A Pilot Trial of Prazosin, an Alpha-1 Adrenergic Antagonist, for Comorbid Alcohol Dependence and Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) and alcohol dependence (AD) commonly co-occur and are associated with greater symptom severity and costs than either disorder alone. No pharmacologic interventions have been found to decrease both alcohol use and PTSD symptom severity relative to matched placebo. Prazosin, an alpha-1 adrenoreceptor antagonist, has demonstrated the efficacy of reducing PTSD and AD symptoms among individuals with one or the other disorder and may be useful in addressing comorbid PTSD/AD.

Methods: Prazosin and matched placebo were compared in the context of an outpatient 6-week double-blind randomized controlled pilot trial involving 30 individuals with comorbid PTSD/AD. Medication was titrated to 4 mg q AM, 4 mg q PM and 8 mg qhs by the end of week 2. Participants in both conditions received 5 medical management sessions. Information regarding alcohol use, craving, and PTSD was gathered daily using a telephone interactive voice response system.

Results: Participants randomized to prazosin had a greater reduction in percent days drinking per week and percent days heavy drinking per week between baseline and week 6 than did placebo participants. No significant differences were detected within or between groups in change from weeks 1 to 6 in total PTSD symptoms. Participants in the prazosin condition reported drowsiness on significantly more days than those in the placebo condition.

Conclusions: Consistent with the extant research evaluating medications for comorbid PTSD/AD, the current evaluation of prazosin also found decreased alcohol consumption but no medication effect on PTSD symptomatology.

Key Words: Noradrenergic, Prazosin, Alcohol Dependence, Posttraumatic Stress Disorder, Human Clinical Trial.

POSTTRAUMATIC stress disorder (PTSD) and alcohol dependence (AD) frequently co-occur. Estimates from the National Epidemiologic Survey on Alcohol and Related Conditions indicate lifetime prevalence of PTSD/AD comorbidity in the United States of 1.59%, using DSM-IV criteria (Blanco et al., 2013). Compared with individuals with only one or the other disorder, those with both are more likely to have attempted suicide, to have additional psychiatric disorders, and to endorse more symptoms associated with both PTSD and AD (Blanco et al., 2013). Individuals with comorbid PTSD/AD also report greater disability and treatment seeking than those with AD only (Blanco et al., 2013; Drapkin et al., 2011).

Overview of Comorbid PTSD and Alcohol Use Disorder Psychopharmacology

Despite the need for effective interventions to address PTSD/AD comorbidity, the current evidence base provides little guidance regarding optimum treatment for these patients (McCarthy and Petrakis, 2010; Norman et al., 2012; Sofuoglu et al., 2014). To date, 5 published randomized clinical trials (RCTs) have evaluated medications to treat comorbid PTSD/alcohol use disorder (AUD) (Batki et al., 2014; Brady et al., 2005; Foa et al., 2013; Petrakis et al., 2006, 2012). The results from these studies suggest that commonly used medications for AD (i.e., disulfiram, naltrexone, and topiramate), as well as desipramine, confer some benefit on drinking outcomes for those with comorbid PTSD/AD. However, thus far, no medications appear to outperform placebo convincingly with regard to PTSD outcomes.

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Noradrenergic Brain Systems are Implicated in Both AUD and PTSD

None of the aforementioned medications, except desipramine, directly target the noradrenergic system, which has integral involvement in the pathophysiology of both AUD and PTSD. Norepinephrine contributes substantially to the rewarding effects of alcohol (Ventura et al., 2006; Weinshenker et al., 2000). Proposed mechanisms posit that noradrenergic neurons in prefrontal cortex project caudally to the ventral tegmental area and promote dopamine release into the nucleus accumbens (Ventura et al., 2003) and that norepinephrine, acting via α-1 adrenergic receptors located presynaptically on dopaminergic neurons projecting to nucleus accumbens, directly drives dopamine release in that location (Mitrano et al., 2012). Norepinephrine levels in the periphery and in the central nervous system are elevated in animals and humans during alcohol withdrawal (Hawley et al., 1981; Kovacs et al., 2002; Patkar et al., 2003), and elevated norepinephrine levels in the extended amygdala are proposed to play a role in stress-induced relapse (Kash, 2012; Koob, 2009).

Among individuals with PTSD, the central nervous system is especially sensitive to noradrenergic activation in response to stress (Bailey et al., 2013; Strawn and Geracioti, 2008), and elevated central nervous system noradrenergic activity is common at night and is associated with trauma-related nightmares (Cukor et al., 2009; Shad et al., 2011). Imaging research indicates that individuals with PTSD have decreased numbers of norepinephrine transporters on locus coeruleus neurons (Pietrzak et al., 2013), which produce the majority of norepinephrine in the brain. Fewer transporters imply higher levels of norepinephrine available to bind to postsynaptic receptors.

Increased noradrenergic activity in AUD and PTSD provides a rationale for pharmacologic interventions that reduce noradrenergic activity. Prazosin, an α-1 adrenergic receptor antagonist, has been found to ameliorate PTSD-related nightmares and sleep disturbance and improves overall clinical status (Germain et al., 2012; Raskind et al., 2007, 2013; Taylor et al., 2008). Prazosin also suppresses ethanol (EtOH) consumption by EtOH-dependent outbred male rats and by selectively bred EtOH-preferring male rats (Rasmussen et al., 2009). Prazosin additionally blocks reinstatement of alcohol consumption in response to stress among rats previously trained to self-administer alcohol (Lê et al., 2011). Results from a pilot RCT of prazosin for AD (without PTSD) indicate that prazosin is associated with significantly reduced alcohol consumption in men and is well tolerated (Simpson et al., 2009). A human laboratory trial involving recently abstinent, treatment-seeking individuals with AD found that those receiving prazosin were less reactive to stress and reported lower alcohol craving when confronted with alcohol-related cues than those receiving placebo (Fox et al., 2012).

Petrakis (2014) conducted a double-blind RCT of prazosin for comorbid PTSD and AD among veterans and found that, although both conditions were associated with decreased PTSD symptoms and decreased drinking over 12 weeks, there were no medication treatment effects. Because most participants were involved in either a partial hospitalization or a residential substance abuse program, the investigators concluded that treatment setting was a more powerful determinant of outcome than medication assignment. Thus, it is unclear whether prazosin would be beneficial to individuals with this comorbidity in outpatient settings where drinking is not constrained, and PTSD-related triggers are likely more abundant.

The current study was a pilot double-blind RCT comparing prazosin to placebo using outpatient medical management (MM; Anton et al., 2006) as the behavioral platform and a daily interactive voice response (IVR) telephone monitoring system for daily assessment over the course of treatment. We hypothesized that participants in the prazosin condition would show greater improvement over the study course in alcohol use, craving, and PTSD symptoms relative to those randomized to placebo.

MATERIALS AND METHODS

Participants

A total of 354 people inquired about the study, 54 provided written consent and completed an in-person screen, and 30 were eligible and randomized (Fig. 1). The 19 men and 11 women were between the ages of 21 and 59 (M age ± SD = 43.3 ± 11.7) and met inclusion criteria including current DSM-IV diagnoses of AD and PTSD (American Psychiatric Association, 2000) and recent alcohol consumption at or above 14 (women) or 21 (men) drinks per week and at least 2 days of heavy drinking (≥ 4 drinks per occasion for women and ≥ 5 drinks for men) over a 30-day period in the last 90 days.

Study exclusion criteria were as follows: (i) uncontrolled psychosis or mania; (ii) current opioid dependence or abuse or positive urine screen (Urine Drugs Analysis System [UDAS]) for opioids, methamphetamines, benzodiazepines, or sedative hypnotics; (iii) systolic blood pressure <110 mmHg or preexisting orthostatic hypotension; (iv) health conditions including unstable angina, Meniere's disease, narcolepsy, benign positional vertigo, chronic renal or hepatic failure, pancreatitis or insulin-dependent diabetes mellitus; (v) use of any anti-alcohol medication (e.g., naltrexone, acamprosate, or disulfiram); (vi) unstable psychiatric medication regimen in the past month; (vii) engagement in trauma-focused PTSD treatment or behaviorally focused addiction treatment; and (viii) for males only, concomitant use of trazodone, tadalafil, or vardenafil due to increased risk of priapism. Female participants of child-bearing age were excluded unless they reported using a birth control method judged by the study clinician to be effective. During their 6 weeks of medication, all subjects were asked to forgo any concurrent behavioral or pharmacological treatment for AD or PTSD other than Alcoholics Anonymous and concurrent supportive therapy or counseling.

Procedures

The study was originally designed as a 12-week trial (2-week dose titration, 10-week achieved dose). However, participants had greater difficulty than expected adhering to this protocol length, with 39% withdrawing prior to week 12. After enrolling 18 participants, we scaled back to 6 weeks of active medication (2-week dose titration,

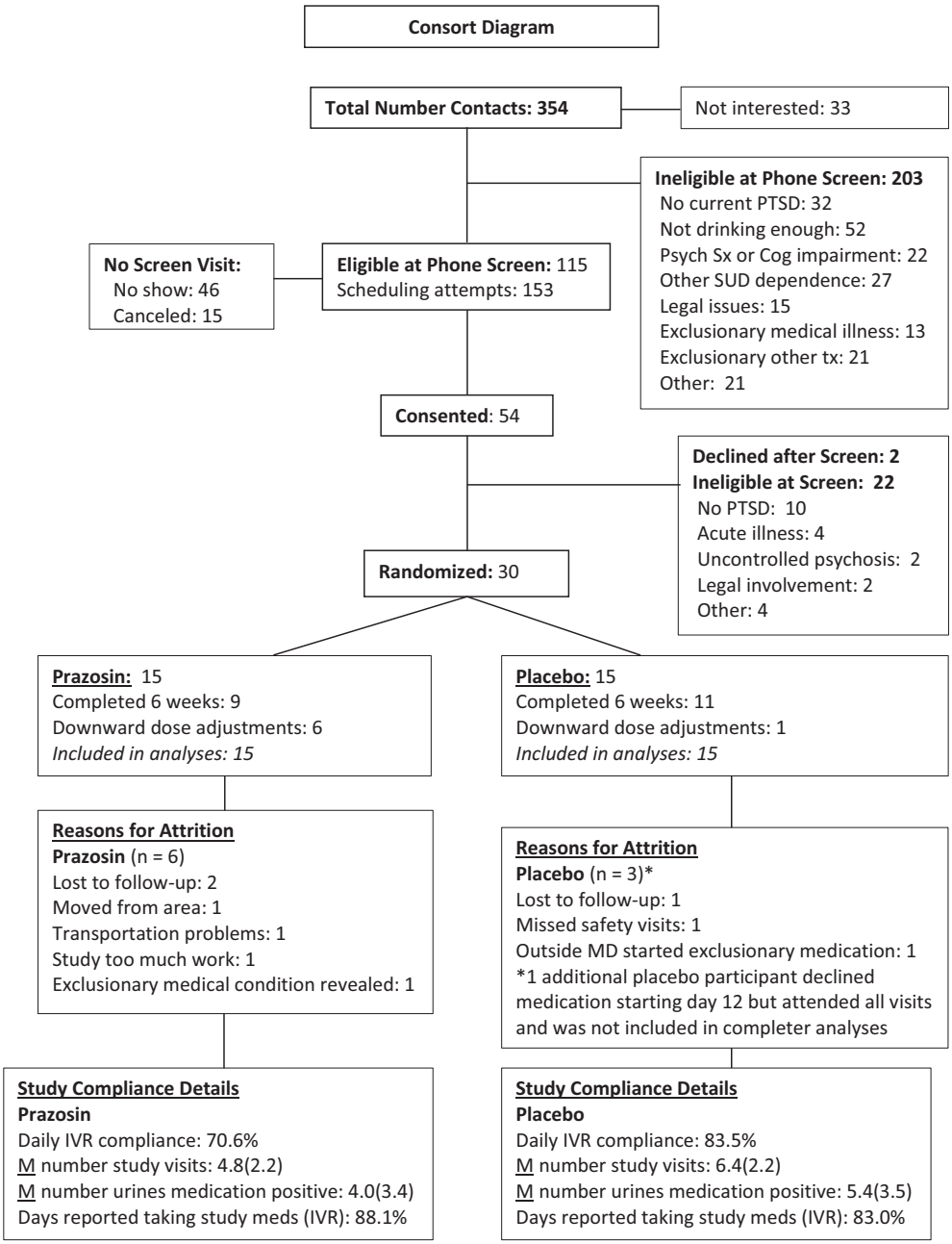

Fig. 1. Study consort diagram.

4-week achieved dose). The decision to reduce the study to 6 weeks was made without breaking the study blind; thus, we did not know at the time whether there was differential dropout based on group assignment. We present the procedures and results through week 6 here for all 30 participants. With regard to study completion for the 12-week time frame, 45.5% of those in the prazosin condition completed and 85.7% of those in the placebo condition completed. For participants who entered the study after the transition to the 6-week time frame, 100% of those in the prazosin condition completed and 62.5% of those in the placebo condition completed.

Recruitment and Screening. Human subjects' approval was provided by the institutional review board at the VA Puget Sound Health Care System. Participants were recruited between June 2010 and June 2012 through advertisements in local newspapers and posted flyers. The study is registered through ClinicalTrials.gov (NCT01518972).

After signing the informed consent and demonstrating a breath alcohol level of 0, participants underwent screening, which consisted of a physical examination; a medical history; diagnostic measures of substance dependence and abuse and psychiatric disorders; and laboratory assessment of complete blood count, liver function panel, and urine pregnancy. A UDAS test cup was used to screen for controlled substances.

Those found eligible at screening were invited to participate in a baseline assessment to complete additional study measures and receive study medication.

Randomization. Participants were randomized to prazosin or placebo by our center's research pharmacist. Randomization was

stratified by gender, veteran status, and ≥ 10 days of drinking in the last 30 days. All study personnel and participants remained blind to participants' group assignment throughout the course of the study.

Study Visits. During weeks 1–2, participants completed twice weekly study visits that decreased to weekly for weeks 3–6 for a total of 10 visits for the 6-week study length. All visits included orthostatic vital sign checks and adverse events monitoring. To ascertain likely medication compliance, pill counts were conducted, and participant urine toxicology specimens were examined for the presence of a riboflavin tracer added to all study medication. Participants were classified as receiving a full course of medication treatment if they received study medication at the week 4 visit to last through week 6.

Measures

Mental Health Diagnoses and Symptoms. The "Substance Use Disorder" and "Psychotic and Associated Symptoms" sections of the Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 1995) were administered at screening to assess diagnosis of AD, opioid abuse or dependence, schizophrenia, schizoaffective, or schizophreniform disorder. To assess current PTSD diagnostic status, we administered the Life Events Checklist (Blake et al., 1995) to ascertain trauma exposure and the PTSD Symptom Scale-Interview version (PSS-I; Foa et al., 1993); the PSS-I includes 17 items that assess the frequency and severity of PTSD symptoms. Item responses range from 0 (not at all) to 3 (5 or more times per wk/very much), and total scores range from 0 to 51.

Substance Use and Craving. The Form-42 was adapted from the Form-90 (Miller and Del Boca, 1994) and uses the timeline follow-back and steady drinking pattern methods to assess alcohol use and treatment for 6 weeks prior to baseline and at follow-up for the 6 weeks of study involvement. The Penn Alcohol Craving Scale (PACS; Flannery et al., 1999) was used to assess craving at baseline.

IVR Daily Monitoring. Daily IVR symptom monitoring was used to track outcomes. Participants were given a watch with preset alarms to remind them to take their medication and call a toll-free number to report on their alcohol craving (4 items from the PACS adapted to the daily time frame), daily alcohol use (beer, wine, spirits queried separately and totaled), PTSD (12 symptoms adapted from the PTSD Checklist–Civilian version (Weathers et al., 1993), the degree to which alcohol was reinforcing on drinking days (4 items; Ray and Hutchison, 2007), reasons for not drinking on nondrinking days (6 yes/no items), and medication compliance (1 item ranging from 0 to 3 doses) over the prior 24 hours. Items assessing craving, PTSD symptoms, and alcohol reinforcement followed a Likert scale, with minimum response of 0 indicating "not at all" and a maximum response of 8 indicating "extremely."

Study Treatments

Medications. Medications were titrated to a target dose of 4 mg q AM, 4 mg q PM, and 8 mg qhs (or highest tolerated dose) by the end of week 2, which was continued for an additional 4 weeks. Dosing was held at 1 mg qhs for the first 2 nights to minimize the chance of first-dose syncope. Participants' titration was slowed if they experienced symptomatic orthostatic hypotension or intolerable side effects; the prior titration could resume at cessation of participants' reported side effects. Dosing was targeted for 3 times per day because prazosin has a short half-life (Jaillon, 1980), and steady noradrenergic antagonism during likely drinking times was indicated to test the medication effects on the target behavior.

Placebo and study medication were identically matched and were prepared by a local compounding pharmacy. Quality assurance testing was performed by the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center in Albuquerque, NM. Prazosin concentration in 2-mg and 4-mg capsules measured by high-performance liquid chromatography had a coefficient of variation of <6%.

Medical Management. Participants received 5 MM counseling visits with a study clinician over the course of the 6-week study.

Outcomes

Primary outcomes were change in self-reported percent drinking days per week and percent heavy drinking days per week between baseline and week 6. Heavy drinking was defined as 5 or more drinks per day for men and 4 or more drinks per day for women. We also evaluated the number of standard drinks per week over the 6-week study period. Drinking data were collected via the Form-42 at baseline and via IVR daily monitoring at weeks 1 through 6. Weekly IVR data were treated as missing if participants called in on fewer than 4 days in a given week. However, in these cases, we used data from the follow-up Form-42 so that some drinking information about those otherwise missing weeks could be included in the models. Secondary outcomes were changes in PTSD symptomatology, including total symptoms, re-experiencing, avoidance/numbing, hypervigilance, and a single dream item, and changes in average craving per week via IVR daily monitoring. PTSD scores were derived by computing the daily average of the item totals for overall PTSD and the symptom clusters so that each score is scaled to the original 0 to 8 metric. Exploratory analyses evaluated average rating of alcohol reinforcement on drinking days (i.e., degree of satisfaction, enjoyment, liking, and highly associated with alcohol consumption), and percent endorsement of reasons associated with not drinking on nondrinking days (i.e., (i) alcohol was not appealing or no had desire to drink, (ii) having no money or opportunity to drink or being ill, and (iii) wish to maintain sobriety).

Data Analysis

All primary analyses were examined for the entire sample as randomized (intent-to-treat) and for participants receiving the full course of medication through week 6 ($n = 20$).

Demographic, baseline, and compliance variables are presented descriptively. Differences between the placebo and prazosin groups were analyzed with the chi-square statistic for categorical variables and with Student's t-test for continuous variables.

Longitudinal drinking (percent any and heavy drinking days per week) and craving outcomes between baseline and week 6 were examined using multilevel mixed-effects linear regression models with random slope that included treatment group, time, and treatment group × time interaction. Time was modeled as a categorical variable. We used similar multilevel mixed-effects linear regression models to examine change by condition in PTSD outcomes (total score, re-experiencing, avoidance/number, hypervigilance, and the dream item) between weeks 1 and 6; because measures comparable to the IVR PTSD measures were not available at baseline, models were adjusted for baseline PTSD severity as measured by corresponding PSS-I scores and subscores (i.e., analyses of change in re-experiencing were adjusted by the baseline PSS-I re-experiencing score). Because women and men have been found to respond differently to medications for AD (Garbutt et al., 2005), analyses were adjusted for gender.

Exploratory analyses examining average alcohol reinforcement on drinking days and percent endorsement of reasons associated with not drinking on nondrinking days between weeks 1 and 6 were each examined using linear regression models adjusted for baseline craving levels as measured by the PACS.

Blood pressure was evaluated across groups at baseline by Student's *t*-test as were average changes in blood pressure from week 1 to week 6. Percent of patients experiencing core adverse events (dizziness on standing, headache, lightheadedness, nausea, lack of energy, drowsiness, blood pressure drop sitting to standing) between weeks 1 and 6 were compared across conditions using chi-square statistics. In addition, the mean number of days that participants in each condition experienced each adverse event was compared using Student's *t*-tests.

Analyses were conducted with Stata version 13.1 (StataCorp LP, 2013) and SPSS 22 for Windows (IBM Corporation, 2013). Two-sided *p*-values of <0.05 were considered statistically significant and statistical trends at the $p < 0.10$ level are noted.

RESULTS

Baseline Group Comparisons

The prazosin and placebo groups did not differ significantly with respect to demographic characteristics, the amount or frequency of drinking, or PTSD severity at baseline (Table 1). The 2 groups did not differ with regard to number of traumas that met the Criterion A requirements for a PTSD diagnosis (Table 2). Those in the prazosin condition endorsed higher craving levels at baseline. Additionally, at baseline, 10 participants in the prazosin condition and 9 in the placebo condition reported receiving some supportive therapy in the past 90 days. With regard to concurrent medications reported at baseline, 2 participants in each condition reported use of the noradrenergic blood pressure medication atenolol, 5 prazosin and 2 placebo participants were on an antidepressant, and 2 prazosin participants were prescribed stimulants (one for chronic fatigue and the other for weight loss). Overall, 5 prazosin and 2 placebo participants were on at least 1 psychiatric medication at baseline.

Completion and Compliance Rates

Twenty of the 30 (66.7%) randomized individuals received study medication through week 6, with somewhat higher rates of completion in the placebo condition (prazosin: 9 [60.0%]; placebo: 11 [73.3%], ns). The compliance rate on the IVR daily monitoring was 77.0% (prazosin: 70.6%, placebo: 83.5%, ns) between randomization and week 6 (or date of termination for those who dropped prior to week 6). Among participants who received medication at the week 4 visit, the IVR compliance rate was 90.5% (prazosin: 86.2%, placebo: 93.9%, ns). The 2 groups did not differ significantly on medication compliance via riboflavin trace, pill counts, or daily IVR monitoring, nor on safety visits attended.

Drinking Outcomes

As seen in Fig. 2 and Table 3, participants randomized to prazosin had a greater reduction in percent drinking days per week between baseline and week 6 than did those randomized to placebo, $\chi^2(6) = 19.3$, $p = 0.004$. The difference remained significant when only those receiving medication at

Table 1. Demographics and Baseline Characteristics

Characteristics	Placebo (n = 15) M (SD) or n (%)	Prazosin (n = 15) M (SD) or n (%)	p-Value
Age	43.5 (12.4)	43.1 (11.3)	ns
Race			
White	4 (26.7)	8 (53.3)	ns
Black	8 (53.3)	4 (26.7)	
Other	3 (20.0)	3 (20.0)	
Female	5 (33.3)	6 (40.0)	ns
Veteran	5 (33.3)	4 (26.7)	ns
Marital status			
Never married	8 (53.3)	6 (42.9)	ns
Married	0 (0.0)	2 (14.3)	
Divorced/separated	5 (33.3)	6 (42.9)	
Other	2 (13.3)	0 (0.0)	
Employment			
Employed	0 (0.0)	2 (14.3)	ns
Disability/pension	7 (50.0)	7 (50.0)	
Unemployed	7 (50.0)	3 (21.4)	
Other	0 (0.0)	2 (14.3)	
College/postgraduate education	12 (80.0)	11 (78.6)	ns
Living situation			
Stably housed	12 (85.7)	10 (66.7)	ns
Homeless	1 (7.1)	2 (13.3)	
Other	1 (7.1)	3 (20.0)	
Drinks per day, past 90 days	8.5 (5.1)	11.0 (10.8)	ns
Total drinks, past 7 days	49.6 (44.6)	80.1 (75.1)	ns
Drinking days, past 7 days	4.2 (2.8)	5.1 (1.7)	ns
PACS (craving) score	17.5 (6.8)	22.1 (4.5)	0.037
PSS-I (Posttraumatic Stress Disorder) score	31.6 (7.7)	31.5 (8.9)	ns

PACS, Penn Alcohol Craving Scale; PSS-I, PTSD Symptom Scale-Interview version.

Table 2. Trauma Exposures by Condition and Total Sample

Trauma type	Placebo, %	Prazosin, %	Total, %
Physical assault	100.0	93.3	96.7
Weapon assault	80.0	60.0	70.0
Natural disaster	40.0	73.3	56.7
Transportation accident	66.7	66.7	66.7
Sexual assault	66.7	60.0	63.3
Witnessing sudden violent death	33.3	66.7	50.0
Serious work accident	33.3	53.3	43.3
Fire or explosion	26.7	26.7	26.7
Combat exposure	20.0	20.0	20.0
3 or more Criterion A	53.3	60.0	63.3
1 or more childhood trauma	86.7	73.3	80.0

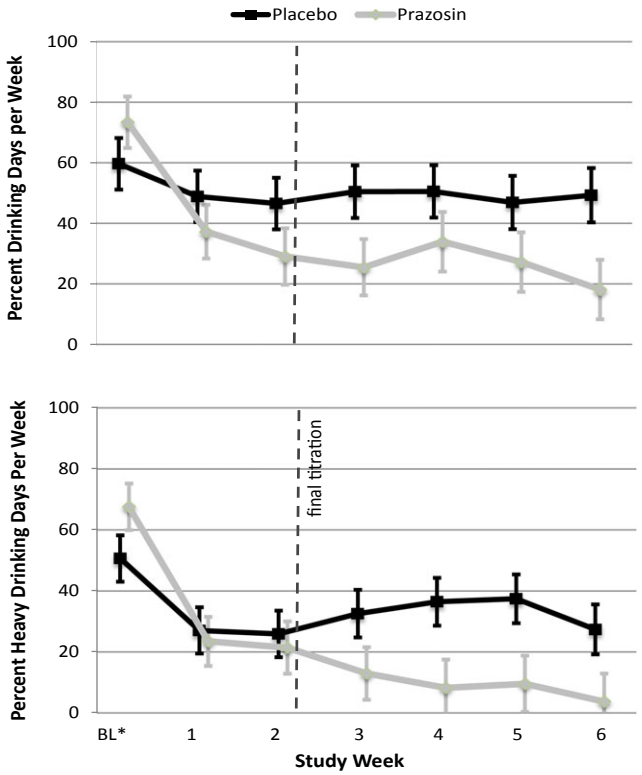

Fig. 2. Patients randomized to prazosin had a greater reduction in percent drinking days per week, $\chi^2(6) = 19.3$, $p = 0.004$, and percent heavy drinking days per week, $\chi^2(6) = 21.3$, $p = 0.002$, between baseline and 6 weeks than those randomized to placebo after adjusting for gender. *Data from timeline follow-back. Error bars represent ±1 SEM.

the week 4 visit were included, $n = 20$, $\chi^2(6) = 26.4$, $p < 0.001$. Participants randomized to prazosin also showed a greater reduction in percent heavy drinking days per week relative to those randomized to placebo, $\chi^2(6) = 21.3$, $p = 0.002$, which held among those receiving medication at the week 4 visit, $\chi^2(6) = 28.4$, $p < 0.001$. Estimated average drinks per week fell from 80.3 to 7.9 in the prazosin condition, compared to a drop from 50.0 to 27.0 in the placebo condition, $\chi^2(6) = 19.0$, $p = 0.004$.

This same pattern of results was seen for the 7- to 12-week time frame for the 10 participants (5 in each condition) enrolled in the 12-week trial with adequate data, whereby those in the prazosin condition reported significantly less drinking over time than those assigned to placebo. Specifically, the prazosin participants reported lower percent drinking days ($M = 13.0$, SD = 14.7) compared to the placebo participants ($M = 46.1$, SD = 25.4) between weeks 7 and 12. Likewise, the percent of heavy drinking days was lower in the prazosin condition ($M = 2.1$, SD = 4.6) compared to the placebo condition ($M = 18.3$, SD = 22.3).

PTSD Symptom Change

As shown in Table 3, after adjusting for baseline scores and gender, no differences were detected within or between groups in change from weeks 1 to 6 in total PTSD symptoms or the PTSD symptom clusters (hypervigilance, avoidance/numbing, re-experiencing, or the dream item). The same pattern of results was seen among those who received medication at the week 4 visit.

Potential Treatment Mediators and Craving, Alcohol Reinforcement, and Reasons Associated with Not Drinking

Both groups experienced a drop in craving between baseline and week 6, $\chi^2(6) = 47.2$, $p < 0.001$; while the prazosin condition tended to experience a greater decrease in craving relative to the placebo condition, the difference between conditions in change over time was only at the trend level, $\chi^2(6) = 11.9$, $p = 0.064$. We did not find significant differences between the prazosin and placebo conditions on the average degree of reinforcement associated with alcohol consumption on drinking days between weeks 1 and 6 (see Table 4). With regard to reasons for not drinking, after adjusting for baseline craving, the average percent of nondrinking days that "alcohol was not appealing or no desire to drink" was endorsed as a reason for not drinking between weeks 1 and 6 and was higher in the prazosin condition than the placebo condition. No differences were seen between conditions in endorsement of lack of money/lack of opportunity/illness or maintaining sobriety as reasons for not drinking.

Safety Findings

There were 2 nonstudy-related serious adverse events: 1 psychiatry admission for suicidality and 1 admission for surgery for a preexisting condition. The most frequently reported side effects were headaches, nausea, lightheadedness, and drowsiness (see Table 5). The prazosin group endorsed significantly higher mean number of days of drowsiness relative to placebo as well as higher mean days of dizziness on standing and low energy, both the latter 2 at the

Table 3. Estimated[a] Mean Baseline and Week 6 Drinking and Posttraumatic Stress Disorder (PTSD) Scores

	Placebo		Prazosin	
	Est. Mean (95% CI)		Est. Mean (95% CI)	
	Baseline[a]	Week 6	Baseline[a]	Week 6
Drinking outcomes				
Percent drinking days per week	59.7 (43.0 to 76.4)	49.3 (31.7 to 66.9)	73.4 (56.7 to 90.1)	18.1 (−1.1 to 37.4)*
Percent heavy drinking days per week	50.6 (35.7 to 65.6)	27.4 (11.3 to 43.5)	67.6 (52.7 to 82.5)	3.7 (−14.4 to 21.8)*
Drinks per Week	50.0 (30.3 to 69.7)	27.0 (5.9 to 48.1)	80.3 (60.7 to 100.0)	7.9 (−15.7 to 31.4)*
PTSD outcomes[b]				
Total PTSD score	2.7 (1.6 to 3.8)	2.5 (1.4 to 3.6)	3.7 (2.6 to 4.8)	3.1 (1.9 to 4.2)
Re-experiencing	2.6 (1.4 to 3.8)	2.6 (1.4 to 3.8)	3.8 (2.7 to 5.0)	3.2 (1.9 to 4.4)
Avoidance/numbing	2.7 (1.5 to 3.9)	2.4 (1.2 to 3.6)	3.6 (2.4 to 4.8)	2.9 (1.6 to 4.2)
Hypervigilance	2.8 (1.7 to 3.9)	2.4 (1.3 to 3.6)	3.6 (2.5 to 4.8)	3.2 (2.0 to 4.4)
Disturbing dreams	2.4 (1.1 to 3.7)	2.8 (1.5 to 4.1)	3.2 (1.9 to 4.6)	2.5 (1.0 to 3.9)

[a]The PTSD outcomes include those with adequate interactive voice response (IVR) data at week 1 (at least 4 of 7 days completed; $n = 26$).
[b]Week 1 IVR scores are presented for PTSD rather than baseline PTSD Symptom Scale-Interview version (PSS-I) scores because the daily IVR questions and the PSS-I interview items were scaled differently.
*$p < 0.01$.

Table 4. Potential Treatment Mediators

Potential treatment mediators	Placebo mean (95% CI)	Prazosin mean (95% CI)
Change in interactive voice response PACS score baseline to week 6	−1.1 (−2.0, −0.3)	−2.4 (−3.4, −1.4)
Average alcohol reinforcement ($n = 24$) on drinking days	3.9 (3.2, −4.6)	4.5 (3.4, −5.5)
Reasons for not drinking ($n = 28$)	% of nondrinking days endorsed	
No desire/not appealing	35.9 (16.1, 55.8)	67.7 (48.6, 86.8)*
Lack of money, opportunity, illness	54.7 (37.1, 72.4)	37.4 (15.7, 59.1)
Maintain sobriety	51.7 (27.6, 75.9)	66.8 (44.1, 89.5)

PACS, Penn Alcohol Craving Scale.
*$p = 0.029$.

trend level ($p < 0.10$). Those in the prazosin condition reported the presence of 3 or more adverse events at nearly 25% (SD 33.1) of the study visits versus 13% (SD 10.6) for the placebo condition (ns). Six participants (4 women, 2 men) in the prazosin condition and 1 man in the placebo condition received downward dose adjustments. One placebo participant stopped study medication at day 12 but completed all study visits.

There were no differences in blood pressure at baseline between the 2 conditions, and there were also no between-group differences in blood pressure changes from baseline to the 6-week safety check across the 2 conditions. There was one instance observed by a study clinician of orthostatic hypotension including a systolic drop of greater than 20 mmHg for a male prazosin participant addressed effectively by dose reduction (4 mg q AM, 4 mg q PM, 4 mg qhs).

DISCUSSION

This pilot study evaluated whether the α-1 adrenergic antagonist, prazosin, was useful in reducing drinking behavior and PTSD symptomatology among individuals with comorbid AD and PTSD. Although participants in both conditions improved over time on drinking outcomes, the results indicate that prazosin conferred significant benefit over and above placebo with regard to the percent drinking days per week, percent heavy drinking days per week, and the number of drinks consumed per week. This pattern was found in the main intent-to-treat analyses as well as in the analyses involving only those who received medication through the week 4 visit. The results, however, do not indicate that prazosin was helpful in reducing PTSD symptomatology.

We also found that 60% those in the prazosin condition completed the 6-week treatment window and 73% of those in the placebo condition did so. Six individuals in the prazosin condition required dose reductions, and those in the prazosin condition reported significantly greater number of days of drowsiness than those assigned to placebo. We also saw a similar pattern with regard to lack of energy and dizziness at the trend level. These findings are not consistent with a previous study evaluating prazosin among individuals with AD only (see Simpson et al., 2009). Thus, despite promising findings with regard to drinking outcomes, prazosin at the target dosage of 4 mg q AM, 4 mg q PM, and 8 mg qhs may be difficult for some patients with PTSD/AD to tolerate during the day, and it does not appear to be optimal for addressing PTSD symptoms.

Table 5. Adverse Events[a]

	Placebo *n* (%) or *M* (SD)	Prazosin *n* (%) or *M* (SD)
Dizziness on standing		
% endorsing; *n* (%)	5 (35.7)	7 (50.0)
Days endorsed; *M* (SD)	1.9 (3.6)	5.4 (7.0)*
Headaches		
% endorsing; *n* (%)	9 (64.3)	7 (50.0)
Days endorsed; *M* (SD)	3.0 (4.7)	4.5 (7.9)
Lightheadedness		
% endorsing; *n* (%)	6 (42.9)	9 (64.3)
Days endorsed; *M* (SD)	3.8 (7.8)	6.4 (7.7)
Nausea		
% endorsing; *n* (%)	9 (64.3)	6 (42.9)
Days endorsed; *M* (SD)	2.9 (4.5)	1.5 (2.9)
Lack of energy		
% endorsing; *n* (%)	8 (57.1)	8 (57.1)
Days endorsed; *M* (SD)	7.8 (8.9)	13.9 (14.7)*
Drowsiness		
% endorsing; *n* (%)	7 (50.0)	9 (64.3)
Days endorsed; *M* (SD)	5.7 (7.9)	19.0 (18.8**
Blood pressure drop sitting to standing		
% observed; *n* (%)	0	1 (7.1)

[a]Participants with at least 1 postbaseline visit (i.e., those receiving medication and providing information on adverse events/side effects at least 1 safety visit) were included here; $n = 28$.

*$p < 0.10$, **$p < 0.05$.

The present findings are, however, generally consistent with the extant literature pertaining to medications for the treatment of comorbid PTSD/AD. Most of the previous research has found some improvement on drinking outcomes for the active medications versus placebo, but no strong evidence of additional benefit of these medications over placebo for PTSD outcomes (Brady et al., 2005; Foa et al., 2013; Petrakis et al., 2006, 2012), although Batki and colleagues (2014) found a trend regarding PTSD hyperarousal symptoms favoring topiramate. While it is noteworthy that individuals with comorbid PTSD/AD can realize some improvement with regard to their drinking from a variety of medications, PTSD symptomatology is not as readily attenuated. For those individuals whose drinking is motivated at least in part by self-medication of their PTSD symptomatology (see Simpson et al., 2014), persistently elevated PTSD symptoms likely increase the risk for relapse and thus represent a high-priority target for improved interventions.

Given previous research that prazosin is helpful for ameliorating PTSD symptomatology (Germain et al., 2012; Raskind et al., 2013; Taylor et al., 2008), the present negative results were unexpected. It is possible that the dosing schedule used in the present study that included a maximum of 8 mg at bedtime was not sufficient to fully impact the hallmark nightmares and sleep disturbance associated with PTSD. Raskind and colleagues (2013) titrated to a maximum nighttime dose of 20 mg of prazosin for men and 10 mg for women (no daytime doses were included). Dose-ranging studies are needed to ascertain the optimal dosing regimen for prazosin for PTSD/AUD. In light of the prior work on PTSD and the findings from the current study, we posit that lowering the doses during the day to reduce drowsiness, in particular, along with increasing the final nighttime dose to better address nightmares and other sleep disturbances associated with PTSD would be reasonable to evaluate in further research.

Another possible explanation for the lack of congruence on PTSD outcomes across prazosin studies is that most of the previous work on this medication for PTSD has included veteran or civilian samples with more clearly delineated focal traumas than was the case in the present study. Well over half the individuals in our sample reported 3 or more traumatic experiences that met DSM-IV Criterion A requirements, and most reported at least 1 trauma experience prior to age 18, signaling that this group has complex trauma histories, many of which were of a very personal nature (sexual assault, physical assault) that may not be amenable to the same interventions as those with more discrete trauma histories. It is also conceivable that, as all participants in this study were trying to reduce alcohol use, subclinical alcohol withdrawal symptoms occurred that were misinterpreted by participants as PTSD symptoms given the known overlap between the two (Jacobsen et al., 2001).

Most of the other medication trials involving individuals with comorbid PTSD/AD found overall improvements in PTSD outcomes (Batki et al., 2014; Foa et al., 2013; Petrakis et al., 2006, 2012), although as noted above, the active medications for the most part did not outperform placebo. In the present study, we did not find a main effect of time with regard to PTSD. It is possible that the lack of a robust behavioral treatment platform directed at PTSD was partly responsible for this finding.

With regard to secondary outcomes, although we did not find a strong indication that prazosin conferred an advantage over placebo for alcohol craving, there was a trend on this outcome favoring prazosin. We also found that on nondrinking days, those in the prazosin condition were significantly more likely to report that the idea of alcohol was not appealing than were those in the placebo condition. Not drinking due to other issues did not differ by condition. We did not find differences between the 2 conditions with regard to the reinforcing qualities of alcohol on drinking days despite preclinical studies indicating that norepinephrine plays a role in alcohol's reinforcing effects (Ventura et al., 2006; Weinshenker et al., 2000). These findings together suggest that rather than causing alcohol to be less satisfying or enjoyable when it is consumed, at least in humans with PTSD, prazosin may be dampening interest in drinking on nondrinking days and lowering craving.

The present study has some strengths along with some limitations that need to be considered. With regard to strengths, we included a varied and quite severe actively drinking study sample that closely resembles individuals with PTSD/AD comorbidity who are likely to be seeking clinical care. Additionally, these individuals were treated in an outpatient setting and did not have to be abstinent to initiate study engagement, both of which are typical for individuals

presenting for clinical care. We also included a daily monitoring symptom assessment protocol that allowed us to capture information on drinking and PTSD symptoms in close to real time. The limitations include the small sample size and somewhat poor study retention. Further, we found that compliance with the daily monitoring was poorer than found in previous clinical trials with either AD only (Simpson et al., 2009) or PTSD/AD comorbidity (Stappenbeck et al., 2015), which raises concerns regarding the influence of missing data on the findings. These concerns are mitigated by the fact that our drinking analyses of those who received medication at the week 4 visit where IVR compliance was very strong were virtually identical to the intent-to-treat analyses.

In conclusion, the present study found that prazosin produced better drinking outcomes among individuals with comorbid PTSD/AD than did placebo. However, this positive finding is tempered by the lack of effect on PTSD symptoms. As prazosin has shown efficacy for PTSD alone in other studies, additional research using it or other α-1 adrenergic antagonists for treatment of comorbid PTSD/AD in larger sample sizes exploring different dosing regimens appears warranted.

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