A Double-Blind Randomized Controlled Trial of Doxazosin for Co-Occurring PTSD and Alcohol Use Disorder in Veterans

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ABSTRACT

Objective: The aim of this study was to determine the efficacy of doxazosin, an α_1-adrenergic antagonist, for the treatment of co-occurring posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD).

Methods: This 12-week, double-blind, randomized controlled trial of doxazosin (16 mg/d) was conducted between June 2016 and December 2019 at the Ralph H. Johnson VA Medical Center in Charleston, South Carolina. Participants were military veterans (N = 141) who met *DSM-5* criteria for current PTSD and AUD and were randomly assigned to receive doxazosin (n = 70) or placebo (n = 71). Primary outcome measures were the Clinician Administered PTSD Scale (CAPS-5), the PTSD Checklist for *DSM-5* (PCL-5), and the Timeline Follow-Back (TLFB).

Results: Findings from the intent-to-treat analyses revealed that participants in both groups demonstrated statistically significant reductions in CAPS-5 and PCL-5 scores ($P < .0001$), but, contrary to hypotheses, no significant differences were observed between groups. Percent drinking days and percent heavy drinking days also decreased significantly during treatment, but there were no differences between groups ($P < .0001$). Abstinence during treatment was significantly higher in the doxazosin versus the placebo group (22% vs 7%, $P = .017$); however, participants in the doxazosin group consumed a greater number of drinks on drinking days (6.15 vs 4.56, $P = .0096$). A total of 74.5% of the sample completed the treatment phase, and there were no group differences in retention or adverse events.

Conclusions: Doxazosin was safe and tolerable but was not more effective than placebo in reducing PTSD or AUD severity in this dually diagnosed sample. Clinical considerations such as heterogeneity of PTSD and AUD presentation and potential moderators are discussed in the context of future research directions.

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A robust literature documents the frequent co-occurrence of posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD).[1,2] Individuals with co-occurring PTSD/AUD often report consuming alcohol to "self-medicate" or reduce distressing PTSD symptoms.[3–5] The co-occurrence of PTSD and AUD is particularly prevalent among military service members and veterans.[6] One of the largest studies to date[7] examined over one million US veterans and found that 41% of those with a substance use disorder (mostly AUD) also met criteria for PTSD. The combination of PTSD and AUD is associated with numerous deleterious outcomes, including medical problems, family dysfunction, increased suicidal ideation and attempts, homelessness, HIV risk behaviors, and poor treatment outcomes.[2,8–13] As such, effective treatments to address both PTSD and AUD are critically needed.

To date, research on pharmacologic treatments for co-occurring PTSD/AUD has been limited, and there are no established medications for PTSD/AUD.[14–18] The noradrenergic system plays a key role in stress responding, and noradrenergic dysregulation has been demonstrated in PTSD, alcohol withdrawal, and response to substance-related cues.[19–22] Central noradrenergic tone plays an important role in executive control, cognitive flexibility, selective attention, and arousal as well as fear conditioning and extinction,[23,24] and increases in noradrenergic activity have been implicated in hyperarousal, flashbacks, and heightened physiologic responses to trauma cues.[25] In addition, provocation of the noradrenergic system with the α_2-noradrenergic antagonist yohimbine increases anxiety in veterans with PTSD, but not those without PTSD, suggesting that PTSD is associated with increased central noradrenergic tone.[26] Increases in noradrenergic tone in regions of the extended amygdala have been implicated in drug-seeking behavior,[27] and substance-related

Clinical Points

- Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur, and effective medications for treating this comorbidity are lacking.
- In this sample of veterans with co-occurring PTSD and AUD, doxazosin (16 mg) was not more effective than placebo in reducing PTSD or AUD.

cues have been found to increase noradrenergic activity in individuals with substance use disorders.[22] Taken together, these findings suggest that agents targeting the noradrenergic system may be pharmacologic candidates for decreasing PTSD and AUD severity.[19,28,29]

Previous studies of noradrenergic agents in the treatment of PTSD, AUD, or co-occurring PTSD/AUD have typically evaluated prazosin, an α_1-noradrenergic antagonist. The findings have been mixed, with some studies showing significant reduction in PTSD symptoms, such as nightmares, sleep quality, and hyperarousal,[30–33] and reduction in AUD symptoms,[34–36] while other studies find no differences in prazosin versus placebo for AUD or PTSD symptoms.[37,38] Several studies[37,39–42] have found significant reductions in drinking with prazosin, but only among subgroups with higher pretreatment blood pressure or strong family history of AUD. Sinha and colleagues[40] examined prazosin among individuals with AUD (N = 100) and found baseline withdrawal symptoms were a significant moderator of treatment efficacy; prazosin was more effective than placebo in reducing percent days drinking and percent days heavy drinking, but only among those with high baseline alcohol withdrawal symptoms.

Doxazosin, a selective inhibitor of the α_1 subtype of α-adrenergic receptors, is approved by the US Food and Drug Administration (FDA) for treatment of hypertension and benign prostatic hyperplasia. In comparison to prazosin, doxazosin has a significantly longer half-life (approximately 18–22 hours vs 2–4 hours), which allows for once-per-day dosing, which is generally preferred by patients and may enhance medication adherence.[43] Moreover, the slower onset of action may reduce risk of first-dose postural hypotension as compared to prazosin.[44,45] In preclinical studies, doxazosin results in significantly reduced ethanol self-administration among rats,[46] and this effect is most robust in rats exposed to stress (eg, forced swim test).[47] Pilot clinical studies provide initial support for the safety and potential therapeutic effects of doxazosin in reducing symptoms of AUD or PTSD.[48–50]

While previous studies have evaluated doxazosin for the treatment of PTSD or AUD separately, the current study is the first to examine doxazosin in reducing PTSD and AUD concurrently in individuals with co-occurring PTSD/AUD. It was hypothesized that participants randomized to receive doxazosin, as compared to placebo, would evidence significantly greater reductions in (1) PTSD severity as measured by the Clinician Administered PTSD Scale (CAPS-5)[51] and the PTSD Checklist for *DSM-5* (PCL-5)[52] and (2) alcohol consumption as measured by the Timeline Follow-Back (TLFB).[53]

METHODS

Participants

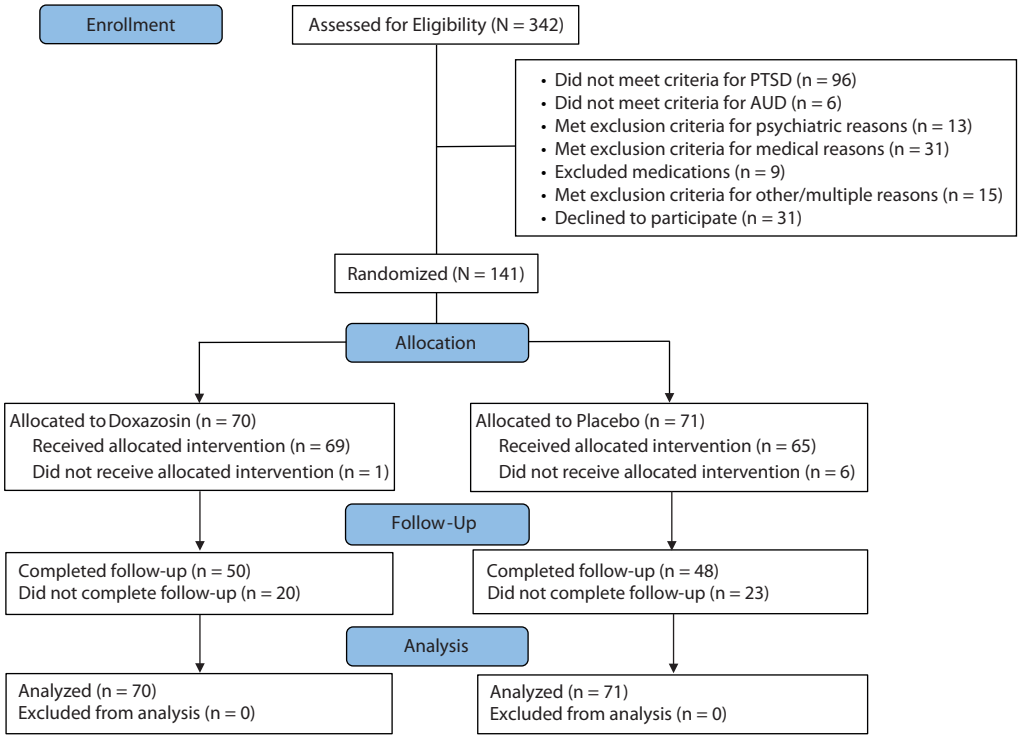
Participants (N = 141) were treatment-seeking US military veterans aged 18–65 years. All participants were enrolled at the Ralph H. Johnson VA Medical Center or affiliated community-based outpatient clinics (CBOCs). Recruitment methods included clinician referrals, social media, newspaper advertisements, and flyers. Participants were required to meet *DSM-5* criteria for current (past 6 months) moderate or severe AUD as assessed by the Mini-International Neuropsychiatric Interview (MINI)[54] and current (past month) PTSD as assessed by the CAPS-5.[51] Participants were not required to report a minimum amount of alcohol consumption or abstain from alcohol prior to study enrollment. At baseline, 11 participants reported abstinence from alcohol in the 60 days prior to enrollment (6 in the doxazosin condition and 5 in the placebo condition). Twenty-three participants reported abstinence in the 30 days prior to enrollment (15 in the doxazosin condition and 8 in the placebo condition).

Primary exclusion criteria included previous treatment with doxazosin, history of adverse reactions to quinazolines or other α_1 antagonists, currently taking α-blockers (eg, prazosin) or a medication for AUD (eg, naltrexone), current enrollment in an evidence-based psychosocial treatment for PTSD or AUD, and significant medical/psychiatric conditions that may adversely affect safety or study participation (eg, suicidal intent). Women who were pregnant or nursing were excluded. Veterans taking psychotropic medications were required to be maintained on a stable dose for at least 4 weeks prior to study start. Individuals presenting with significant alcohol withdrawal symptoms, as evidenced by score ≥ 10 on the Clinician Institute Withdrawal Assessment of Alcohol (CIWA-Ar),[55] were referred to a higher level of care and were eligible for reevaluation after stabilization.

General Procedures

This study was part of the national Consortium to Alleviate PTSD (CAP[56]) and was approved by the Institutional Review Boards of the Principal Investigators' academic and VA institutions, and the University of Texas Health Science Center at San Antonio. In addition, an independent data and safety monitoring board (DSMB) through the CAP reviewed the unblinded data every 6 months. The study was conducted between June 2016 and December 2019 (ClinicalTrials.gov Identifier: NCT02500602). All participants provided written informed consent prior to any study procedures. As part of the study, eligible and interested individuals were also able to participate in pre- and posttreatment neuroimaging scans; only the data from the medication trial are presented here. Vital signs and adverse events were obtained weekly by the study medical clinician. Participants provided monthly urine samples to assess riboflavin for medication adherence.

Figure 1. CONSORT Diagram



Abbreviations: AUD = alcohol use disorder, PTSD = posttraumatic stress disorder.

Participants were remunerated for each component of the study they completed and could receive up to $725 in cash, gift cards, or electronic funds transfer if they completed all aspects of the study. Additional details regarding study procedures are described in the study methods article[57] (see Figure 1 for the CONSORT diagram). More information about the CAP is available at https://patriot.uthscsa.edu/strongstar/cap.asp.

Study Medication and Dosing

Participants were randomly assigned (1:1) to receive doxazosin (16 mg/d, immediate-release formulation) or placebo. At the medication initiation visit, they were provided study medication and instructed to take the medication at bedtime. Drug condition assignment followed a prearranged randomization order and was carried out by a research pharmacist not involved in the clinical management of participants to preserve the double-blind design. Active study medication capsules consisted of United States Pharmacopeia (USP)–grade doxazosin and 25 mg riboflavin. Participants interested in taking a multivitamin during the treatment phase were provided a multivitamin (Tri-Vi-Sol) that does not contain riboflavin. All placebo capsules were brought to proper packing level in color-matched, opaque, identically sized capsules. Doxazosin was initiated at 1 mg/d and titrated up as follows: 2 mg at week 2, 4 mg at week 3, 8 mg at week 4, and then 16 mg during weeks 5–12. At the end of week 12, downward titration occurred and participants were titrated down to 8 mg on day 1, 6 mg on day 2, 4 mg on day 3, 2 mg on day 4, and 1 mg on day 5.[42] The majority (87.9%) of participants reached full medication titration to 16 mg at week 5, and there were no significant differences by group.

Measures

The primary outcomes for the current study were the CAPS-5,[51] PCL-5,[52] and TLFB.[53] The CAPS-5 is a semistructured interview used to assess PTSD diagnosis and symptom severity. The CAPS-5 has 20 items rated on a 5-point scale (0 = absent to 4 = extreme/ incapacitating) with a total score ranging from 0 to 80.[51] The CAPS-5 was administered by independent evaluators (IEs) trained and certified by the Consortium to Alleviate PTSD Assessment Core and blind to treatment condition. The CAPS-5 was administered to assess symptoms during the past 30 days at baseline, weeks 6 and 12, and follow-up. The PCL-5 is a 20-item, self-report measure that assesses PTSD severity using a Likert scale (0 = not at all to 4 = extremely).[52] The PCL-5 was administered at baseline, weekly during the treatment phase, and at follow-up.

The TLFB is a self-report measure of alcohol and drug use using a calendar and memory prompts to stimulate recall.[53] Quantity and frequency of daily standard alcohol drink units were obtained at baseline (past 60 days) and weekly during treatment. Primary drinking outcomes were assessed weekly during the 12-week treatment phase and included percent drinking days (any alcohol use), percent heavy drinking days (≥ 4 standard drinks for women or ≥ 5 for men), and abstinence (no alcohol).

Table 1. Baseline Demographic and Clinical Characteristics of the Sample[a]

Variable	Total Sample (N = 141)	Doxazosin (n = 70)	Placebo (n = 71)	Effect Size[b]
Age, mean (SD), y	45.7 (11.1)	45.5 (11.4)	45.9 (10.8)	$d = 0.04$
Sex				
Male	119 (84)	62 (89)	57 (80)	$\phi_c = 0.11$
Female	22 (16)	8 (11)	14 (20)	
Race[c]				
African American	68 (49)	36 (52)	32 (45)	$\phi_c = 0.07$
White	63 (45)	29 (42)	34 (48)	
Other	9 (6)	4 (6)	5 (7)	
Hispanic ethnicity[d]	10 (7)	5 (7)	5 (7)	$\phi_c = 0.00$
Marital status[e]				
Married	51 (35)	23 (33)	26 (37)	$\phi_c = 0.06$
Single	38 (27)	20 (29)	18 (25)	
Divorced	51 (36)	27 (39)	24 (34)	
Widowed	3 (2)	0 (0)	3 (4)	
Military branch[f]				
Army	95 (67)	54 (77)	41 (58)	$\phi_c = 0.23$
Navy	16 (11)	4 (7)	12 (17)	
Air Force	15 (11)	5 (7)	10 (14)	
Marines	14 (10)	6 (9)	8 (11)	
Coast Guard	1 (1)	1 (1)	0 (0)	
Years of military service, mean (SD)	9.4 (6.8)	9.1 (6.7)	9.8 (7.0)	$d = 0.09$
Psychotropic medications	84 (59.6)	37 (52.9)	47 (66.2)	$\phi_c = 0.14$
CAPS-5 total score, mean (SD)	33.7 (9.0)	34.2 (9.6)	33.1 (8.3)	$d = 0.12$
PCL-5 total score, mean (SD)	47.3 (14.8)	47.0 (15.2)	47.7 (14.4)	$d = 0.05$
AUDIT total score, mean (SD)	19.4 (9.4)	19.5 (10.2)	19.3 (8.7)	$d = 0.03$
TLFB, mean (SD)[g]				
% Drinking days	54.3 (37.1)	52.1 (39.7)	56.5 (34.4)	$d = 0.11$
% Heavy drinking days	41.2 (37.8)	42.8 (37.7)	39.7 (38.2)	$d = 0.08$

[a]Values are shown as n (%) unless otherwise noted.
[b]Effect sizes are Cohen d[71] for mean differences standardized by the baseline standard deviations and Cramér V[72] for categorical variables. Cohen's conventions for small, medium and large effects are 0.20, 0.50, and 0.80 for d and 0.10, 0.30, and 0.50 for V.
[c]Race data were missing for 1 participant in the doxazosin group.
[d]Ethnicity data were missing for 1 participant in each arm.
[e]Effect size calculations for marital status excluded rows with n < 5.
[f]Effect size calculations for military branch excluded rows with n < 5.
[g]TLFB data were missing for 1 participant in the doxazosin group.
Abbreviations: AUDIT = Alcohol Use Disorder Identification Test, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder, TLFB = Timeline Follow-Back.

Secondary measures included the number of drinks per drinking day assessed weekly during treatment using the TLFB. A visual analog scale assessed amount of craving for alcohol over the past week using anchors of 0 (not at all) to 10 (extreme). The Alcohol Use Disorder Identification Test (AUDIT)[58] was administered at baseline to characterize the sample. The AUDIT includes 10 items rated on a 5-point scale, with total scores of 15 or higher indicating moderate-to-severe AUD. As the study was part of the CAP,[56] participants also completed the Common Data Elements (CDE) battery of measures,[59] which included, for example, demographic and military history information, trauma exposure, psychiatric symptoms, traumatic brain injury, and pain.

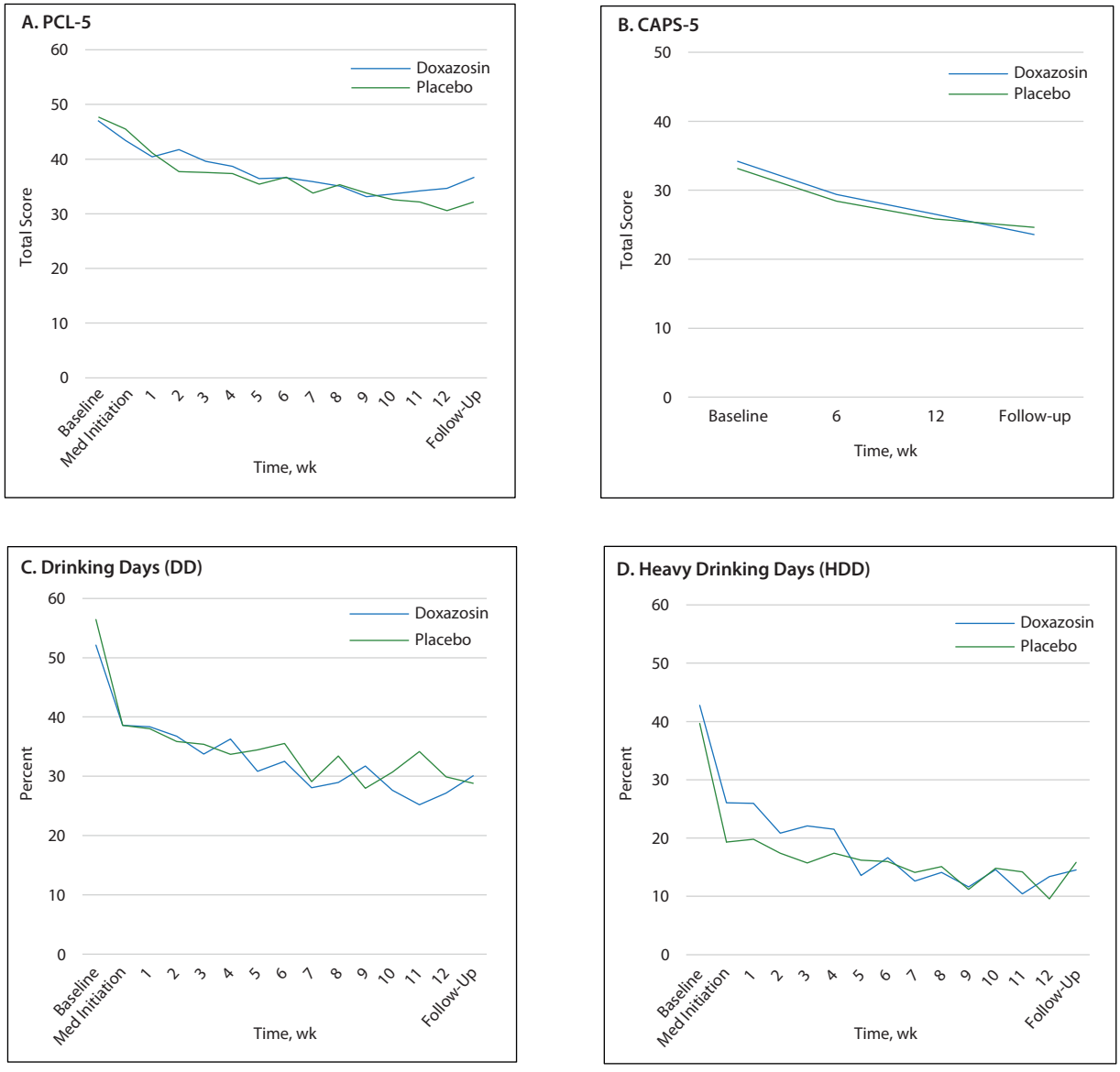
Urine riboflavin levels were obtained monthly to assess medication adherence. Urine samples were assessed fluorometrically by the South Carolina Clinical and Translational Research (SCTR) Institute's Research Nexus Laboratory at the Medical University of South Carolina, and the cutoff level of adherence was > 900 ng/mL.[60] Nine participants had missing riboflavin data and were not included in the analysis. Participants were also asked about medication adherence during each weekly study visit and reminded to take study medication as instructed.

Statistical Power and Data Analysis

As described in the study methods article,[57] the a priori power analysis indicated that a sample size of N = 100 was sufficient to provide 80% power with a 0.05 type 1 error rate to detect meaningful differences in the primary outcomes. The target sample size was inflated to 144 to account for an anticipated 30% dropout rate, although the actual dropout rate was lower (25.5%). The analyses were intent-to-treat (ITT) using all available data from the 141 randomized participants.

Primary outcomes were PTSD severity (total CAPS-5 score and total PCL-5 score) and alcohol consumption (percent drinking days, percent heavy drinking days, and abstinence) as measured by the TLFB from baseline through the end of the 12-week treatment phase (weekly TLFB and PCL-5 assessments). The number of drinks per drinking day was included as a secondary outcome. The statistical models were population-averaged (marginal) regression models with repeated measures, using procedures from the SAS/STAT

Figure 2. Changes in PTSD Symptoms and Alcohol Use Over Time by Medication Group[a]



[a]Graphs depict changes over time, starting at baseline and including the medication initiation visit (Med Initiation), treatment weeks 1–12, and follow-up visit at 6 weeks posttreatment for the PTSD Checklist for *DSM-5* (PCL-5, Panel A), Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5, Panel B), percentage of drinking days (DD, Panel C), and percentage of heavy drinking days (HDD, Panel D). HDD was defined as 5 or more standard drinks per day for men and 4 or more standard drinks per day for women.

9.4 statistical library for linear (MIXED) and generalized (GLIMMIX) mixed models. The MIXED procedure, which assumes normally distributed error, was used to analyze total scores (eg, CAPS-5, PCL-5). GLIMMIX provides for non-normal distributions, such as binomial (eg, weekly alcohol abstinence) and Poisson (eg, percent days drinking). Both procedures provide a variety of alternative structures for the covariance matrix of the repeated measures. The fixed design effects in these models were treatment arm, visit (consecutive integers from baseline through follow-up), and their interaction. Planned contrasts were used to test the significance of change during treatment (difference in least-squares [LS] means ± standard errors [SEs]) within each treatment arm and differences between arms. Some simpler analyses used *t* tests and contingency tables with χ^2 tests. Effect sizes were estimated mean differences standardized by the baseline standard deviations. Hypothesis tests were conducted at $P = .05$.

RESULTS

Demographic Variables and Baseline Characteristics

The majority of participants were male (n = 119; 84.4%) with a mean age of 45.7 years (see Table 1). Almost half of the sample (n = 68, 48.57%) identified as African American, 45.0% (n = 63) as White, and 7.14% (n = 10) as Hispanic. Mean (SD) baseline PTSD severity on the CAPS-5 total score was 33.7 (9.0), and the baseline PCL-5 total score was

Table 2. PTSD and Alcohol-Related Outcomes During Treatment[a]

Outcome	Doxazosin (n = 70)	Placebo (n = 71)	Difference[b]
CAPS-5			
CAPS-5 total			
Baseline	34.2 (1.07)	33.1 (1.07)	
Week 12	26.5 (1.72)	25.8 (1.70)	
Change	7.7 (1.43)	7.3 (1.40)	0.4 (2.00)
P	< .0001	< .0001	.84
Cohen *d*	0.86	0.81	0.04
CAPS-5 B			
Baseline	8.0 (0.37)	7.4 (0.36)	
Week 12	5.9 (0.54)	5.6 (0.53)	
Change	2.1 (0.49)	1.8 (0.48)	0.3 (0.69)
P	< .0001	.0003	.70
Cohen *d*	0.68	0.59	0.09
CAPS-5 C			
Baseline	4.0 (0.15)	4.3 (0.15)	
Week 12	3.1 (0.26)	3.0 (0.25)	
Change	0.9 (0.25)	1.3 (0.25)	−0.3 (0.36)
P	.001	< .0001	.35
Cohen *d*	0.73	1.00	−0.27
CAPS-5 D			
Baseline	11.8 (0.52)	11.7 (0.52)	
Week 12	8.9 (0.78)	8.7 (0.76)	
Change	2.9 (0.72)	3.1 (0.70)	−0.2 (1.01)
P	< .0001	< .0001	.88
Cohen *d*	0.68	0.71	−0.04
CAPS-5 E			
Baseline	10.4 (0.39)	9.7 (0.39)	
Week 12	8.6 (0.50)	8.4 (0.49)	
Change	1.8 (0.43)	1.3 (0.42)	0.4 (0.60)
P	< .0001	.002	.47
Cohen *d*	0.54	0.41	0.13
PCL-5 Total			
Baseline	47.0 (1.77)	47.7 (1.76)	
Week 12	34.6 (2.36)	30.6 (2.33)	
Change	12.4 (1.93)	17.1 (1.89)	−4.8 (2.70)
P	< .0001	< .0001	.08
Cohen *d*	0.84	1.16	−0.32
TLFB			
% Drinking days (DD)			
Baseline	52.1 (4.47)	56.5 (4.41)	
Week 12	27.2 (4.35)	29.9 (4.32)	
Change	25.0 (4.84)	26.6 (4.80)	−1.6 (6.81)
P	< .0001	< .0001	.81
Cohen *d*	0.67	0.72	−0.04
% Heavy drinking days (HDD)			
Baseline	42.8 (4.57)	39.7 (4.50)	
Week 12	13.4 (3.06)	9.5 (3.01)	
Change	29.3 (4.51)	30.1 (4.44)	−0.8 (6.33)
P	< .0001	< .0001	.90
Cohen *d*	0.78	0.80	−0.02

[a]Entries are model-based estimated least-squares means and standard errors (SEs) and within-group change from baseline to week 12.
[b]Between-group difference in pre-post change. Cohen *d* values are the estimated change and differences standardized by the baseline standard deviations. Degrees of freedom are the Kenward-Roger estimates.
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CAPS-5 B = intrusion symptoms. CAPS-5 C = avoidance symptoms, CAPS-5 D = negative alterations in mood and cognition, CAPS-5 E = alterations in arousal and reactivity, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder, TLFB = Timeline Follow-Back.

47.3 (14.8). Participants consumed alcohol 54% of days prior to study entry, with 41% heavy drinking days. The mean (SD) AUDIT total score at baseline was 19.4 (9.4) and similar between groups. Approximately 60% (n = 84) of the sample reported taking a psychotropic medication. The most common type of psychotropic medications reported were antidepressants (82.1%) and there was no difference between treatment groups. Few participants reported taking antianxiety medications (n = 4) or antipsychotics (n = 7). Anticonvulsants were reported by 30 participants (16 in doxazosin, 14 in placebo) primarily to treat pain or migraine headaches. No group differences in demographics or baseline PTSD or AUD severity were observed.

Primary Outcomes

PTSD symptom severity. Examination of the CAPS-5 total scores revealed a significant effect of time ($F_{3, 139} = 30.4$, $P < .0001$), as depicted in Figure 2. Neither the medication main effect nor the time × medication group interaction was significant (see Table 2). Examination of the CAPS-5 subscales also showed significant main effects of time (all $P < .0001$). Both groups improved significantly on all CAPS-5 subscales, but none of the tests of differences between medication groups were significant. Similar results were found for the PCL-5 total score, ie, a significant main effect of time ($F_{14, 139} = 10.97$, $P < .0001$) with comparable improvement in both medication groups ($P < .0001$) but no significant difference between them.

Alcohol consumption. Examination of alcohol consumption outcomes collected using the TLFB included percent drinking days (DD), percent heavy drinking days (HDD), and abstinence. Main effects of time were revealed for DD and HDD ($P < .0001$), as shown in Figure 2, but no significant effects of medication or interactions of time × medication were observed (both $P > .20$; see Table 2). Participants in the doxazosin group were more likely to abstain from alcohol during the 12-week treatment phase (22% abstinence for doxazosin vs 7% for placebo, $\chi^2_1 = 5.7$, $P = .017$). None of the demographic variables (ie, age, race, ethnicity, gender, education, marital status, military grade, or years of military service) differentiated between those who were or were not abstinent in the doxazosin group.

Secondary Outcomes

Analysis of drinks per drinking day revealed that participants in the doxazosin group consumed a greater number of drinks on the days they consumed alcohol (mean [SD] = 6.15 [3.51]) compared to participants in the placebo group (4.56 [2.91]; $t_{111} = 2.63$, $P = .0096$, $d = 0.50$). Overall, craving decreased from baseline (mean [SD] = 5.0 [2.9]) to week 12 (mean [SD] = 3.7 [3.2]), but there was no significant difference between groups.

Retention and Medication Compliance

About 75% of participants (n = 105/141) completed the treatment phase, and there was no difference between medication groups in retention (75.7% doxazosin vs 73.0% placebo; $\chi^2_1 = 0.11$, $P = .74$). Consistent with existing literature from prazosin trials,[37] completers were defined as participants with complete data at the end of treatment (week 12), whether or not they remained on the medication. Medication compliance (ie, ≥ 900 ng/mL of riboflavin)[60] was 75.5%, and there were no differences between medication groups.

Safety and Adverse Events

Common adverse events (AEs) included dizziness, gastrointestinal symptoms (eg, nausea), joint/muscle pain, cold or sinus congestion, sleep problems, and vivid dreams/nightmares. No differences in the overall frequency of side effects were observed by treatment group (101 total AEs among participants randomized to doxazosin and 112 total AEs among those randomized to placebo reported at least one AE). Twenty-one AEs (8 medical, 13 psychiatric) occurred during the study that were considered serious adverse events (SAEs), with 12 in the doxazosin group (5 medical, 7 psychiatric) and 9 in the placebo group (3 medical, 6 psychiatric). The most common SAEs were hospital admissions for medical reasons (eg, hemorrhoids, hernia surgery, chest pain, viral gastroenteritis, diabetes complications), psychiatric problems (eg, depression, suicidal ideation, panic attack/anxiety), or inpatient treatment for alcohol use.

DISCUSSION

This randomized, placebo-controlled trial is the first to evaluate the efficacy of the α_1-adrenergic antagonist doxazosin among individuals with co-occurring PTSD and AUD. Participants randomized to both treatment conditions evidenced significant reductions in primary outcome measures of PTSD and alcohol consumption during the 12-week treatment phase, and there were no differences between groups. Contrary to hypotheses, participants who received doxazosin did not demonstrate significantly greater overall reductions in PTSD or AUD severity (ie, percent drinking days, percent heavy drinking days) compared to those who received placebo. Rates of abstinence were higher in the doxazosin group. However, the number of drinks consumed per drinking day (secondary outcome) was higher in participants who received doxazosin than in those who received placebo (approximately 1.5 drinks more on drinking days). High rates of retention were observed in both groups, and minimal AEs were reported during the study, which supports the safety, feasibility, and tolerability of doxazosin (16 mg) in this patient population.

Although unexpected, the findings are similar to outcomes published since the time of study initiation examining the α_1-adrenergic antagonist prazosin,[37,38] which has a comparable mechanism of action and is used off-label to treat PTSD. While most studies of prazosin demonstrate reductions in nightmares, which are hallmark nocturnal symptoms of PTSD,[61] and daytime hyperarousal,[62–65] the findings are mixed.[66,67] A phase 3 randomized controlled trial[38] among veterans (N = 304) at 12 VA medical centers did not find significant differences in PTSD symptoms between prazosin and placebo. The authors posit that selection bias due to certain inclusion and exclusion criteria resulted in a sample that was fairly clinically stable and may have been less likely to respond to prazosin. More recently, Hendrickson and colleagues[63] conducted a post hoc secondary analysis of a randomized controlled trial of prazosin among active duty soldiers (N = 67) and found prazosin had the largest effects on nightmares, sleep disruption, difficulty concentrating, and hypervigilance (mainly hyperarousal symptom) that cross the traditional *DSM-5* PTSD symptom clusters. The findings align with the neurobiological and behavioral rationale for targeting the noradrenergic system in pharmacologic treatment of PTSD and AUD and reinforce the emerging concept that noradrenergic-targeted medications may have differential efficacy depending on individual patient characteristics, clinical trial population characteristics, and the severity of specific pathophysiologically related symptoms.[63]

Indeed, accumulating findings suggest that prazosin and doxazosin may be most effective for a subgroup of patients who evidence more severe adrenergic dysfunction. Several studies examining the efficacy of doxazosin or prazosin among patients with AUD demonstrate differential effects of pretreatment blood pressure,[39,68] family history density of AUD,[42] and alcohol withdrawal symptoms.[40] In these studies, individuals with higher blood pressure, more severe family history density, and more severe alcohol withdrawal symptoms derived greater treatment benefit from α_1-adrenergic antagonists. For example, the findings of Sinha and colleagues[40] among community-recruited adults (N = 100) showed that alcohol withdrawal severity moderated prazosin's efficacy in reducing alcohol consumption. An earlier, proof-of-concept randomized controlled trial[42] of doxazosin (16 mg/d) among 41 individuals with AUD found no overall group differences; however, patients with high family history density evidenced significantly decreased drinks per week and heavy drinking days on doxazosin as compared to placebo.

Among individuals with co-occurring PTSD/AUD, two randomized controlled trials have investigated the efficacy of prazosin.[35,37] Simpson and colleagues[35] conducted a 6-week, double-blind pilot trial of prazosin among individuals (N = 30) with PTSD/AUD and found that prazosin resulted in greater reduction in percent days drinking and percent heavy days drinking than placebo, but no significant group differences were observed in PTSD symptoms. Petrakis and colleagues[37] conducted a 13-week randomized, double-blind, placebo-controlled trial of prazosin among 96 veterans with PTSD/AUD. Both alcohol use and PTSD symptoms improved over the course of treatment, but no significant differences in medication group were observed. The rate of abstinence during treatment was higher in the prazosin as compared to the placebo group (46% vs 35%), but this difference did not reach statistical significance. In the current study, the rate of abstinence was significantly higher among participants who received doxazosin as compared to placebo (22% vs 7%). The overall abstinence rate in the current study, however, was lower than in the study by Petrakis and colleagues[37] and may be due to methodological differences. Participants in the study by Petrakis and colleagues were required to be abstinent prior to randomization, and most participants were living in sober housing during the study, which may have influenced motivation for abstinence. The current study

also found that, on days that participants randomized to doxazosin consumed alcohol, they consumed significantly more alcohol than participants randomized to placebo. This finding was unexpected, and much remains to be learned regarding person and event-level factors that might influence α_1-adrenergic antagonist efficacy.[69,70] The extant literature is clear that treating co-occurring PTSD/AUD is more complex and challenging than treating either condition alone, and the overall null findings in the present study may reflect that doxazosin has diminished effects among those with co-occurring PTSD and AUD. In addition, it is possible that combination regimens of medications with different mechanisms of action may be useful to consider for patients with both PTSD and AUD.

The current study has several limitations that warrant consideration. The sample consisted of primarily male military veterans, and the results may not generalize to other populations. The study dose and medication taper used in the current study were fixed and were not adjusted as would be done in clinical practice. Although participants were treatment-seeking, they were not required to report a minimum level of readiness to change their drinking behavior or engage in PTSD treatment. Future research should examine readiness to change drinking behavior. The primary outcome measures were self-report and may be limited by recall bias and memory. Although a small proportion of participants reported alcohol abstinence at baseline, and those proportions were similar between treatment arms, outcomes might have been influenced by the lack of a run-in period in this study. All participants were enrolled in services at the VA, and although individuals were excluded if enrolled in evidence-based treatments for AUD or PTSD, they were allowed to receive standard psychosocial services during the study, which may have influenced the outcomes.

In summary, the current study is the largest study to date to examine the role of doxazosin, a long-acting α_1-adrenergic antagonist, for the treatment of co-occurring PTSD and AUD. Contrary to hypotheses, no overall treatment group differences were observed, and although the doxazosin-treated group had a higher rate of abstinence, participants in the doxazosin group consumed more alcohol on drinking days than participants in the placebo group. Additional research and replication of the findings are needed before definitive conclusions can be made. Future data analyses will evaluate potential moderators, such as family history density of AUD and baseline physiologic factors such as blood pressure. Critical questions remain regarding how to optimize pharmacologic strategies that target the persistent and debilitating symptoms of comorbid PTSD and AUD.

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