Prazosin for Veterans with Posttraumatic Stress Disorder and Comorbid Alcohol Dependence: A Clinical Trial

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Background: Posttraumatic stress disorder (PTSD) is an important and timely clinical issue particularly for combat veterans. Few pharmacologic options are available to treat PTSD, particularly among military personnel, and they are not based on rational neurobiology. The evidence for noradrenergic dysregulation in PTSD is strong, and the alpha-adrenergic agonist prazosin is one of the most promising medications to treat sleep disturbances associated with PTSD as well as PTSD symptoms among both veterans and civilians. Evidence also implicates noradrenergic dysregulation in the pathophysiology of alcohol dependence (AD); prazosin also may have efficacy in treating this disorder. The use of prazosin represents a rational and compelling approach for the treatment of PTSD and comorbid AD. Given the high rates of comorbid AD in trauma survivors with PTSD, and the enormous impact that these comorbid disorders have on psychosocial function and well-being, finding effective treatments for this population is of high clinical importance.

Methods: Ninety-six veterans with PTSD and comorbid AD were randomized to receive prazosin (16 mg) or placebo in an outpatient, randomized, double-blind, clinical trial for 13 weeks. Main outcomes included symptoms of PTSD, sleep disturbances, and alcohol use.

Results: Symptoms of PTSD improved over time, but contrary to the hypothesis, there was no medication effect on PTSD symptoms, or on sleep. Alcohol consumption also decreased over time, but there were no significant differences in outcomes between medication groups.

Conclusions: Prazosin was not effective in treating PTSD symptoms, improving sleep, or reducing alcohol consumption overall in this dually diagnosed group. This does not support the use of prazosin in an actively drinking population and suggests that the presence of a comorbid condition affects the efficacy of this medication. This study highlights the importance of conducting clinical trials in "real-world" patients, as results may vary based on comorbid conditions.

Key Words: Posttraumatic Stress Disorder, Alcoholism, Prazosin, Veterans, Clinical Trial.

POSTTRAUMATIC STRESS DISORDER (PTSD) is a serious mental disorder and a public health issue particularly among military personnel. The risk of developing PTSD among combat-exposed military personnel is very high (Hoge et al., 2006), and screenings of soldiers returning from the recent conflicts in Iraq and Afghanistan have found rates of PTSD up to 24.5% (Hoge et al., 2004, 2006, 2007; Milliken et al., 2007). This is also an issue for the Veterans Health Administration, which has experienced a 3-fold increase in numbers of veterans presenting for treatment over the last 8 years.

The serotonergic reuptake inhibitors (SRI) paroxetine and sertraline are first-line medications and the only medications approved by the Food and Drug Administration (FDA) to treat PTSD. However, their efficacy is modest at best, and they are less effective for combat veterans than for civilian trauma survivors (Hertzberg et al., 2000). SRIs may have limited efficacy for PTSD for a number of reasons (Friedman, 2013): SRIs are nonspecific in their actions and were chosen because they are effective in other disorders such as major depression, rather than based on an understanding of the neurobiology of PTSD.

In contrast, the use of adrenergic agents to treat PTSD represents a rational approach based on preclinical and clinical neurobiological findings. The noradrenergic system is thought to play an integral role in the development and maintenance of PTSD (Southwick et al., 1999). The data from both preclinical and clinical studies are compelling and include evidence for heightened physiologic responsivity to trauma-related cues, elevated 24-hour urinary noradrenaline (NE) excretion, elevated plasma NE, and increased cerebrospinal fluid NE, decreased platelet alpha-2 adrenergic receptor number, reduced norepinephrine transporter avail-

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Received for publication June 2, 2015; accepted October 10, 2015.

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DOI: 10.1111/acer.12926

ability in the locus coeruleus, and exaggerated responses to the alpha-adrenergic antagonist, yohimbine. These data have linked noradrenergic reactivity to a number of trauma-related symptoms including hypervigilance, exaggerated startle response, aggression, intrusive memories, and nightmares. Thus, reducing NE activity represents a rational approach to treating PTSD.

To date, a number of adrenergic agents have been tested for their efficacy in treating PTSD. These include the alpha-2 adrenergic agonists clonidine and guanfacine, the nonselective beta-adrenergic agent propranolol, and most promising prazosin, which is an alpha-1 adrenergic receptor antagonist that blocks the actions of NE on alpha-1 receptors. Preclinical data predicts alpha-1 blockade in the locus coeruleus (Aston-Jones et al., 1994), amygdala (Nader and LeDoux, 1999), thalamus (McCormick et al., 1991), and prefrontal cortex (Arnsten et al., 2015) would help to preserve prefrontal cortical function and reduce hypervigilance, insomnia, intrusive memories, sleep disturbances, and nightmares in humans suffering with PTSD. Clonidine and guanfacine have demonstrated limited efficacy for the treatment of PTSD, although larger clinical trials are needed. Several studies have assessed the effects of beta-blockers on memory consolidation if administered immediately following a traumatic event.

Since 2003, there have been 4 randomized placebo-controlled trials of prazosin for PTSD which include combat veterans. All 4 trials (*n* ranging from 10 to 67) reported a significant reduction in daytime hyperarousal, nightmares, and global clinical status. In the largest and most recent of these trials, a significantly greater reduction in total score of the Clinician Administered PTSD Scale (CAPS) was also observed for prazosin compared to placebo. A large multisite cooperative study evaluating prazosin for the treatment of PTSD symptoms, insomnia and nightmares, in veterans has recently been completed, but results have not yet been published. Of note, veterans with alcohol dependence (AD) were excluded in that study (ClinicalTrials.gov NCT00532493). The success of prazosin, a theory-driven rational pharmacological intervention for PTSD, has been greeted with enthusiasm by clinicians and researchers, and led to its inclusion in the Department of Veterans Affairs and Department of Defense Treatment Guidelines for PTSD as a recommended adjunctive treatment for sleep/nightmares in trauma survivors with PTSD.

The lack of effective pharmacotherapies to treat PTSD is even more glaring when considering those individuals who have a concurrent alcohol use disorder (AUD). A recent Institute of Medicine Report (2014) has highlighted the alarmingly high rate of substance abuse (including alcohol) among servicemen and women and how it undermines military readiness. AUD, including AD, are prevalent among military personnel and are associated with substantial medical, psychiatric, and economic impact (Goetzel et al., 2003). There is a high rate of comorbidity between PTSD and AUD, and co-occurring disorders are associated with worse treatment outcome than either disorder alone (McCarthy and Petrakis, 2010; Riggs et al., 2003) and significantly lower quality of life (Kalman et al., 2004). Few studies have evaluated treatments in those with active comorbid conditions.

As in PTSD, overactivity of the noradrenergic systems has been implicated in excessive alcohol use: repeated alcohol administration results in a sensitized noradrenergic system (Lanteri et al., 2008); alcohol withdrawal is associated with increased sympathetic activation and elevated NE in animals (Rasmussen et al., 2006) and humans (Patkar et al., 2003); and heightened sympathetic activation has been reported long after terminating chronic use of alcohol. Prazosin, through its actions on alpha-1 adrenergic receptors, has been shown to decrease self-administration of alcohol in ethanol (EtOH)-dependent rodents (Rasmussen et al., 2009; Verplaetse et al., 2012); suppress operant responding for EtOH in EtOH-dependent but not in non-dependent animals (Walker et al., 2008); block initiation of drinking in rodents bred for high intake of alcohol (Froehlich et al., 2013); and block yohimbine-induced reinstatement of food and alcohol seeking (Le et al., 2011). In humans, prazosin reduces stress- and cue-induced alcohol craving in the laboratory (Fox et al., 2012; Simpson et al., 2009) and in a pilot trial significantly reduced drinking days per week and average total number of drinks compared to placebo among AD subjects without PTSD (Simpson et al., 2009). In a recently published study, prazosin decreased alcohol consumption among individuals with AD and comorbid PTSD; interestingly, there was no medication effect on PTSD symptoms (Simpson et al., 2015). Further, ongoing clinical studies evaluating prazosin are under way.

At least some studies suggest noradrenergic agents may be effective in the treatment of comorbidity. In work by our group, the noradrenergic antidepressant, desipramine, was as effective as the FDA-approved SRI sertraline in treating PTSD, and more effective than sertraline for alcohol use outcomes (Petrakis et al., 2012). In this study, we wished to test the hypothesis that prazosin would be significantly more effective than placebo in treating sleep disturbance, symptoms of PTSD, and alcohol consumption in military veterans with PTSD and comorbid AD.

MATERIALS AND METHODS

This study was approved by the Human Subjects Subcommittees of the VA Connecticut Healthcare System (West Haven, CT), by the Bedford VA Medical Center (Bedford, MA), and by the Yale Human Investigations Committee (New Haven, CT). The participants ($n = 96$) were veterans who were patients from West Haven (CT) and Bedford (MA) VAs ($n = 41$ from CT, and $n = 55$ from MA) and were recruited during the funding period of the Department of Defense-funded grant awarded to the first author. Recruitment was primarily from clinicians in the substance abuse treatment programs and the PTSD treatment programs at both sites, and recruitment was augmented with advertisements at the VA facilities and in the community. After signing written informed consent, potential participants were evaluated and included if they were men or women, ages of 21 to 65, met DSM-IV criteria for

current PTSD and AD (determined by structured clinical interview) (First et al., 1996), and reported at least 1 episode of heavy drinking (defined as >5 for men and >4 for women on 1 occasion) over the past 14 days. Participants were medically healthy by physical and laboratory examination, and for females, not pregnant, and using adequate birth control. Exclusion criteria included unstable or current serious psychotic symptoms, suicidal or homicidal ideation, or medical problems that would contraindicate the use of prazosin. Participants could not be taking medications thought to influence alcohol consumption (such as naltrexone, disulfiram, or acamprosate), but other psychiatric medications were allowed. Subjects were also required to be abstinent for 2 days prior to randomization; abstinence was determined by self-report and a negative breathalyzer reading (see Fig. 1).

Treatments

Following completion of baseline assessments, 96 subjects were randomized to 1 of 2 groups for 13 weeks. Randomization was conducted by the pharmacy using a 1:1 randomization in blocks of 4 and stratified by site, gender, and psychiatric medication status which included prazosin 16 mg per day or placebo in a double-blind fashion. Prazosin was titrated upward during the first 2 weeks, starting at 2 mg per day, and then increased over the 2 weeks to 16 mg per day in divided doses. Study medications were dispensed in identical looking capsules and in blister packs. Medication compliance was monitored at every visit for each blister pack. All subjects also received medical management therapy (Pettinati et al., 2000) administered by a trained research nurse.

Assessments

Baseline Measures. All subjects completed an intake assessment including the Structured Clinical Interview for DSM-IV (SCID)-I to be sure they met eligibility criteria and to establish accurate diagnoses, which were confirmed by a psychiatrist. Alcohol Dependence Severity (ADS) (Skinner and Horn, 1984), CAPS for DSM-IV (Blake et al., 1990), Obsessive-Compulsive Drinking Scale (OCDS) (Anton et al., 1996), and Timeline Follow Back (TLFB) (Sobell and Sobell, 1992) were used to assess measures of alcohol use, PTSD symptoms, craving, and consequences.

Outcome Measures. Primary outcomes were measures of PTSD severity, alcohol use, and sleep disturbances. PTSD symptom severity was assessed every 4 weeks by the CAPS. TLFB was administered weekly to collect a detailed self-report of daily alcohol and other substance use throughout the 84-day treatment period as well as for the 90-day period prior to randomization. Alcohol

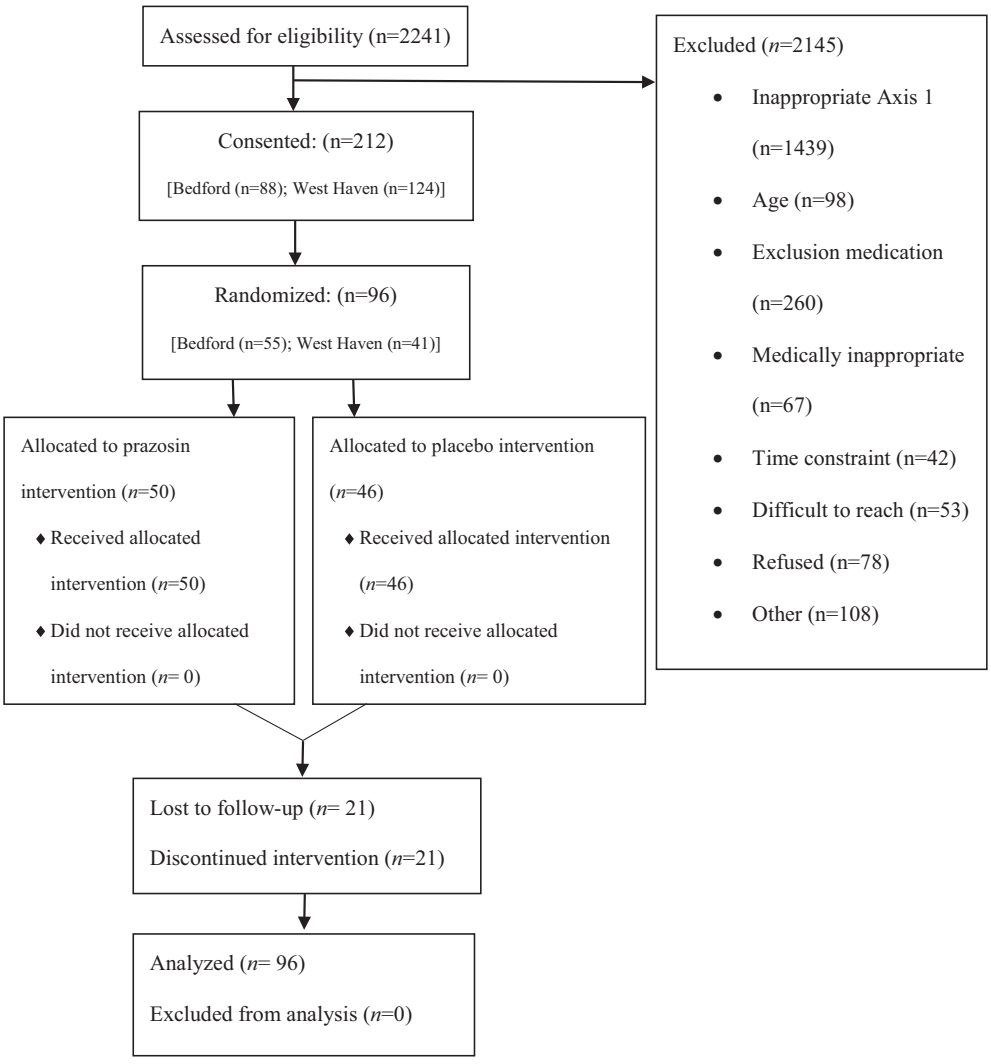


Fig. 1. Consort table.

consumption was confirmed using serum gamma-glutamyl transferase (GGT), collected 4 times during the study (baseline, weeks 4, 8, and 12). Craving was assessed weekly using the OCDS. Sleep was measured weekly using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and 2 questions from the CAPS: recurrent distressing dreams, and difficulty falling/staying asleep.

Side effects and common adverse symptoms were evaluated by the research nurse weekly using a modified version of the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Levine and Schooler, 1986). The symptoms that are known to be associated with treatment with prazosin were specifically screened for on a weekly basis. The symptoms were then clustered into the following categories: gastrointestinal, central nervous system, general, dermatological, genitourinary, cardiovascular, ophthalmological, and musculoskeletal.

Data Analysis

Descriptive statistics were used to summarize the data on all randomized subjects. All continuous variables were examined for adherence to the normal distribution using normal probability plots and Kolmogorov–Smirnov tests. The alcohol data were not normally distributed. As log transformations did not achieve normality, the data were ranked and nonparametric tests were used (Brunner et al., 2002). Demographic characteristics for the 2 treatment groups (prazosin vs. placebo) were compared using chi-square tests for categorical and analysis of variance (ANOVA) for continuous variables. All analyses were performed on the intent-to-treat sample with a 2-tailed alpha level of 0.05, and using 19.0 version of SPSS (IBM Corporation, Armonk, NY). Bonferroni adjustments were applied to the analysis of CAPS subscales (3 subscales; $\alpha = 0.016$), the alcohol data (6 drinking outcome measures; $\alpha = 0.008$), craving data (2 subscales: $\alpha = 0.025$), sleep data (2 CAPS questions: $\alpha = 0.025$), and side effects (8 symptom groups; $\alpha = 0.006$).

The outcome variables included: (i) PTSD symptoms (CAPS total scores and CAPS subscales); (ii) measures of alcohol consumption (percent of subjects who abstained from heavy drinking, average number of drinks per week, number of drinking days, number of heavy drinking days, consecutive days of abstinence, and number of drinks per drinking day) and craving (OCDS total scores and subscales); and (iii) changes in sleep (PSQI sleep quality index, CAPS recurrent distressing dreams, and CAPS difficulty falling/staying asleep). Mixed effects models were used to assess changes in PTSD symptoms, alcohol consumption, and sleep over time. We selected the best-fitting variance–covariance structure based on Schwartz–Bayesian information criterion. The treatment comparisons and site were between-subject factors in the models, and time (12 weeks) was used as a within-subject factor (when applicable).

Table 1. Demographic/Diagnostic Characteristics of Veterans Who Were Assigned to Either Prazosin or Placebo

Variables	Prazosin $n = 50$		Placebo $n = 46$		Statistics	
Demographic/diagnostic characteristics						
	Mean	SD	Mean	SD	*F*	*p*
Age	44.50	13.20	43.40	12.95	0.169	0.682
	n	%	*n*	%	X^2	*p*
Gender					0.506	0.477
Male	46	92.00	43	95.56		
Female	4	8.00	2	4.44		
Ethnicity					2.796	0.247
Caucasian	40	80.00	38	82.60		
African American	7	14.00	7	15.21		
Other	3	6.00	0	0		
Marital status					2.124	0.547
Single	16	32.60	13	28.26		
Married/cohabitating/ partner	10	20.00	11	23.91		
Separated/divorced	22	44.00	21	45.65		
Widowed	2	4.00	0	0		
Comorbid disorders						
Major depression	22	44.90	15	33.33	1.134	0.252
Anxiety disorders	9	18.00	9	19.57	0.093	0.844
Marijuana abuse/ dependence	6	12.24	5	11.90	0.002	0.960
Cocaine abuse/ dependence	10	20.41	6	13.95	0.664	0.415
PTSD and drinking characteristics						
	Mean	SD	Mean	SD	*F*	*p*
CAPS						
Severity of PTSD symptoms	71.86	20.32	75.86	14.44	1.16	0.284
Re-experience	19.62	8.22	21.14	7.23	0.890	0.348
Hypervigilance	22.94	7.37	22.52	6.15	0.087	0.768
Avoidance	29.30	9.04	31.76	7.08	2.098	0.151
Alcohol consumption						
Number of drinking days (over 90 days)	47.02	29.87	43.11	27.79	0.433	0.512
Number of heavy drinking days (over 90 days)	41.30	29.34	39.51	28.2	0.091	0.763
Number of drinks per drinking day	17.33	10.73	21.90	13.24	3.410	0.068
Percent drinking days	45.89	32.60	43.90	31.36	0.091	0.763
Total ADS	18.94	6.86	20.20	9.54	0.555	0.458

RESULTS

Demographic Variables

Ninety-six veterans participated in this study. As shown in Table 1, the sample was primarily male (94%), Caucasian (81%), and on average 43.98 (SD = 12.96) years old. This sample of veterans exhibited severe PTSD symptoms (mean = 73.7, SD = 17.86) and consisted of heavy drinkers. They averaged about 19.47 drinks per drinking day (SD = 12.12). ADS scores indicated an intermediate level of AD (mean = 19.53, SD = 8.21) among participants, a level often associated with psychological problems related to drinking. Thirty-nine percent of participants also had a diagnosis of current major depression, 19% had another anxiety disorder, 11% had current marijuana abuse/dependence, and 18% had current cocaine abuse/dependence. There were no significant differences between those who were randomized to prazosin versus those on placebo on any demographic or clinical variables.

Concomitant Treatment

As subjects were recruited primarily from clinics at both sites, the majority of participants (94 of 96 or 98%) were also enrolled in other treatments. Of those who received treatment, 59% percent were in substance abuse treatment only, 22%

were in treatment for PTSD only, and 19% were enrolled in both. There were no differences between sites among those enrolled in substance abuse treatment (58% in CT vs. 59% at MA). However, there were differences among those receiving PTSD treatment alone (40% in CT vs. 9% at MA) and among those who received both substance use and PTSD treatment (2% in CT vs. 32% in MA) ($\chi^2 = 19.81$, $p = 0.0001$). There was also a significant difference in those who were in sober housing during this study (49% in CT vs. 78% at MA) ($\chi^2 = 9.00$, $p = 0.003$).

Dosing and Retention

Fifty-eight percent of subjects reached the 16 mg dose of prazosin within 2 weeks. The average maintenance dose of medication was 14.5 mg (SD = 3.14). In this study, 78.1% of the subjects completed the study (75/96). Completers were defined as subjects for whom we had complete data at the end of the treatment period (week 12) whether they remained on medication or not. There was a significantly higher rate of completion in the prazosin group (43/50 or 86.0%) compared to placebo (32/46 or 69.6%), $\chi^2(1) = 3.78$, $p = 0.05$; 56.3% of the subjects (54/96) remained on study medication for 12 weeks. There was no difference in the medication dropout rate between the treatment groups (20/50 or 40.0% in the prazosin group and 22/46 or 47.8% in the placebo group, $\chi^2(1) = 0.596$, $p = 0.44$). There was no difference between the groups on the average number of days in the study, $F(1, 516.49) = 0.89$, $p = 0.34$, (mean = 74.9, SD = 22.00 for prazosin and mean = 70.1, SD = 26.09 for placebo).

PTSD Outcomes

One analysis was performed using time, medication, and site in the model. The analysis of total scores revealed only significant effect for time, $F(4, 76.09) = 44.27$, $p = 0.000$, and no other significant main effects, 2-way or 3-way interactions including time × medication group, or time × medication × site (see Table 2). Similarly, the results for the 3 subscales, including hyperarousal, avoidance, and re-experiencing, showed a main effect of time, but no effect of medication, medication × time, or medication × time × site. There were no significant site effects on any of the CAPS variables (total or any of the subscales).

Sleep

The analysis of the PSQI sleep quality index revealed only a significant main effect of time, $F(3, 66.58) = 14.85$, $p = 0.0001$, and no other significant main effects or interactions. The results were similar using the CAPS distressing dreams item showing only a significant main effect for time, $F(4, 75.61) = 26.89$, $p = 0.0001$, but no other significant main effects or interactions. For the CAPS difficulty falling/staying asleep item, there was a significant main effect of time, $F(4, 77.04) = 9.00$, $p = 0.0001$, and a nonsignificant medication × time interaction, after Bonferroni adjustment, $F(4, 77.04) = 2.77$, $p = 0.03$ (see Table 2).

Drinking Outcomes

During the treatment phase of the study, there was a significant decrease in the average number of drinks over time, $F(11, 73.18) = 3.64$, $p = 0.0001$, but no significant effect of medication. This was confirmed by GGT levels that significantly declined over time (baseline, weeks 4, 8, and 12), $F(4, 66.22) = 7.30$, $p = 0.0001$. There were no significant differences in GGT levels based on medication assignment ($p = 0.39$) or medication by time interaction ($p = 0.17$). There was also no medication effect on the number of drinking days, $F(1, 80.3) = 0.294$, $p = 0.58$, on the number of heavy drinking days, $F(1, 33.17) = 0.202$, $p = 0.65$, on consecutive days of abstinence, $F(1, 3{,}221.2) = 3.64$, $p = 0.05$, or on the number of drinks per drinking day, $F(1, 72.09) = 1.358$, $p = 0.24$. In this sample, 52% of subjects were heavy drinkers overall; there was no significant difference in percentage of heavy drinkers between the medication groups (54.7% [placebo] vs. 51.0% [prazosin]), $\chi^2(1) = 0.13$, $p = 0.72$. In this study, 39 of 96 (41%) of subjects abstained from drinking throughout the trial. In the prazosin group, 23 of 50 (46%) subjects abstained from drinking throughout the trial while in the placebo group, only 16 of 46 (34.8%) abstained from drinking, but this did not reach statistical significance, $\chi^2(1) = 1.25$, $p = 0.26$.

There were significant site differences on some drinking outcomes, including consecutive days of abstinence, $F(1, 18{,}100.15) = 20.48$, $p = 0.000$, and on number of drinking days, $F(1, 3{,}914.37) = 14.33$, $p = 0.000$, but not on number of drinks per week over time, $F(1, 55.41) = 2.79$, $p = 0.10$, percentage of subjects with heavy drinking, $F(1, 2{,}058.75) = 6.63$, $p = 0.01$, drinks per drinking days, $F(1, 3.63) = 0.068$, $p = 0.79$, or heavy drinking days, $F(1, 1{,}056.15) = 6.44$, $p = 0.01$. Also, there were no significant interactions involving site for any of the drinking variables.

Craving

Craving for alcohol was assessed using the OCDS total score including the 2 subscales. For the total OCDS, there was a significant main effect for time, $F(12, 59.8) = 6.92$, $p = 0.0001$, a nonsignificant medication effect, $F(1, 88.9) = 0.40$, $p = 0.52$, and a nonsignificant time × medication interaction after Bonferroni adjustments, $F(12, 59.8) = 1.89$, $p = 0.05$. The results were similar for each of the subscales, including obsessions and compulsions, and there was no effect of site on craving.

Adverse Events/Side Effects

The most frequently reported adverse event (AE) was alcohol relapse. Twelve subjects in this study were either seen in

Table 2. Means and Standard Deviations for Main Outcome Measures

	Prazosin		Placebo			
	Mean	SD	Mean	SD	*F*	*p*
Clinician Administered PostTraumatic Stress Disorder Scale (CAPS)						
Total					Drug 0.04	0.84
Baseline	71.86	24.65	75.71	26.36	Time[a] 54.31	0.00
Week 12	37.94	37.62	37.93	41.13	Drug × Time[a] 1.72	0.16
Re-experience					Drug 0.19	0.67
Baseline	29.30	10.79	31.76	11.44	Time[a] 45.15	0.00
Week 12	15.57	12.67	14.89	13.93	Drug × Time[a] 1.68	0.16
Avoidance					Drug 0.02	0.90
Baseline	19.62	11.32	20.99	12.13	Time[a] 44.27	0.00
Week 12	10.41	16.76	8.87	18.59	Drug × Time[a] 2.21	0.08
Hyperarousal					Drug 0.41	0.52
Baseline	22.94	9.46	22.44	10.04	Time[a] 25.80	0.00
Week 12	15.65	13.87	14.84	15.09	Drug × Time[a] 1.47	0.22
Sleep						
Pittsburgh Sleep Quality Index (PSQI)					Drug 0.05	0.82
Baseline	21.47	0.94	22.80	0.97	Time[a] 14.85	0.00
Week 12	17.05	1.31	16.76	1.45	Drug × Time[a] 0.62	0.60
CAPS difficulty/falling/staying asleep					Drug 0.26	0.87
Baseline	4.69	0.31	4.77	0.32	Time[a] 9.00	0.00
Week 12	2.50	0.38	2.41	0.41	Drug × Time[a] 2.77	0.03[b]
CAPS recurrent distressing dreams					Drug 0.02	0.88
Baseline	5.92	0.32	5.44	0.34	Time[a] 26.89	0.00
Week 12	4.25	0.46	4.91	0.50	Drug × Time[a] 0.30	0.88
Drinking						
Number of drinking days						
Baseline	47.02	29.87	43.11	27.79	Drug 0.29	0.59
Active treatment phase	11.04	18.86	9.21	16.64		
Heavy drinking days						
Baseline	41.30	29.34	39.51	28.20	Drug 0.20	0.65
Active treatment phase	7.16	13.78	6.05	12.56		
Drinks per drinking day						
Baseline	17.33	10.73	21.90	13.24	Drug 1.36	0.25
Active treatment phase	4.44	5.71	6.91	9.12		
Consecutive days abstinence						
Baseline					Drug 0.00	0.96
Active treatment phase	49.71	34.74	48.86	31.94		
Craving						
Obsessive-Compulsive Drinking Scale total (OCDS)					Drug 0.40	0.53
Baseline	17.36	1.77	19.86	1.89	Time[a] 6.92	0.00
Week 12	10.12	1.41	6.70	1.58	Drug × Time[a] 1.89	0.05[b]

[a]Although means and standard deviations are presented for baseline and week 12, time was calculated using data across 12 weeks.
[b]These were not significant after Bonferroni correction.

the emergency room or hospitalized briefly for alcohol relapse (5 of those subjects were receiving prazosin and 7 were receiving placebo). One subject (placebo) reported homicidal ideation after 7 doses; he discontinued from the study for other (time commitment) reasons. None of these AEs were thought to be related to study medication or participation.

There were 6 medically related AEs (all participants were on active medication). Three AEs (partial thrombus, chest pain, appendicitis) were determined to be unrelated to study medication/participation and all subjects completed the study. Three AEs were thought to be study related (an episode of fainting: subject discontinued treatment; 2 incidents of falling: 1 subject completed treatment, 1 dropped out). There were 2 other incidents reported to the Human Subjects Subcommittee. In 1 case, the "medication blind" envelope was not properly filed and in the other, the wrong medication was dispensed (both subjects on placebo).

There was no difference between the medication groups on the overall rate or frequency of side effect reporting. Analysis of individual symptoms most frequently reported with prazosin–dizziness, dizziness when standing up, and loss of balance revealed a nonsignificant medication effect for dizziness, $F(1, 27.8) = 3.92$, $p = 0.05$, after a Bonferroni adjustment, although subjects on prazosin reported this symptom more frequently than those on placebo. There were no other significant findings in the reporting of symptoms.

DISCUSSION

The findings from this study suggest that while subjects as a group showed improvement in measures of sleep and symptoms of PTSD and overall drinking over time, there was no advantage of prazosin over placebo in treating symptoms of PTSD or sleep disturbance or in any of the drinking-related outcomes. These results are in contrast with most of

the data on prazosin, suggesting that it is effective, particularly not only in attenuating sleep disturbance but also in improving some symptoms of PTSD among those without comorbid AD.

The results are unexpected in that prazosin was not effective in ameliorating sleep disturbances, including nightmares in this population. There is a growing body of literature supporting its efficacy including a meta-analysis, suggesting that prazosin has a moderate effect size and is comparable to other nonpharmacologic interventions for the treatment of PTSD (Seda et al., 2015). Further, the attenuation of sleep disturbance seems to be related to an improvement in PTSD symptoms (Ahmadpanah et al., 2014).

The lack of efficacy may be due to recent and/or ongoing alcohol consumption that could interfere with prazosin's effect. Alcohol has a clear impact on sleep architecture, affecting maintenance of sleep and rapid eye movement (REM) sleep, particularly at high doses of alcohol (Roth et al., 1985). After alcohol is metabolized, during the later hours of the night, there can be a rebound effect of REM sleep, the period in which dreaming occurs. Sleep disturbances are also an important clinical feature particularly during early abstinence over the first few months. In fact, sleep abnormalities tend to persist for 1 to 2 years during recovery and abstinence (Landolt and Gillin, 2001).

It is also possible that prazosin was not effective because of the overall severity of psychiatric illness in this study population. In addition to meeting DSM-IV criteria for PTSD, with a mean CAPS score in the severe range, subjects were heavy drinkers who met criteria for AD and some continued to drink throughout the study. While prazosin has been shown to significantly reduce trauma-related symptoms in PTSD studies, and to reduce drinking quantity and frequency in separate studies of AD, it appears to be ineffective for the combination of severe PTSD and comorbid AD with heavy drinking. It is possible that prazosin would be effective with individuals who have less severe PTSD and/or less heavy AD-related drinking. The lack of medication effect on PTSD symptomatology in this comorbid sample is similar to the finding by Simpson and colleagues (2015). The authors of that study hypothesized that psychiatric severity may explain the negative results, as the majority of subjects reported 3 or more traumatic experiences. Other explanations included the possibility that subjects were experiencing subthreshold alcohol withdrawal symptoms that may have mimicked or exacerbated PTSD symptoms, which is relevant for this sample as well.

It should be stated that prazosin's effectiveness for PTSD has not been definitively established. While previous studies with prazosin were promising, this negative study represents the largest study published to date ($n = 96$). The VA Cooperative Study evaluating prazosin for PTSD among veterans was recently completed, but the results have not yet been reported; the results from this study should shed light on this question. Factors like adrenergic responsiveness may influence outcome and require further study (Raskind et al., 2014).

The results from this study also do not support the use of prazosin as an agent for preventing relapse and decreasing alcohol consumption or craving in this group of subjects. These results are in contrast to several recent studies: a laboratory study suggesting prazosin-attenuated stress and cue-induced craving for alcohol in alcohol-dependent individuals (Fox et al., 2012) and the recently completed clinical trial of prazosin in comorbid individuals (those with PTSD and comorbid AD) which showed that prazosin was effective in treating alcohol use but not PTSD (Simpson et al., 2015). It should be noted that there was a high rate of abstinence in the current study. This might be due to the close follow-up and support by the research team and the concurrent psychosocial treatment, which may have overwhelmed any potential medication effect. There is evidence of a high placebo effect in alcohol pharmacology trials (Litten et al., 2013), which has been discussed in the naltrexone literature. Further, in this study, the site differences in drinking outcomes were more robust than the medication effects. The higher rates of abstinence at MA may reflect the programs which include a residential treatment program (78% were in sober housing in MA compared to 49% in CT), suggesting that environmental factors outweigh medication effects for this group of patients.

Limitations include that the study was conducted with primarily male veterans and results may not be generalizable to other populations. Further, the dose and the medication taper were set by the research protocol, and not adjusted for symptoms as is performed in clinical practice, and lower doses might have been more effective. Finally, and perhaps most importantly, a high percentage of subjects were in sober housing, and the percentages differed by site. Therefore, the psychosocial treatments may have overwhelmed any medication effect, as there were better outcomes in settings that provided a substance-free living environment

Nevertheless, studies such as this one are important for evaluating the role of alpha-blockade in AUD and PTSD. This study is the largest study to date in a veteran population evaluating this medication for a comorbid group. Future directions could include medications with a longer half-life such as doxazosin which have shown promise in laboratory studies (O'Neil et al., 2013). It would be important to evaluate moderating factors, such as family history of alcoholism as doxazosin's efficacy in reducing drinking and craving in AUD individuals may be limited to those with a high density of family history for alcoholism (Kenna et al., 2015). The current study also highlights the importance of conducting studies in those with comorbidity, as studies establishing efficacy for medications should be conducted in subjects who resemble the "real-world" patients in clinical practice.

ACKNOWLEDGMENTS

This work was conducted with support from the Department of Defense (W81XWH-08-2-0075-PT075375) and the

VISN I Mental Illness Research Education and Clinical Center (MIRECC).

DISCLOSURE

Dr. Petrakis has served as a consultant to Alkemes (>$10,000 per year). Dr. Nitigna Desai, Dr. Ralitza Gueorguieva, Dr. Albert Arias, Dr. Erin O'Brien, Dr. J. Serrita Jane, Dr. Kevin Sevarino, Dr. Steven Southwick, and Dr. Elizabeth Ralevski declare no conflict of interest.

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