

# Daytime Prazosin Reduces Psychological Distress to Trauma Specific Cues in Civilian Trauma Posttraumatic Stress Disorder

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**Background:** Persons with posttraumatic stress disorder (PTSD) whose trauma-related nightmares improve or resolve with bedtime administration of the alpha-1 adrenergic antagonist prazosin often continue to experience PTSD symptoms during the day. This study addressed whether daytime prazosin compared to placebo would alleviate psychological distress provoked experimentally by a trauma-related word list included in the emotional Stroop (E-Stroop) paradigm.

**Methods:** Eleven persons with civilian trauma PTSD who continued to experience daytime PTSD symptoms despite a stable bedtime prazosin dose that suppressed trauma-related nightmares were studied. Prazosin and placebo were administered on two different occasions in the early afternoon followed two hours later by the E-Stroop. Effects of drug on psychological distress were assessed by the Profile of Mood States (POMS).

**Results:** POMS total score and an "emotional distress" POMS subscale score following trauma-related words were significantly lower in the prazosin than placebo condition. There were no treatment effects on E-Stroop completion time. In 10 subjects who continued open label daytime prazosin, there was a reduction in global PTSD illness severity at 2-week follow-up.

**Conclusions:** Daytime prazosin pretreatment reduced psychological distress specifically to trauma cues. Adding daytime prazosin to bedtime prazosin may further reduce overall PTSD illness severity and distress.

**Key Words:** Posttraumatic stress disorder, PTSD, prazosin, emotional Stroop, norepinephrine, alpha-1 adrenoceptor

Bedtime administration of prazosin, a generically available alpha-1 adrenergic antagonist, effectively and substantially reduces trauma-related nightmares and sleep disturbance and improves global illness severity in chronic combat trauma posttraumatic stress disorder (PTSD) (Raskind et al 2003). A case series suggests similar prazosin therapeutic effects in civilian trauma PTSD (Taylor and Raskind 2002). However, many PTSD patients whose nocturnal PTSD symptoms are alleviated following bedtime prazosin continue to experience psychological distress to trauma cues and other PTSD symptoms during the day (Raskind et al 2003; Taylor and Raskind 2002). A potential explanation for the persistence of daytime PTSD symptoms despite benefit from bedtime prazosin is the short two to four hour half-life of the drug (Hoffman 2001). It is predictable, therefore, that a bedtime prazosin dose effective for trauma nightmares might not continue to provide adequate drug concentrations to alleviate potentially prazosin-responsive PTSD symptoms the following day. Consistent with its pharmacokinetics, prazosin is prescribed twice or three times daily when used in general medicine as an antihypertensive (Medical Economics 2005). We have observed in clinical practice that adding a daytime prazosin dose to a stable bedtime prazosin dose has

been associated with further reduction of daytime PTSD symptoms (Taylor and Raskind 2002).

In the present study, we evaluated the effects of daytime prazosin compared to placebo on experimentally induced psychological distress to verbal trauma cues in civilian trauma PTSD. These patients had continued to experience daytime PTSD symptoms despite reduction of nocturnal PTSD symptoms with bedtime prazosin. The emotional Stroop (E-Stroop) paradigm was used to produce "real time" emotional responses to words evoking reminiscence of etiologic trauma as well as to words unrelated to etiologic trauma (McNally et al 1990). We hypothesized that prazosin would reduce PTSD-like psychological distress specifically in response to a trauma-related word list contained in the Emotional Stroop (E-Stroop) paradigm. Because persons with PTSD take longer to complete the trauma word list than other word lists in the E-Stroop (McNally 1998; Field et al 2001), a secondary hypothesis was that prazosin would improve cognitive performance on the trauma-related word list.

## Methods and Materials

### Subjects

Eleven outpatients recruited from the practice of investigator FT (8 women and 3 men, age =  $47 \pm 7$  years [mean  $\pm$  SD]) gave written informed consent for participation in this study, which was approved by the Western Institutional Review Board. Subjects met DSM-IV criteria for PTSD caused by civilian trauma. Each had persistent daytime PTSD symptoms despite a reduction of trauma nightmares and sleep disruption in response to a stable (at least one month) bedtime prazosin dose. Prior to beginning bedtime prazosin, baseline scores on the PTSD Checklist-Civilian Version for DSM-IV (PCL-C) (Weathers et al 1993) were  $67 \pm 11$  (range 47 to 80) and on the Clinical Global Impression of Severity (CGIS) (Guy 1976) were  $4.1 \pm .5$ . All subjects had experienced distressing trauma-related nightmares and sleep disruption more than twice a week over the month prior to beginning bedtime prazosin. Subjects had been free of substance abuse for at least three months, and were in good general health. Seven subjects met DSM-IV criteria for major

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depressive disorder. In addition to prazosin, all subjects had been maintained on at least one concomitant psychotropic medication. These included a selective serotonin reuptake inhibitor (SSRI) ( $n = 6$ ), a nonSSRI antidepressant ( $n = 6$ ), an atypical antipsychotic ( $n = 1$ ), a benzodiazepine or zolpidem as a hypnotic ( $n = 2$ ), and buspirone ( $n = 3$ ).

**Procedure.** All subjects participated in a pre-study phase of open-label titration and maintenance bedtime prazosin and a study phase single-dose double-blind daytime prazosin versus placebo augmentation. Ten of 11 then participated in a post-study open-label daytime plus bedtime prazosin maintenance phase.

**Pre-Study Phase.** Subjects were titrated to a bedtime dose of open label prazosin that reduced trauma-related nightmares. Prazosin was initiated at 1 mg at bedtime and increased by 1 mg every 3 to 6 days until trauma-related nightmares had decreased by at least 1-point on the 5-point PCL-C “distressing dreams” item. Subjects were maintained at this bedtime prazosin dose for at least one month and during the subsequent study phase (see below). The subject then completed the PCL-C, and the Clinical Global Impression of Severity (CGIS) (Guy 1976) was completed by investigator FT prior to beginning prazosin and after one month on the achieved pre-study phase prazosin dose. The maximum titration period was 3 weeks. The bedtime prazosin dose achieved was  $3.2 \pm 1.3$  mg (mean  $\pm$  SD), range 1 to 5 mg. Throughout all study phases, any concomitant medication dosages were held constant.

**Study Phase (E-Stroop Test-Retest Method).** The study phase investigating the effects of daytime prazosin on psychological distress to verbal trauma cues utilized a double-blind placebo-controlled within subjects design. In the early afternoon, subjects were administered a single dose of prazosin capsule(s) or identical appearing placebo capsule(s), equal in mg to their maintenance bedtime prazosin dose. Prazosin and placebo capsules were identical in shape, color and number. When asked to guess which condition was active drug, only five of eleven guessed correctly. The prazosin dose and the placebo dose were administered in random order one week apart. Two hours following administration of prazosin or placebo, blood pressure and heart rate in the sitting position were recorded. Then subjects were administered the E-Stroop, composed of 5 different consecutive word category lists (color only, neutral words, positive words, negative words, and trauma-related words) as described below. Participants completed the Profile of Mood State (POMS) (McNair et al 1971) after each E-Stroop word category. Time to completion and errors in each word category were recorded. Subjects were instructed to continue their bedtime prazosin and all other medications during the study phase.

**Post-Study Phase.** After the study phase 10 of the 11 subjects elected to continue taking an open label daytime prazosin dose in addition to their bedtime prazosin dose. After two weeks of twice daily prazosin (early afternoon and bedtime), investigator FT completed the CGIS.

Instruments

The E-Stroop is a modification of the Stroop Color-Word Interference Test (Golden 1976) that has been used for decades to assess cognitive function. The E-Stroop was developed to study cognitive effects of increased emotional arousal in PTSD in a controlled laboratory setting (McNally et al 1990). The E-Stroop version used in this study consisted of four control word category lists and one experimental trauma-related word category list. For each list, five different words were printed in random order using five different (randomized) ink colors: black, blue, brown, red, and green. The four control word lists were patterned after the E-Stroop version most commonly used (McNally 1998): 1) colored bars (columns of “oooo”s); 2) neutral words (e.g., curtain, lamp); 3) positive words (e.g., loyal, happy); and 4) negative (contamination) words (e.g., dirty, germs). The experimental trauma-related word list consisted of five words chosen by each participant from their personal narrative of their etiologic trauma event (e.g., “fire” and “9/11” for a World Trade Center occupant who survived the September 11, 2001, terrorist attack; and “revolver” and “incest” for a victim of parental rape at gunpoint).

For each word list, the subject named the colors in which the words are printed as quickly and accurately as possible. Time to completion and number of errors were recorded. Immediately following each reading, the subject completed the POMS. Subjects always completed the word list categories in the order described above. The trauma related word list was always last to avoid carryover effects of the trauma-related word list confounding interpretation of subsequent lists (McNally et al 1990). During a 15-minute recovery period the POMS was administered every 5 min. Ten min into the recovery period, participants were asked to read the neutral word list a second time (Figure 1).

The PCL-C was used as an aid in establishing entry diagnostic criteria and as a measure of change. The PCL-C is a 17-item checklist in which respondents rate the presence and severity of PTSD symptoms on a five-point scale. It has well-established reliability and validity (Weathers et al 1993) and is widely used in PTSD research (Saxon et al 2001).

The CGIS is a clinician rated global illness scale used to determine overall severity level of mental illness (Guy 1976). Ratings are on a scale of “1” (“normal, not ill at all”) to “7” (“among the most extremely ill patients”). The CGIS can be used to measure clinical response to treatment.

The POMS was used to quantify psychological distress fol-

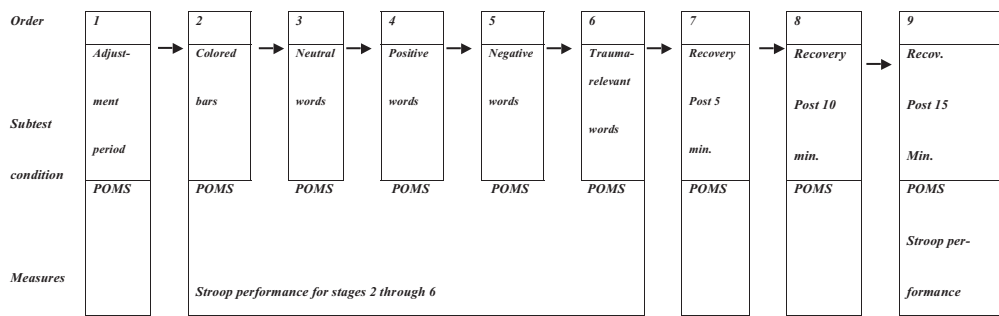


Figure 1. Stroop Testing procedure sequence.

lowing each word list. The POMS consists of adjectives with intensity rated using a Likert scale in which 1 = “not at all” and 5 = “extremely.” From the original version (McNair et al 1971) 25 words were selected that pertained to PTSD symptoms. These words were divided into four subscales: emotional distress (“anxious,” “nervous,” “afraid,” etc.), autonomic sensations (“sweaty,” “dry mouth,” “flushed,” “chilled,” etc.), cognition (“forgetful,” “confused,” “mind going blank,” etc.), and somatic sensations/ behaviors (“trembling,” “jumpy,” “watchful,” etc.). Additionally, the descriptor “detached from feelings” was included.

The primary analysis used ANOVA for repeated measures to address the effect of daytime prazosin versus placebo on the POMS responses to the E-Stroop. Analyses were assessed for violations of the ANOVA test assumptions, including order effect (prazosin or placebo given first) and none were found. For drug effects on the POMS and time scores for each E-Stroop word list, the initial color bar list scores served as baseline values.

To determine if PTSD symptom improvement during open-label prazosin in the pre-study phase predicted prazosin effect in the study phase, a Pearson Product-Moment Correlation was performed between the decrease in PCL-C score from study entry to end of pre-study phase, and the difference between prazosin and placebo condition POMS “emotional distress” subscore responses to the trauma word list in the study phase.

## Results

### Pre-Study Phase

All subjects reported at least a 1-point decrease on the 5-point PCL-C Recurrent Distressing Dreams item. Although after one month of bedtime prazosin total PCL-C scores and CGIS scores had decreased significantly ( $67 \pm 11$  to  $54 \pm 12$  and  $4.1 \pm .5$  to  $3.2 \pm .6$ , both  $p < .01$ ), all subjects continued to have persistent distressing daytime PTSD symptoms.

### Study Phase

A protective prazosin effect on psychological distress upon exposure to trauma cues was demonstrated by the POMS scores following the trauma-related word list (Figure 2). The total POMS score for the trauma-related word list was significantly lower after prazosin pretreatment than after placebo

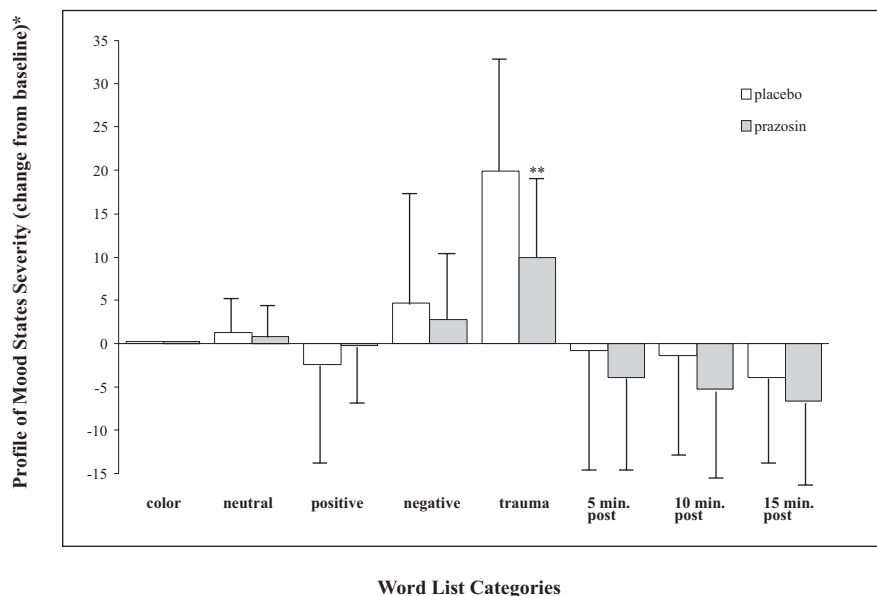
pretreatment ( $10 \pm 10.2$  vs.  $20 \pm 15$ ,  $F = 5.4$  (1,10),  $p < .05$ ). No statistically significant protective effects were found for any of the control word lists. Examining the POMS subscale response scores following the trauma-related word list (Figure 3), it was apparent that the prazosin effect on total POMS scores was accounted for by a substantial and significant prazosin protective effect on the “emotional distress” (e.g., anxious, nervous, afraid) POMS subscale. Although “autonomic” subscale scores were numerically lower in the prazosin than placebo conditions, differences were not significant. Prazosin and placebo scores on the “somatic,” “cognition,” and “dissociation” POMS subscale scores following the trauma word list were very similar in prazosin and placebo conditions.

Consistent with earlier studies, placebo-condition color naming completion time for the trauma word list ( $28 \pm 22$  sec) was substantially slower than for neutral word list ( $10 \pm 12$  sec), positive word list ( $8 \pm 9$  sec) or negative word list ( $17 \pm 18$  sec). There was no difference in trauma word list completion time between placebo and prazosin conditions ( $28 \pm 22$  vs.  $29 \pm 24$  sec), or for any control word list, or all of the word lists taken together. Errors also did not differ between conditions. There were no significant differences between prazosin and placebo two hours after drug administration for systolic blood pressure ( $124.7 \pm 23.4$  vs.  $132.2 \pm 25.0$ ), diastolic blood pressure ( $75.0 \pm 9.0$  vs.  $77.4 \pm 5.3$ ), or heart rate ( $91.6 \pm 21.5$  vs.  $82.6 \pm 13.5$ ). A reduction of psychological stress to trauma cues as measured by the POMS “emotional distress” subscale in the prazosin condition was significantly related to total PCL-C score response to open-label bedtime prazosin in the pre-study phase ( $r = .86$ ,  $p < .05$ ).

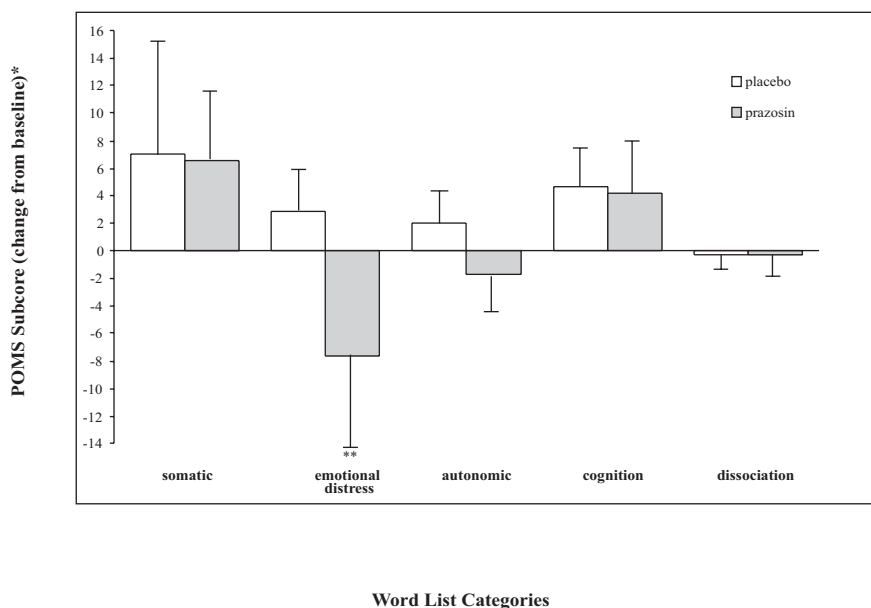
During E-Stroop testing, two participants reported mild sedation on prazosin and one reported mild sedation on placebo. There were no participant reports of dizziness or other symptoms to suggest clinically significant blood pressure reduction following either prazosin or placebo, nor were there any other adverse effects.

### Post-Study Phase

Ten of the 11 participants chose to continue daytime prazosin treatment following the study but daytime doses were adjusted downward for some patients because of mild subjective daytime



**Figure 2.** The protective effects of prazosin vs. placebo on emotional reactivity across E-Stroop Word Categories. \* Lower score indicates less emotional distress. \*\*  $p = .042$ .



**Figure 3.** The effects of prazosin on the profile of Mood States Subcategories during modified Stroop Trauma Word Category Testing. \* Negative score indicates emotional distress less than at baseline. \*\*  $p = .001$ .

sedation ( $3.2 \pm 1.3$  mg daytime dose administered during study phase;  $1.6 \pm 1.7$  mg daytime dose during open label post-study maintenance phase). CGIS ratings two weeks following the addition of daytime prazosin decreased from  $3.2 \pm .6$  at the end of pre-study phase to  $1.5 \pm 1.6$  ( $F = 12.9$ ,  $df = 1,9$ ,  $p < .01$ ). This response was significantly correlated with reduction of total POMS scores in the prazosin condition compared to the placebo condition in the study phase ( $r = .70$ ,  $p < .02$ ).

## Discussion

The primary hypothesis of this study was supported. A prazosin daytime dose significantly reduced psychological distress compared to placebo in response to verbal trauma cues in persons with PTSD. These results suggest that in addition to the demonstrated efficacy of bedtime prazosin for PTSD trauma-related nightmares and sleep disruption, additional daytime prazosin may relieve at least some PTSD symptoms during daytime hours. That prazosin reduced psychological distress only for the trauma-relevant word list suggests that prazosin specifically reduces psychological distress in response to trauma reminders and not to generally unpleasant verbal cues such as those in the “negative” word list. The prazosin effect on the E-Stroop was only observed for the “emotional distress” subcategory of POMS descriptors (“anxious,” “nervous,” “afraid,” etc.) and not for the POMS subcategories, autonomic sensations and somatic sensations, suggesting that reduced psychological distress to trauma cues during the prazosin condition was unlikely secondary to reduced perception of somatic anxiety sensations.

The usefulness of adding a daytime prazosin dose to bedtime prazosin is also suggested by the substantial reduction in PTSD global severity in subjects who continued to take a daytime prazosin dose in addition to their nighttime dose during the two-week follow-up. Given the short half-life of prazosin, daytime PTSD symptom benefiting from a daytime prazosin dose is consistent with prazosin pharmacokinetics. Although these latter observations were during open-label treatment, they provide rationale for a traditional double-blind placebo-controlled clinical trial in which daytime prazosin or placebo is added to maintenance bedtime prazosin for an extended time period. For clinicians treating PTSD, a practical dosing regimen might first

optimize a bedtime dose and then add a midmorning dose of 1/3 to 1/2 the optimum bedtime dose if distressing daytime PTSD symptoms persist. It is also possible that an “as needed” prazosin dose taken within two hours of an anticipated stressor may provide some daytime protection from excessive psychological distress and other PTSD symptoms.

Several effects of brain alpha-1 adrenergic blockade provide potential neurobiologic mechanisms by which prazosin could alleviate PTSD symptoms. The anxiogenic neuropeptide corticotropin releasing factor (CRF) (Bakshi et al 2002; Heinrichs and Koob 2004) is under alpha-1 adrenergic stimulatory regulation (Kiss et al 2000). Excessive CRF activity at amygdala, locus coeruleus and other brain sites is potentially involved in the pathophysiology of PTSD (Bremner et al 1997; Heinrichs and Koob 2004; Friedman 2000). By blocking brain alpha-1 adrenergic receptors, prazosin should reduce brain CRF release. Moreover, excessive alpha-1 adrenergic stimulation at the prefrontal cortex disrupts rational cognition (Arnsten et al 1999) and increases primitive fear responses (Harari et al 2003). Finally, the startle response also is under alpha-1 adrenergic stimulatory regulation (Stevens et al 2004) possibly via release of CRF at brainstem nuclei mediating startle (Risbrough et al 2003). Excessive startle response induced by alpha-1 agonists is reversed by prazosin (Carasso et al 1998).

The alpha-1 adrenoceptor is not the only postsynaptic adrenoceptor relevant to PTSD symptom expression. Brain beta adrenoceptors mediate aversive memory storage (Cahill et al 1994; Ferry et al 1999) and appear involved in PTSD pathophysiology (Taylor and Cahill 2002). The alpha-1 adrenoceptor may modulate this mechanism. In the basolateral nucleus of the amygdala, alpha-1 adrenoceptor activity modulates beta adrenoceptor enhancement of inhibitory avoidance learning, an effect that is blocked by prazosin injections at that site (Ferry et al 1999).

The secondary hypothesis that prazosin would reduce the time to complete the E-Stroop trauma-related word list over placebo was not supported. Prazosin had no effect on cognitive function as measured by completion times for the E-Stroop. Clinically, the absence of prazosin adverse effects on cognitive measures in this study provides some assurance that a low dose



of daytime prazosin is unlikely to interfere with cognition and skilled tasks in military and civilian settings.

Use of prazosin may also inform neuroimaging studies using daytime symptom provocation. Low prefrontal cortical activity has been demonstrated in the waking state during the intrusive recollections of PTSD trauma (Shin et al 2001; 2004). This finding potentially could be reversed by prazosin pretreatment.

To our knowledge, the E-Stroop test-retest method of symptom provocation is the first “real time” method of measuring drug efficacy for PTSD. Consistent with many prior studies, the color naming of trauma-relevant words was slower than for control word categories (McNally 1998). This is an indication that the E-Stroop test-retest method may have reliability across investigators, and that attentional bias towards trauma-relevant words was specific to individuals with PTSD. A neuroimaging study recently showed that attentional bias to threat cues changed neural activity in brain regions relevant to PTSD (Monk et al 2004). Thus the E-Stroop test-retest method including measures of psychological distress (POMS) and brain activity may be useful in assessing treatment effects on anxiety symptoms.

Limitations of this study included the small sample size and the selection bias of choosing subjects from PTSD patients already receiving a nighttime prazosin dose that reduced trauma nightmares. Another limitation was that during E-Stroop testing, prazosin efficacy was assessed over one testing period, not over weeks as is customary in drug efficacy study designs. Further placebo-controlled studies investigating the effects of daytime prazosin administration on daytime PTSD symptoms should broaden our understanding of the effects of alpha-1 adrenergic blockade on the expression of PTSD symptoms and are needed to support these preliminary studies. The response to the E-Stroop as a measure of change would be informative in such studies.

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