Prazosin Reduces Nightmares in Combat Veterans With Posttraumatic Stress Disorder

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Background: Preclinical and clinical observations suggest that the centrally active α_1-adrenergic antagonist prazosin might alleviate trauma content nightmares and other symptoms in combat veterans with chronic posttraumatic stress disorder (PTSD).

Method: In this retrospective chart review study, we analyzed data from 59 consecutive combat veterans with previously treatment-resistant chronic PTSD (DSM-IV criteria) and severe intractable trauma content nightmares to whom prazosin had been prescribed. Nightmare severity was quantified using the recurrent distressing dreams item of the Clinician Administered PTSD Scale (CAPS). Change in overall PTSD severity exclusive of nightmares was estimated by assigning a Clinical Global Impressions-Change scale (CGI-C) score based on chart review.

Results: Mean ± SEM recurrent distressing dreams item scores improved significantly (7.0 ± 0.2 to 3.5 ± 0.3, $p < .0001$) in the 36 patients who completed at least 8 weeks of prazosin treatment at their maximum titrated dose. The mean maximum prazosin dose achieved in these 36 patients was 9.6 ± 0.9 mg/day. Recurrent distressing dreams scores also improved in the total group who filled their prazosin prescriptions ($N = 51$) (7.1 ± 0.2 to 4.2 ± 0.3, $p < .0001$). In a comparison group of 8 patients who did not fill their prazosin prescriptions but continued in outpatient treatment, there was no significant change in CAPS recurrent distressing dreams score (6.8 ± 0.5 to 6.7 ± 0.4). There also was at least some improvement in CGI-C ratings of overall PTSD severity exclusive of nightmares in a substantial majority of patients receiving prazosin, but not in the 8 comparison subjects. There were no serious adverse effects attributable to prazosin.

Conclusion: These observations suggest that prazosin may relieve symptomatic distress in PTSD, and they provide rationale for placebo-controlled trials of prazosin for PTSD trauma content nightmares and other PTSD symptoms.

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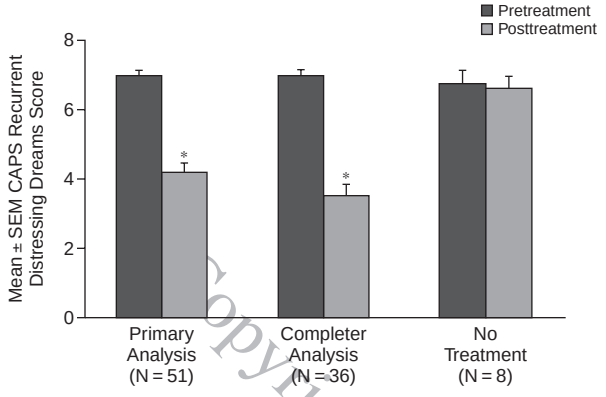
Frequent combat trauma nightmares occur in 15% of Vietnam combat veterans with chronic posttraumatic stress disorder (PTSD)[1] and often are resistant to psychopharmacologic treatment.[2] We recently reported that the centrally active α_1-adrenergic antagonist prazosin eliminated or substantially reduced PTSD trauma content nightmares in small samples of combat veterans[3] and persons with PTSD secondary to civilian trauma.[4] Here we report further experience with prazosin treatment in a large consecutive sample of combat veterans with PTSD and chronic treatment-resistant combat trauma nightmares that provides additional information about both therapeutic and adverse effects of this treatment approach.

METHOD

A retrospective chart review study of prazosin treatment for trauma-related nightmares in combat veterans with PTSD was approved by the University of Washington Human Subjects Review Committee. Prazosin had been prescribed to 59 consecutively identified male Vietnam and Gulf War combat veterans (mean ± SEM age = 51 ± 1.2 years) who met the following criteria: DSM-IV PTSD; chronic severe combat trauma–content nightmares as defined by a score ≥ 5 (of a maximum of 8) on the recurrent distressing dreams item of the Clinician Administered PTSD Scale (CAPS)[5]; and absence of alcohol or other substance abuse for at least 6 months. All had persistent nightmares despite ongoing treatment with at least one and often multiple psychoactive medications (e.g., selective serotonin reuptake inhibitors, trazodone, sedating antihistamines, valproic acid, benzodiazepines). Ongoing concurrent medications were maintained during the prazosin titration period and subsequent 8-week treatment evaluation period.

Figure 1. Pretreatment and Posttreatment Scores on the Clinician Administered PTSD Scale (CAPS) Recurrent Distressing Dreams Item



*Decrease in CAPS recurrent distressing dreams item scores was greater in primary analysis and completer analysis subjects compared with no-treatment subjects, $p < .0001$.

Prazosin was started at 1 mg at bedtime for several days, increased to 2 mg, and then gradually increased until nightmares were substantially improved, unacceptable adverse effects occurred, or a maximum daily dose of 20 mg was reached. If higher than 10 mg h.s. was prescribed, additional prazosin was given as a separate early evening dose. The CAPS recurrent distressing dreams item was administered by one of the authors (C.T.) at baseline (prior to prazosin titration) and at posttreatment, 8 weeks after a stable dose of prazosin had been achieved. A posttreatment Clinical Global Impressions-Change scale (CGI-C)[6] score for change in overall PTSD severity exclusive of nightmares was assigned by another author (E.R.P.) at week 8 on the basis of chart review. The CGI-C is a 7-point scale in which a score of 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." For patients who started prazosin but did not complete 8 weeks of treatment (N = 15), posttreatment ratings were those at the visit closest to prazosin discontinuation. For patients who did not fill their prescriptions for prazosin but did return for follow-up (N = 8), ratings were performed 12 weeks after prazosin prescription to achieve time-equivalent ratings with completer subjects who were rated after an approximately 4-week prazosin dose titration plus the 8-week treatment evaluation period at stable dose.

The 8 patients who did not fill their prazosin prescriptions but remained in therapy and continued to take their other medications were designated a "no-treatment" comparison group. The remaining 51 subjects were included in the primary analysis. Of these 51 subjects, 36 completed the prazosin titration and at least 8 weeks of further prazosin treatment and were included in an additional completer analysis. The 3 groups did not differ with respect to age or pretreatment CAPS recurrent distressing dreams item scores. Change in CAPS recurrent distressing dreams item scores (deltas) within groups was analyzed by a paired t test. Recurrent distressing dreams item deltas as well as CGI-C scores for overall PTSD severity exclusive of nightmares were compared between the 51 primary analysis prazosin patients and the 8 no-prazosin–treatment patients using unpaired t tests. All significance levels are 2-tailed. Results are reported as mean ± SEM.

RESULTS

The 51 primary analysis patients received a mean maximum prazosin dose of 6.3 ± 0.8 mg/day, and the 36 completer patients received a mean maximum dose of 9.6 ± 0.9 mg/day. CAPS recurrent distressing dreams item scores (Figure 1) substantially decreased from baseline to posttreatment in both the 51 primary analysis patients (7.1 ± 0.2 to 4.2 ± 0.3; $t = 9.1$, $p < .0001$) and the 36 completer subjects (7.0 ± 0.2 to 3.5 ± 0.3; $t = 9.6$, $p < .0001$). Distressing dream scores did not change in the no-treatment group (6.8 ± 0.5 to 6.7 ± 0.4, NS). Change scores in each treatment group were significantly greater than in the no-treatment group (each $p < .01$). Overall PTSD severity exclusive of nightmares as estimated using the CGI-C in the 51 primary analysis patients was "markedly improved" in 2 patients, "moderately improved" in 14 patients, "minimally improved" in 24 patients, and "unchanged" in 11 patients. None was rated as "worsened." Thus, 78% of prazosin-treated patients were rated improved to some degree in overall PTSD severity exclusive of nightmares. In the 36 completer patients, overall PTSD severity exclusive of nightmares was "markedly improved" in 2 patients, "moderately improved" in 13 patients, "minimally improved" in 19 patients, and "unchanged" in 2 patients. In the 8 no-treatment comparison patients, 1 was rated minimally improved and 7 were unchanged. Using the numerical equivalent of the verbal CGI-C descriptors, in which a lower score denotes greater improvement, CGI-C scores were more improved in the 51 primary analysis subjects than in the 8 no-treatment subjects (2.9 ± 0.1 vs. 3.9 ± 0.1; $t = 3.5$, $p < .01$).

Adverse effects resulting in prazosin discontinuation occurred in 15 patients (29%). Even in these 15 patients, recurrent distressing dreams item scores improved (7.0 ± 0.3 to 5.7 ± 0.5; $t = 3.35$, $p < .01$). The most frequently reported adverse effects were orthostatic dizziness (3 patients), headache (3 patients), and nausea (2 patients). Only 3 of the 36 study completers reported adverse effects: orthostatic dizziness, headache, and lethargy. Consistent with extensive clinical experience with prazosin administration for hypertension and benign prostatic hypertrophy, adverse effects tended to occur at initial low dose ranges and were uncommon at higher doses.[7,8] No subject experienced either syncope or a fall. Sedation was rarely re-

ported, and patients frequently noted improved sleep quality and resumption of often long-absent normal dreaming.

DISCUSSION

The association of prazosin treatment with substantial reduction in chronic and previously treatment-resistant trauma content nightmares as well as at least some reduction of overall PTSD severity exclusive of nightmares in combat veterans suggest potential efficacy for central α_1-adrenergic blockade for distressing PTSD symptoms. Although a minority of patients experienced bothersome adverse effects that led them to discontinue prazosin, none of these adverse effects were serious, and prazosin was well tolerated by most patients.

Preclinical and clinical observations provide rationale for amelioration of PTSD symptoms by central α_1-adrenergic blockade. Several neurobiological systems believed to be involved in the pathophysiology of PTSD are regulated by α_1-adrenergic receptors. These include components of sleep architecture relevant to PTSD nightmare emergence,[9–11] corticotropin-releasing hormone (CRH) neurons that contribute to the expression of stress responses,[12–15] prefrontal cortical systems that modulate fear and cognitive processing,[16–18] and brain stem mechanisms contributing to the startle response.[19] For each of these systems, excessive α_1-adrenergic stimulation would be expected to contribute to emergence of PTSD symptoms.

PTSD trauma content nightmares most likely emerge from stage 1 and stage 2 sleep (the "light" stages of non–rapid eye movement sleep) and/or from disrupted rapid eye movement (REM) sleep.[10] In preclinical studies, stimulation of central α_1-adrenergic receptors increases stage 1 and stage 2 sleep and disrupts REM sleep; these effects are reversed by administration of prazosin.[20,21] If prazosin also reduces stages 1 and 2 sleep and normalizes REM sleep in humans with PTSD, such effects would be consistent with the reported decrease in nightmares and frequent resumption of normal dreaming reported in our subjects during prazosin treatment. Polysomnographic studies are needed to explore this hypothesis. The increased nocturnal noradrenergic outflow demonstrated in combat veterans with PTSD[9] also provides a mechanism that would increase α_1-adrenergic activation contributing to nightmares in this disorder.

Increased concentrations of CRH in cerebrospinal fluid have been reported in PTSD[22,23] and appear to represent increased central nervous system (CNS) CRH release.[24] Studies in rodents and nonhuman primates implicate central CRH in the expression of anxiety, fear, and startle responses.[12–15] Amygdalar CRH neurons that project to locus ceruleus and stimulate CNS norepinephrine release appear to be particularly important to these responses.[13] Amygdalar as well as other CNS CRH neurons are under α_1-stimulatory regulation.[25,26]

Excessive α_1-adrenergic stimulation of prefrontal cortex also could contribute to expression of PTSD symptoms by differential stimulation of postsynaptic adrenergic receptor subtypes.[17,18] Low levels of noradrenergic outflow to prefrontal cortex preferentially stimulate postsynaptic α_2-adrenergic receptors that enhance cognitive processing and appropriate responses to emotionally salient stimuli. In contrast, high levels of noradrenergic outflow to prefrontal cortex most likely occurring in response to strongly stressful stimuli in PTSD would preferentially stimulate α_1-adrenergic receptors. Such prefrontal α_1-adrenergic stimulation disrupts cognitive processing and increases the likelihood of automatic and primitive responses to stressors reminiscent of the cognitive and emotional symptoms manifested in PTSD.[16–18]

These encouraging results during open prazosin treatment in this large sample of previously treatment-resistant combat veterans with chronic PTSD suggest that pharmacologic blockade of CNS α_1-adrenergic receptors may provide symptomatic relief in this difficult-to-treat population. In addition to the observed reduction in nightmares, overall PTSD severity exclusive of nightmares was globally rated as improved to some degree in the majority of patients receiving prazosin. Although the CGI-C does not provide an analysis of change in individual symptoms, it appears that a range of PTSD symptoms improved during prazosin treatment. This would be consistent with α_1-adrenergic receptor involvement in multiple brain processes implicated in PTSD pathophysiology. The full CAPS should be administered in future studies of prazosin in PTSD to evaluate treatment effects on the array of discrete symptoms manifested in this disorder.

That the naturalistic comparison PTSD group who did not take the prescribed prazosin but continued to receive psychotherapy and their maintenance psychotropic medications reported no symptomatic improvement is also supportive of a prazosin therapeutic effect. However, we are aware that other unknown factors may have selected for this small comparison group's both not filling their prazosin prescription and not reporting symptomatic improvement. This comparison group clearly is not as informative as a group prospectively randomly assigned to a placebo drug condition. The current open treatment results must be interpreted cautiously until prazosin efficacy in PTSD is established by blinded placebo-controlled trials. The low cost of this generically available α_1-adrenergic antagonist is an additional reason to pursue such controlled outcome trials.

Drug names: prazosin (Minipress and others), valproic acid (Depakene and others).

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