat veterans with chronic PTSD (Raskind *et al.* 2003). They extend those results by using a parallel group design, by including a larger number of subjects, and by using validated measures of sleep quality (the PSQI), trauma-related nightmare characteristics (the NFQ and PDRS), and depression (the HAM-D).

The use of the NFQ and PDRS as secondary outcome measures provided a more detailed look at the specificity of prazosin effects on trauma nightmares as compared to other "normal" dreams (distressing and not distressing) unrelated to subjects' traumatic events. The NFQ demonstrated that the largest reductions (and the only changes significantly greater with prazosin than placebo) occurred in military trauma nightmares. Consistent with the NFQ results, the PDRS indicated a significant prazosin effect on the characteristics of recalled dreams. These changes were away from those of trauma nightmares (e.g., threatening content of actual past combat event with death possible) and toward "normal" dream characteristics (e.g., home/work setting in present time that would not occur in reality). This shift is consistent with preclinical studies that demonstrate normalization of REM sleep by prazosin (Hilakivi *et al.* 1984; Kleinlogel, 1989) and our clinical experience with many veterans receiving open label prazosin who report "normal" dreaming (pleasant and unpleasant) returning with prazosin treatment as their trauma nightmares recede or disappear.

Although the reduction in the total 17-item CAPS score was numerically greater in prazosin than placebo subjects, differences between groups did not reach statistical significance. That the CGIC results substantially favored prazosin despite the absence of a significant group difference in total 17-item CAPS score change suggests that combat veterans with chronic PTSD perceive the impact of nighttime PTSD symptoms as highly important to their overall well being. To our knowledge, no study has assigned empirically derived weights to individual CAPS items in the combat veteran population. However, these results suggest that combat veterans suffering from trauma nightmares and sleep disturbance consider nighttime PTSD symptoms highly distressing and disabling; and that the nighttime symptoms contribute disproportionately to their global clinical status.

The absence of a significant evening dose prazosin effect on total 17-item CAPS score (that includes 15 predominantly daytime awake hours PTSD symptoms) may in part reflect prazosin pharmacokinetics. Prazosin has a short half-life (2 to 4 hours) and duration of action (6 to 8 hours) (Hardman *et al.* 1996). Consistent with its short half-life, prazosin usually is prescribed two or three times daily in general medicine to treat hypertension or symptoms of benign prostatic hypertrophy over the full 24 hour day (PDR 2002). A single evening dose of prazosin would be unlikely to maintain prazosin concentrations adequate to affect potentially prazosin responsive PTSD symptoms during the following daytime hours. We recently demonstrated that adding a midmorning prazosin dose to evening prazosin can reduce daytime PTSD symptoms in persons with civilian trauma PTSD (Taylor et al 2006). These persons had persistent daytime PTSD symptoms despite substantial reduction of trauma-related nightmares and sleep disturbance following a single evening prazosin dose. When given an additional midmorning prazosin dose at one-third to one-half their evening dose, they experienced significant reduction of residual daytime PTSD symptoms.

Prazosin pharmacokinetic considerations may not entirely explain why evening prazosin in this subject sample was highly effective for nighttime PTSD symptoms but did not significantly reduce total CAPS score. In our previous crossover study in Vietnam combat veterans (Raskind *et al.* 2003) evening prazosin compared to placebo significantly, albeit modestly, reduced total CAPS score as well as nighttime PTSD symptoms. A possible explanation for this outcome difference between that earlier study and the current study is their different temporal relationship to the terrorist attacks of September 11, 2001, and the intense and unavoidable media coverage of subsequent military operations in Afghanistan and Iraq. The earlier crossover study was completed prior to September 11, 2001, and was conducted during a period free of United States involvement in overt military conflict. The parallel group study reported here was initiated in 2003, and completed in 2005. Most veteran participants in the current study reported that they found it impossible to avoid the daily media coverage of military events in Afghanistan and Iraq. Many volunteered that this media exposure frequently stimulated intrusive memories of their own military traumas as well as other PTSD symptoms. Anecdotally, many of these veterans after completion of the study reported that addition of an open-label mid-morning prazosin dose to their evening prazosin regimen substantially reduced their daytime PTSD symptoms. Further placebo-controlled studies in combat veterans and other populations with PTSD are necessary to determine whether twice daily prazosin will reduce distressing daytime PTSD symptoms in addition to the demonstrated beneficial effects of evening prazosin on PTSD trauma nightmares and sleep disturbance. It also is possible and even likely that prazosin alone is not effective for all PTSD symptoms.

The effects of prazosin on sleep physiology in preclinical studies are consistent with the observed therapeutic effects of prazosin on trauma nightmares in PTSD. The physiology of PTSD trauma nightmares differs from that of "normal" dreams. Trauma nightmares largely are expressed during light sleep and disrupted REM sleep, and often are accompanied by motor activity (Ross *et al.* 1994; Woodward 1995). Normal dreams, whether pleasant or unpleasant, most often arise from REM sleep that is characterized by relative paralysis of large muscle movement (Mallick *et al.* 2002). In preclinical studies, stimulation of CNS alpha-1 adrenergic receptors by the alpha-1 agonist methoxamine increases light sleep and disrupts REM sleep (Pickworth *et al.* 1997), thus enhancing sleep stage phenomena associated with emergence of trauma-related nightmares in humans (Woodward 1995). Addition of prazosin reverses these effects by decreasing light sleep and normalizing REM sleep (Hilakivi *et al.* 1984; Kleinlogel 1989; Pellejero *et al.* 1984). Consistent with these preclinical observations, veterans whose trauma nightmares are reduced or eliminated by prazosin report the return of "normal" pleasant (and unpleasant) dreams often not recalled since prior to their military trauma.

Prazosin was well-tolerated by this sample of mostly middle-aged veterans. Except for subjectively distressing transient orthostatic dizziness during drug titration in the 2 subjects who elected to discontinue study participation and in a few other subjects during drug titration, the substantial doses

of prazosin achieved rarely produced symptoms attributable to blood pressure reduction. Orthostatic dizziness was no more frequent in the subjects on prazosin than those on placebo. There were no falls or syncopal episodes, and prazosin did not lower end study blood pressure more than did placebo in subjects completing the study. Consistent with clinical experience, prazosin rarely produced sedation. Nasal congestion and headache in some subjects were the adverse effects most clearly attributable to prazosin in this study. Because several other classes of psychotropic medications sometimes prescribed for PTSD (e.g., atypical antipsychotics and trazodone) have alpha-1 adrenergic antagonist properties, clinicians adding prazosin to regimens including such drugs should be aware that the threshold for emergence of orthostatic hypotension and other prazosin adverse effects may be lower.

These results support the therapeutic use of prazosin for PTSD in combat veterans who present with trauma nightmares and sleep disturbance. Clinical experience suggests that prazosin also is beneficial for PTSD trauma nightmares and sleep disturbance in young civilian trauma victims, young veterans of the current conflict in Iraq and Afghanistan and in elderly World War II and Korean War combat veterans and Holocaust survivors (Taylor and Raskind 2002; Daly *et al.* 2005; Peskind *et al.* 2003). Larger placebo controlled studies with midmorning and evening prazosin dosing are necessary to define prazosin efficacy and tolerability in these populations and to determine prazosin efficacy across the spectrum of PTSD symptoms.

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