Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers With and Without PTSD

NCT02226367

Protocol with Statistical Plan

02/26/2020

EIRB Protocol Template (Version 1.2)

1.0 General Information

***Please enter the full title of your study:**

Prazosin Augmentation of Outpatient Treatment of Alcohol Use Disorders in Active Duty Soldiers With and Without PTSD

***Please enter the Protocol Number you would like to use to reference the protocol:**

Prazosin Alcohol
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
○	**Army** - Madigan Army Medical Center (MAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Edwards, Aaron Paul

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Holmes, Hollie A
Associate Investigator
Peskind, Elaine Roslyn

Associate Investigator
Raskind, Murray Albert, MD
Associate Investigator
Williams, Tammy J
Associate Investigator

B) Research Support Staff

Crews, Laura A, BSN
Research Coordinator
FLYNN, DIANE MCFADDEN
Monitor
Huynh, Anh Hong Thi
Research Coordinator

3.3 *Please add a Protocol Contact:

Edwards, Aaron Paul
Holmes, Hollie A
Huynh, Anh Hong Thi
Williams, Tammy J

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Williams, Tammy J
Lead/Core Investigator

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [ ] Other

4.3 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.5 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

◉ Yes ○ No

4.6 Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.2 Will you have a Research Monitor for this study?

◉ Yes
○ No
○ N/A

Research Monitor Role:

Duties of the Research Monitor include (but are not limited to):

1. Monitoring the conduct of the protocol per the approval plan and ensuring protection of human subjects. This may involve periodic review of medical records of enrolled subjects and the research files being maintained by the PI.
2. Reviewing and keeping abreast of adverse events and protocol deviations that occur during the research (all adverse events, including deaths and serious or unexpected side effects, are reported to the Research Monitor via the PI).
3. If there is concern about the welfare of enrolled subjects, the Research Monitor has the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps necessary to protect the safety and well-being of research subjects until the IRB can assess the Research Monitor's report. Notification of such actions must be forwarded to the IRB via DCI within one (1) working day of receipt of knowledge of actions prompting human subject welfare concerns.
   Any report of the Research Monitor will be forwarded to the Madigan and VA Puget Sound IRBs.

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
☐	DIANE MCFADDEN FLYNN

6.0

Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
: Congressionally Directed Medical Research Program (CDMRP) USAMRMC	: Other	

Total amount of funding:

1400000

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study?

◉ Yes ○ No

IRB Name	Review Date	Determination
: Other If other, please define: VA Puget Sound HCS	09/12/2013	Approved via Full Board procedures Other Determination:

8.2 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

◉ Yes ○ No

8.3 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site	
No records have been added							

Other:

	Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
	VA Puget Sound HCS	Coordinating center	FWA00004617	05/04/2022		

8.4 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.5 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

Alcohol use disorders (AUD) are common debilitating problems in active duty Service Members with posttraumatic stress disorder (PTSD).[1-4] Increased central nervous system (CNS) noradrenergic activity contributes to both AUD and PTSD.[5-10] Prazosin, a brain active inexpensive generic alpha-1 adrenoreceptor (AR) antagonist, is effective for PTSD hyperarousal and reexperiencing symptoms and AUD in Vietnam combat Veterans,[11-14] and for reducing AUD in men without PTSD.[15]

We propose a randomized controlled trial of prazosin for AUD in Service Members (SMs) both with and without comorbid PTSD in order to 1) determine prazosin efficacy for AUD in these SMs who are participating in outpatient AUD treatment; and 2) to determine if the presence of PTSD affects prazosin efficacy for AUD.

The hypotheses are that: 1) prazosin is more effective than placebo for AUD in these SMs; and 2) that prazosin effect size will be greater in SMs with PTSD than without PTSD.

This study will be a collaboration between investigators at VA Puget Sound Health Care System (VA Puget Sound) and Madigan Army Medical Center (Madigan). Murray Raskind, MD, Co-Director of the VA Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC) and Staff Psychiatrist at VA Puget Sound is the overall study PI.

VA Puget Sound will serve as the coordinating center. (VA IRB approval documents have been submitted and also describe the role of VA Puget Sound in this study.) All administrative support, study coordination, data management, and analysis will be provided by VA Puget Sound. Data entry and analysis will be done at VA Puget Sound. In addition, several investigators from VA Puget Sound are credentialed at Madigan and will participate in study visits.

Madigan will serve as the participating site. Study procedures (e.g., participant visits) will be performed at Joint Base Lewis-McChord (JBLM) alcohol treatment program and Madigan clinics.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Alcohol Use Disorders
Stress Disorders, Posttraumatic

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Literature Review and Preliminary Data and/or Findings:

Demonstrate that you have done a comprehensive literature search that includes the following:

a. Date of Search: February 2013

b. Search terms used: AUD, PTSD, prazosin

c. Databases Searched: Pub Med

Scientific Justification:

Alcohol problems in active duty military Service Members: High rates of alcohol problems occur in members of the active duty military, particularly among those recently deployed to combat operations in Iraq and Afghanistan. A survey of 88,205 SMs recently deployed to Iraq found that 12-15% screened positive for alcohol problems.[16] Rates of binge drinking were 53% in a sample of recently deployed personnel with combat exposure.[17] In a 2-item survey among 6,527 U.S. Army Soldiers who were screened after returning from deployment to Iraq, 27% screened positive for alcohol misuse, and rates of drinking and driving and reporting late to duty because of hangovers were high.[18] In a separate survey of 1,120 recently deployed Soldiers, 25% screened positive for alcohol misuse and 12% for alcohol related behavioral problems. Exposures to life threatening situations and to atrocities were significantly associated with a positive screen.[3]

PTSD in active duty military Service Members: Similarly, active duty personnel exhibit high rates of PTSD. In one survey 222,620 personnel recently deployed to Iraq showed a 9.8% positive screen rate for PTSD.[19] One of the studies cited above[16] noted positive screen rates for PTSD of 12.1% among active duty personnel immediately post-deployment with rates increasing to 19.5% after a median follow-up interval of 6 months. Another survey of 2,863 personnel one year after return from Iraq determined that 16.6% met screening criteria for PTSD.[20]

Alcohol use disorders (AUD) and PTSD commonly co-occur:[21, 22] The rates of PTSD among men and women with AUD are at least twice as high as those in the general population,[23] and PTSD afflicts 25-53% of substance use disordered (SUD) patients in treatment.[24-26] This comorbidity is associated with more severe clinical impairment, shorter times to relapse, more treatment recidivism, overall greater use of treatment services, worse physical health status, and greater treatment costs.[4, 25, 27-40] Studies of patients with comorbid PTSD and AUD have found that as PTSD symptoms increase, the severity of AUD symptoms also increases,[41, 42] and that a decrease in PTSD symptoms predicts less alcohol use following

treatment.[43] A recent study of Veterans found that alcohol use mediated the relationship between PTSD hyperarousal symptoms and aggression.[44] Further, patients perceive that their PTSD symptoms contribute to their substance use,[32] and that alcohol use temporarily makes their PTSD symptoms better.[45] In laboratory cue reactivity studies, individuals with co-occurring AUD and PTSD evidence increased alcohol cravings in response to personalized trauma imagery cues,[46, 47] and alcohol intake has been shown to dampen the physiological stress response and emotional memory of trauma-related stimuli.[48] I dentification of effective treatments, including pharmacological interventions, for this common and debilitating comorbidity would be an important contribution to the welfare of SMs and Veterans.

Elevated noradrenergic activity contributes to the pathophysiology of AUD and PTSD: Human studies demonstrate increased peripheral and CNS noradrenergic activity in persons with AUD and those with PTSD.[5-10] This increased noradrenergic activity appears to contribute to the pathophysiology of both disorders. In AUD, increased CNS noradrenergic activity enhances alcohol reward/reinforcement and also increases the hyperarousal and anxiety that lower the threshold for stress-induced relapse to heavy drinking.[49] These two mechanisms likely contribute to the initiation and maintenance of AUD. In PTSD, increased CNS noradrenergic activity likely contributes to nighttime sleep disturbance and trauma nightmares and to daytime hypervigilance, irritability, and increased startle.[10, 50]

Noradrenergic neurons in the pontine locus coeruleus (LC) project broadly to limbic and neocortical areas involved in arousal, attention, and emotional tone.[50, 51] They modulate the midbrain-nucleus accumbens-prefrontal cortical network that contributes to the reward and reinforcement properties of many drugs of abuse including alcohol.[52] LC noradrenergic neurons also project heavily to the extended amygdala where they stimulate release of the anxiogenic peptide corticotrophin releasing factor (CRF). In turn, CRF neuronal projections stimulate further NE release from the LC, forming an anxiogenic loop [53] that appears to be involved in alcohol relapse.

Several lines of neurobiological evidence suggest that the contributions of increased noradrenergic activity to PTSD pathophysiology are mediated, at least in part, by NE stimulation of postsynaptic alpha-1 adrenoreceptors (AR). Such stimulation disrupts sleep architecture to favor emergence of trauma nightmares and distressed awakenings,[54, 55] stimulates release of anxiogenic CRF,[56-61] and favors primitive "fight or flight" cognitive responses.[62, 63]

The alpha-1 adrenoreceptor antagonist prazosin as a treatment for both AUD and PTSD: We have adopted the novel, promising strategy of reducing adrenergic activity to treat these disorders by blocking NE stimulation of post-synaptic alpha-1 receptors via the non-selective, alpha-1 AR antagonist, prazosin.[1 3-15, 64, 65] Prazosin was introduced in 1973 as "Minipress" by Pfizer Pharmaceuticals as an antihypertensive drug. An inexpensive generic drug for many years, prazosin has been used chronically by millions of persons for hypertension and for urinary symptoms caused by later life benign prostatic hypertrophy.[66, 67] Prazosin is the most lipid soluble alpha-1 AR antagonist[11] and the only clinically available alpha-1 AR antagonist demonstrated to be active at CNS sites when administered peripherally.[12, 68] Prazosin reduces rodent self-administration of a variety of addictive substances including alcohol.[64, 65] Prazosin appears to reduce the reinforcing effects of substances both by attenuating noradrenergic input into the nucleus accumbens and by attenuating frontal cortical activity that otherwise would elevate dopamine release in the accumbens.[68-74] Prazosin can attenuate both the behavioral responses to CRF-induced increased noradrenergic activity as well as the reciprocal noradrenergic stimulation of CRF neurons, potentially disrupting the feed-forward loop which, by activating CNS stress response pathways is proposed to precipitate withdrawal/abstinence-induced anxiety, hyper-reactivity and consequent relapse.[53] This effect of prazosin on the stress response pathway in addition to its effects on sleep architecture and cognition also likely explain some of the benefits it exerts on PTSD symptoms.

Pre-clinical and clinical work bolsters these theoretical underpinnings: The hypothesis that prazosin might be effective for AUD arose from Dr. Raskind's clinical observations in the first group of Vietnam Veterans ever treated with prazosin for PTSD nightmares and sleep disruption in 1996. Two of these four Veterans in our first case series[75] met criteria for alcohol dependence with onset subsequent to the onset of their PTSD. These Veterans each described their heavy alcohol use as "self-medication" to "drown" nightmares, achieve a few hours sleep, and reduce daytime hypervigilance and intrusive memories. Each ceased using alcohol soon after prazosin had eliminated trauma nightmares and normalized sleep. Each has continued maintenance prazosin and remains alcohol-free to the present day. Similar observations that prazosin reduced alcohol use in combat trauma PTSD emerged from our two subsequent placebo-controlled trials in Vietnam Veterans. These trials demonstrated large effect size efficacy for sleep disturbance, trauma nightmares, and several other PTSD symptoms as well as for global sense of well-being and ability to function.[13, 14] Because these studies were designed to demonstrate efficacy for combat trauma PTSD, alcohol dependence was an exclusionary criterion. However, we again observed in these studies as well as in clinical practice that reduction of PTSD symptoms with prazosin often was accompanied by reduction in alcohol use. Results of our recent clinical experience treating Iraq and Afghanistan Veterans for PTSD with prazosin are consistent with these earlier observations.

Drs. Tracy Simpson, Andrew Saxon, and Murray Raskind performed a double-blind, placebo controlled pilot trial of prazosin in individuals with alcohol dependence who did not have PTSD.[15] Controlling for drinking days per week at baseline, the 19 male completers in the prazosin group compared to placebo reported fewer drinking days per week during the final 3 weeks of the study (β = -1.84; 95% CI = -2.74, -.93; p < 0.001). The average total number of drinking days was 5.7 ± 1.9 (mean ± SEM) in the placebo group and 0.9 ± 0.5 in the prazosin group. Controlling for drinks per week at baseline, the prazosin group reported fewer drinks per week in the final 3 weeks of the study (β = -4.59; 95% CI = -8.86, -.31; p = 0.035). The average total number of drinks during the last 3 weeks of the study was 20.8 ± 6.5 and 2.6 ± 1.3 for the placebo and prazosin groups, respectively. In this study, there was no apparent effect of prazosin on craving, suggesting that prazosin attenuated the reinforcing effects of alcohol. However, prazosin did reduce PACS measured craving scores in our recently completed trial in active duty SMs at JBLM. These SMs had a range of alcohol drinking behavior, ranging from no drinking to alcohol abuse, which did not meet diagnostic criteria for alcohol dependence. A preliminary analysis of the 53 study completers to date demonstrated greater reduction in craving scores in the prazosin SMs (N=27) than in the placebo SMs (N=26), -2.6 ± 5.8 (mean ± SD) vs. -0.3 ± 3.3, t=-1.74, p=0.04 (one-tailed).

Additionally, Drs. Simpson, Saxon, and Raskind are following-up on the promising pilot results described above. Dr. Simpson has been funded via a National Institutes of Health R01 to conduct a 16-week double-blind, placebo-controlled trial of prazosin in 120 persons with AUD without PTSD. A two-week titration period to 4 mg bid and 8 mg at bedtime is followed by 10 weeks of stable study drug. Forty-one individuals have been recruited to date. Preliminary results show strong trends for reduction of both standard drink units (SDUs) consumed (Figure 1a) and craving (Figure 1b) in the prazosin group compared to placebo.

These clinical studies were carried out in parallel with rodent studies investigating effects of prazosin on alcohol ingestion. Drs. Dennis Rasmussen and Raskind, in collaboration with Drs. George Koob and Brendan Walker at the Salk Institute, demonstrated that prazosin treatment decreased operant ethanol self-administration by Wistar rats during acute ethanol withdrawal.[76] In a second study, conducted in collaboration with Dr. Janice Froehlich at the University of Indiana, they demonstrated that both acute and chronic prazosin treatment decreased ethanol consumption by alcohol preferring "P" rats.[65] In a study evaluating prazosin effects on rewarding properties of alcohol, we demonstrated that prazosin infusion into the ventral tegmentum blocked alcohol-conditioned place preference in mice (manuscript in preparation).

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

The objectives of this study are: 1) determine prazosin efficacy for AUD in Service Members (SMs) who are participating in outpatient AUD treatment and 2) determine if the presence of PTSD affects prazosin efficacy for AUD.

The hypotheses are that: 1) prazosin is more effective than placebo for AUD in these SMs; and 2) prazosin effect size will be greater in SMs with PTSD than without PTSD.

Primary outcome measures will consist of the alcohol use calendar and the Penn Alcohol Craving Scale (PACS). Secondary outcome measures will be the Short Inventory of Problems (SIP), and biological markers of alcohol use (phosphatidyl ethanol [PEth] and gamma-glutamyl transferase [GGT]), and successful completion rate of the alcohol treatment program. PTSD symptoms will be assessed with the Clinician Administered PTSD Scale (CAPS) and the PTSD Checklist-Military (PCL-M). Sleep quality will be monitored by the Pittsburgh Sleep Quality Inventory (PSQI). Depression will be assessed by the Patient Health Questionnaire-9 (PHQ-9). Medication compliance will be monitored with pill counts.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

The proposed study is a 21-week, titration to stable dose, randomized, two-group parallel-design, double-blind, placebo-controlled trial to evaluate the efficacy of prazosin for decreasing alcohol use in 200 active duty Service Members (SMs) who are receiving standard outpatient treatment for AUD at JBLM. Treatment groups will be stratified by presence or absence of PTSD and by assignment to Behavioral Health treatment group, the Moderate Intensity treatment group or the High Intensity treatment group. We are requesting to consent up to 300 Service Members to randomize 200 to study drug to have 120 study completers.

Prazosin is an FDA approved drug that is being used off-label for investigational purposes in this study.

Exemptions for an Investigational New Drug (IND) application to the FDA:
This study will be conducted using the drug, prazosin, which has been approved by the FDA for the following indication(s): treatment of hypertension.

Pursuant to AR 40-7, paragraph 4-12, "Use of an Approved Drug for an Unapproved Indication," this study does not require the acquisition of an IND number from the FDA. All conditions listed in this paragraph as "a-e" are met by this clinical investigation. Additionally, Department of Health and Human Services "Investigational Use of Marketed Products" guidelines, dated February 1989, indicate an IND number is not required in the conduct of this study.

(a) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor intended to be used for any other significant change in the labeling for the drugs.

(b) The drugs undergoing investigation are lawfully marketed as prescription drug products, and the investigation is not intended to support any other significant change in the advertising for the drug products.

(c) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug products.

(d) The investigation is conducted in compliance with the requirements for human use review and informed consent set forth in AR 40-38.

(e) The drug is not represented in a promotional context as being safe or effective for the purposes for which it is being investigated.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Participants will be 300 consented, 200 randomized Service Members with concurrent Alcohol Uuse Disorders (AUD) with or without PTSD. Specific Inclusion and Exclusion criteria for these participants are described in detail elsewhere. All participants will be in stable medical health. Racial, ethnic, and gender distribution of the participants is expected to mirror that of SMs being treated in the DBH clinics from which they will be recruited; i.e., 70% Caucasian, 21% African American, 6% Asian American/Pacific Islander, 3% Native American; Hispanic ethnicity 10%; 10% women, 90% men. Because the proposed study specifically addresses treatment of AUD in active duty SMs, all participants will be over the age of 21.

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Alcohol Use Disorders (AUD) are highly prevalent among SMs returned from Iraq and Afghanistan. AUD impair SMs' ability to function, damage domestic relationships, have adverse effects on health, lower the threshold for dangerous behavior, and can end otherwise promising military careers. As stated by Brigade Command Sergeant Major Robert Prosser, 2nd Stryker Brigade Combat Team: "When a Soldier gets in trouble, alcohol abuse is usually involved" (personal communication). Improved treatments for AUD clearly are needed. AUD also are major public health problems in the general population. If prazosin is effective for AUD in SMs, it likely also will be effective in civilians.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Recruitment: SMs engaged in Department of Behavioral Health (DBH) treatment programs who have reported alcohol issues will be asked if they are willing to speak to a research team member about potential participation in the study. If the individual agrees, the staff member will make the referral by contacting the research team. Study personnel will give a brief overview of the study and ask whether the individual is still interested. For individuals who want to learn more, and who meet basic prescreening inclusion criteria, an appointment will be scheduled with a trained investigator who will explain the study in detail and obtain written informed consent as described below. Potential participants who self-refer to the study will be given information about the study and DBH alcohol treatment options.

Consent Process: The study will be explained to eligible participants by one of the approved study personnel in a private setting. DBH personnel will not conduct the initial consent visit.

Potential participants will be given ample opportunity to read the consent form and will be encouraged to ask questions. If the potential participant wishes to have a relative or friend present during the consent process, we will accommodate the potential participant. If a potential participant wants to take the consent home for further consideration before agreeing to participate, he or she will have that opportunity.

Written informed consent/HIPAA authorization will be obtained from participants. The signed consent form and a note documenting consent will be placed in the participant's research record.

The following elements will be discussed with the potential participant:

- The purpose and objectives of the study
- The length of the study
- Any potential risks, discomfort and inconvenience
- The importance of following study procedures
- The importance of compliance with all assessments and study visits
- The possibility of the need for unscheduled visits
- Randomization – there is a 50/50 chance of being randomized to either treatment (active medication or placebo)
- Participation is entirely voluntary and the participant may withdraw from the study at any time without loss of benefits to which he/she may otherwise be entitled
- Alternative treatments
- Provisions for keeping study data confidential and exceptions to confidentiality\
- Adverse events are treated at no cost to the participant

Care will be taken to assure that each participant's current treatment and future services and benefits are not contingent on participation in this or any research study. The voluntary nature of research study participation will be emphasized. The participant must sign the informed consent/HIPAA authorization form before any study procedures are performed.
Formal psychiatric and medical screening: After written informed consent is obtained, a formal screening visit will be performed. At this visit, basic demographic information will be obtained (gender, age, racial and ethnic identification, and educational attainment). Military/deployment history will be collected and reviewed. Medical records will be reviewed for medical/psychiatric diagnoses, recent treatment, lab results, and medications.

Participants will be interviewed using the Structured Clinical Interview for DSM-IV (SCID-IV) to document DSM-IV diagnosis of Alcohol Abuse or Dependence and to rule out exclusionary psychiatric disorders. The Clinician-Administered PTSD scale (CAPS) will be completed to confirm PTSD diagnosis (used as a stratifying variable) and for baseline measure of PTSD severity.

Medical screening will include review of medical history and medications, and screening physical exam. Blood pressure (BP) and heart rate (HR) will be measured after the participant has been seated or lying down for at least 10 minutes and again after the participant has been standing for 2 minutes (seated /supine and standing BP and HR). Approximately 7 ml of blood will be drawn for liver function tests (AST, ALT). Clinical la Participants who continue to meet all inclusion/exclusion criteria will be randomly assigned 1:1 to prazosin or placebo and will enter the titration period as described below, followed by 10 weeks of stable dose prazosin or placebo. There will be one follow-up assessment 6 weeks after the end of the blind phase of the study. All study participants will also participate in the DBH treatment. Primary

and secondary outcome measures and safety assessments will be administered as described below and outlined on the schedule of study visits. Medication compliance will be monitored with pill counts.

Baseline (Week 0): Baseline assessment instruments will include the full CAPS (CAPS will not be repeated if within two weeks of screen), alcohol use calendar, Penn Alcohol Craving Scale (PACS), Short Inventory of Problems (SIP), Pittsburgh Sleep Quality Index (PSQI), PTSD Checklist-Military (PCL-M), and the Patient Health Questionnaire-9 (PHQ-9). In addition, a blood sample (approx. 10 ml) will be obtained for baseline measurements of biological markers of alcohol use (phosphatidyl ethanol [PEth] and gamma-glutamyl transferase [GGT]).

Study weeks 0-2 —Study Drug Titration: Following completion of baseline assessments, participants will be randomized 1:1 to prazosin or placebo. The initial dose will be 1 mg prazosin or placebo capsule taken at bedtime for 2 nights. The first dose of prazosin/placebo will be taken while the participant is in bed for the night to avoid orthostatic syncope, an uncommon but recognized "first dose" effect of prazosin or any alpha-1 antagonist if started at a high dose. The first dose effect is avoidable by starting treatment with a low dose (1 mg before bedtime) and then titrating the dose upward gradually. Such titration avoids excessive blood pressure reduction.

The participant will be asked to call the study team the morning after the first dose to make sure there was no occurrence of postural dizziness. If there have not been any adverse events, the participant will be instructed to increase the dose to 1 mg three times per day (morning, afternoon and bedtime) on the third day. The participant will be given 24-hour contact number in case of adverse events when the dose is increased. However, in our prior study of prazosin in AUD, there has been no problem with this dose increase.

Participants will undergo 2 additional titration visits (weeks 1 and 2). At each titration visit, seated /supine and standing BP and HR will be measured, and presence of side effects and/or adverse events will be assessed. Concomitant medications and health status will be updated. The alcohol use calendar will be administered at every study visit. P

Mid-week titration increases will occur if the participant does not experience any unacceptable side effects. A 24-hour contact number will be provided should any adverse events occur at any time.

A dose increase will occur if the participant does NOT have unacceptable side effects. Clinical judgement may be used to maintain or decrease the dose as necessary. If the participant has intolerable side effects during the titration period, the dose will be reduced to the previous titration step. The dose may be re-challenged if clinically appropriate.

Titration will proceed according to the following schedule:

Study Drug Dose Schedule

		AM	MIDDAY	BEDTIME
Week 0/BL	Days 1-2			1 mg
	Days 3-4	1 mg	1 mg	1 mg
	Days 5-7	2 mg	2 mg	2 mg
Week 1	Days 8-10	2 mg	2 mg	6 mg
	Days 11-14	4 mg	4 mg	6 mg
Week 2	Days 15-21	4 mg	4 mg	8 mg
Week 3	Days 22-end of study	4 mg	6 mg	10 mg

The titration schedule and target dose were chosen based on clinical experience in treating PTSD with prazosin and on our initial study for AUD in which this titration schedule was well tolerated.[15] Typical, effective, and well-tolerated doses of prazosin in Veterans with PTSD treated at VA Puget Sound range between 5-30 mg/day.[77] In our prior work with prazosin, study participants have tolerated without difficulty abrupt discontinuation of these doses of prazosin with no need for tapered withdrawal.

Weeks 3-5: If participants delay titration for any reason (e.g., dose maintained and not increased due to temporary AE), the dose may be increased/adjusted through week 5. No dose changes will be allowed after week 5. If titration is required, procedures noted for weeks 1-2 (above) will be followed. If no titration is required, procedures for weeks 6-13 (below) will be followed.

Weeks 6-13: Participants will be asked to return at weeks 6, 7, 8, 9, 11, and 13. At each visit, vital signs, including orthostatic BP and HR, will be measured. Side effects and/or adverse events (if any) will be monitored by open-ended AE reporting and the Adverse Symptom Checklist which includes symptoms which may be attributable to prazosin (e.g., lightheadedness, dizziness on standing, palpitations, drowsiness, headache, nausea, lack of energy, weakness, depressed mood). For vital signs parameters, hypotension will be defined as systolic BP< 90 and clinically meaningful orthostatic hypotension defined as $\geq$ 20 mmHg drop in systolic BP accompanied by lightheadedness or syncope. If the participant develops an unacceptable adverse effect considered related to study drug, downward dose adjustment will be made.

Concomitant medications and health status will be updated.

The alcohol use calendar will be administered at every study visit. Outcome assessments (CAPS, PCL-M, PHQ-9, PACS, SIP, PSQI) will be administered at weeks 8 and 13.

A blood sample (approx. 10 ml) will be collected at the weeks 8 and 13 for measurement of biological markers of alcohol use (PEth and GGT). GGT measurements will be performed by a Madigan laboratory and results will be placed in the participant's AHLTA record. GGT results will be reported to the participant as clinically indicated and the participant will be referred for medical follow-up, if clinically indicated. PEth samples will be shipped for analysis; however, results will not be available in real time. These results will not be reported to the study participant or to any person not involved in the research.

Study drug adherence will be tracked by pill counts at each study visit.

The blind will be broken at the end of the week 13 visit. Procedures for breaking the blind are described in detail below.

Week 19—6-week follow-up: On week 19 (6 weeks after completion of the week 13 visit), participants will be asked to return for a follow-up visit. At this visit, all outcome assessments (CAPS, alcohol use calendar, PACS, SIP, PSQI, PCL-M, and PHQ-9) will be administered. A blood sample (approx. 10 ml) will be collected for PEth and GGT measurement. Participants will receive a certificate of appreciation at this visit or at the early discontinuation visit as appropriate.

Study personnel will have access to participants' medical records during the period of study participation and for 30 days after study completion or early discontinuation. Records will be reviewed to monitor for changes in health, adverse events, any laboratory results, and completion status of the treatment program. Laboratory results may include urine toxicology screens performed as part of the participant's treatment. Other than the labs listed as being done at screening visit and the GGT that will be obtained at baseline and weeks 8, 13, and 19, no clinical labs will be done as part of the study.

Procedures for Dispensing Study Drug: The MAMC IND pharmacist has a "master" blister pack that the filler/pharmacist will compare to the finished product. This is done by comparing the completed product to the "master" product from the patient view side. This will facilitate how the completed pack should look when ready to be dispensed providing a visual inspection step. Upon filling the prescription order, the pharmacist will affix the participant label, verify it was filled correctly, then initial the label. A study team member will pick up the study drug card from the IND pharmacy. A study team member will verify that the filled drug card and label matches the written medication order. The card will be marked on the back with the week number the study drug corresponds to as well as the date the participant is to begin taking the study drug. Two participant identifiers will be used to verify the participant's identity prior to dispensing the study drug. When the study drug is dispensed, the study team member will require the participant to verbally confirm their understanding of which dose should be taken that particular week. At the end of the visit, a study team member will emphasize the correct card to be used for the current week. Incorrect study cards will not be dispensed and will be returned to the IND pharmacy for correction/replacement.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

All information collected at study visits will be recorded on standardized case report forms. Forms will be labeled with study code number only. Code numbers will be assigned sequentially and will not include participant initials or any other identifiers. Case report forms (coded without identifying information) will be stored on shelves in a locked room in the VA Puget Sound Mental

Illness Research and Education Center (MIRECC) offices. The CRFs are needed at VA Puget Sound because the data from the CRFs is entered by VA Puget Sound staff and because VA Puget Sound is the study coordinating center.

Source documents (research charts, which may contain identifying information) will be maintained in locked cabinets within a locked room at VA Puget Sound in the MIRECC offices. (Offices are currently located at the Seattle division in Building 1, Rooms B22 and B25.) Only those people on the approved protocol will have access to the secured documents. Research charts must be stored at VA Puget Sound because the bulk of the study staff are located at VA Puget Sound. Participants are asked to call the medical providers at VA Puget Sound if they have an adverse event, and are instructed to call the study coordinators at VA Puget Sound if they need to cancel or reschedule an appointment.

Providers for this study are located in offices at JBLM, Madigan clinics, and VA Puget Sound. If at any time access to a research chart that is stored at VA Puget Sound is required, such information may be faxed to the PI. The study team will meet on a weekly basis to discuss study participants and any study concerns ensuring the PI is continually informed regarding all current participants.

All documents will be stored in compliance with record storage policies at VA Puget Sound. The files will be hand carried in locked boxes or containers between JBLM and VA Puget Sound in a HIPAA-compliant secured container and will only be accessible to the persons named on the protocol. The Database Manager will provide database design and maintenance and any required computer programming. VA Puget Sound and the VA Northwest Network MIRECC will provide maintenance of computer hardware and software at VA Puget Sound. Initial and second data entry will be performed regularly at VA Puget Sound by a Research Assistant under the supervision of the Database Manager. The Database Manager will generate reports of data discrepancies. The Research Assistant under the supervision of the Study Coordinator and Data Manager will be responsible for rectifying data entry errors on a regular basis. Data will be analyzed using Statistical Package for Social Sciences (SPSS) software. Database maintenance includes nightly backup of hard drives and storage of backups at a secure location off-site. Only personnel having the correct user name, password, and signing on from a computer with the appropriate IP address will have access to the database.

Disposition of Data: Case report forms will be stored indefinitely in a locked room accessible only to MIRECC investigators and staff at VA Puget Sound, Seattle division (currently Building 1, Rooms B22 and B25). The Data Managers and Biostatistician will not have access to the link between study code numbers and participant identities. The Project Leader and Study Coordinator will maintain the password-protected link between study code numbers and participant identities. This document will be stored on the VA Research server in a workgroup that is only accessible to approved personnel. The VA Research server is FIPS 140-2 compliant.

Because a Records Retention Schedule approved by National Archives and Records Administration is required to destroy Federal records, and because at this time there is not such a schedule for VA research records, we must retain data pending approval of such a schedule. Therefore, all study data, including the link between participant identities and study code numbers will be maintained until we have permission to destroy them or until data analysis is complete (whichever comes later).

At that time, the code list will be destroyed in compliance with Federal Guidelines in force when the records are destroyed (currently outlined in 44 USC3302§1228.5). The electronic code list will be destroyed in compliance with Federal Guidelines (Currently national Archives and Records Administration rules and National Institute of Standards and Technology 800-88 guidelines for Media Sanitization) and all study data will become anonymous. Anonymous study data will be kept indefinitely.

Description of Assessment Procedures and Instruments:

- *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID):* A widely used structured interview that assesses Axis I psychiatric history. The SCID has very good reliability and validity.[78-80] The SCID will be used at the screen visit to rule out exclusionary diagnoses and to describe the participant sample. All parts of the alcohol use disorders section (abuse and dependence) will be asked regardless of answers.
- *Alcohol use calendar:* We will be utilizing a calendar format to obtain self-reports of alcohol use covering the 60-day period prior to Screen and repeated at every visit cover the period since last visit to obtain a retrospective self-report of alcohol use during the study. This will allow for calculation of the number of alcohol positive days, standard

drink units per day and binge drinking days throughout the trial, which will serve as primary outcome measures.

- *The Penn Alcohol Craving Scale (PACS):* A self-report paper-and-pencil instrument that assesses various dimensions of craving for alcohol and has been found to have good reliability and validity.[81] The PACS will be administered at baseline and on weeks 8, 13 and 19, and will be used as a primary outcome measure to determine whether prazosin is associated with reductions in alcohol craving.

- *Alcohol Use Disorders Identification Test (AUDIT):*[82] A 10-item self-report questionnaire that has served as a screening instrument for alcohol problems in a number of different settings.[83] The AUDIT measures at least two factors, one related directly to alcohol consumption and the other to adverse behavioral effects of excessive consumption.[84, 85] An advantage of the AUDIT is that it can delineate not just individuals likely to have an alcohol use disorder diagnosis but can place respondents on the full spectrum of alcohol misuse from no problem to hazardous drinking to dependence. The AUDIT has well supported reliability, validity, sensitivity, and specificity. The AUDIT will be modified to inquire about the past year, and will be administered at baseline. The AUDIT will be used to characterize the sample.

- *Clinician-Administered PTSD Scale for DSM-IV (CAPS):* [86] The 17-item CAPS uses a structured clinical interview designed to assess the 17 symptoms of PTSD outlined in the DSM-IV. The CAPS will be used by the interviewer to make a current (past month DSM-IV diagnoses of PTSD. The frequency and intensity of each symptom on the CAPS is rated on separate 5-point scales, yielding both dichotomous and continuous scores (range = 0 to 8) for each symptom and for the disorder as a whole (range = 0 to 136). The CAPS will used as a stratification variable for group assignment and as a secondary outcome measure and will be administered at screen, baseline (to be done at baseline only if more than 14 days has elapsed since the screen visit) and weeks 8, 13 and 19.

- *Pittsburgh Sleep Quality Index (PSQI)*[87]: A self-report questionnaire assessing sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven subscale scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global score may be obtained by summing the seven component subscales (total score range: 0-21). The PSQI will used as a secondary outcome measure and will be completed at baseline and weeks 8, 13 and 19.

- *Short Inventory of Problems (SIP):* [88] This 15-item self-report questionnaire will be used to assess problems with alcohol, other than alcohol dependence. The SIP has been found to have adequate test-retest reliability and internal consistency. The SIP will be used as a secondary outcome measure to determine whether prazosin is associated with reductions in alcohol-related problems. This self-report instrument will be completed at baseline and weeks 8, 13 and 19.

- *PTSD Checklist-Military (PCL-Military):*[89] A well validated 17-item self-report measure assessing severity of PTSD symptoms specifically in the military combat operations context consistent with DSM-IV criteria, with scores ranging from 17 to 85. The PCL-M will be completed at baseline and weeks 8, 13 and 19.

- *Patient Health Questionnaire-9 (PHQ-9):*[90] The 9-item depression module of the Patient Health Questionnaire, a self-report version of the PRIME-MD used to diagnose major mental disorders. The PHQ-9 items correspond with DSM-IV criteria for depression, with each item scored from "not at all" to "nearly every day." Items of the PHQ-9 are internally consistent (alpha = 0.86-0.89) and the questionnaire exhibits high test-retest reliability coefficients. Agreement between the PHQ-9 and clinician-based interview diagnosis of major depression is high, with a sensitivity of 88% and a specificity of 88% using a PHQ-9 score ≥ 10. The PHQ-9 will be completed at baseline and weeks 8, 13 and 19.

- *Family History of Drinking Problems*:[94] A study staff administered instrument to collect information regarding family history of alcohol use. The instrument does not identify family members beyond labeling titles of mother, father and siblings 1 through 10. In a study of the prazosin-like alpha-1 adrenoreceptor antagonist doxazosin, a positive family history predicted a positive response to doxazosin. This information may be helpful in predicting which patients may have a positive response to prazosin.

10.3 At any point in the study, will you request, use, or access data from a DoD Database or the Military Health System (MHS)?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance.

The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force

***MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS.**

***MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.**

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

Are you an MHS business associate?

(•) Yes, I am an MHS business associate
( ) No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

( ) Yes, then complete the questions below according to the data consult
(•) No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

[ ] Talking with MHS health care providers or MHS health plans about specific research participants
[ ] Obtaining MHS hard copy records specific to research participants
[x] Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

[ ] Data Extract

☑ Access

10.8 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
AHLTA	Yes
ESSENTRIS	Yes

PII-Only Systems:

MHS Information System	Requesting Data
MHS Genesis	Yes

Information System	Requesting Data
No records have been added	

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

○ Yes, will merge data
◉ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.

If you answered "yes" to question 10.9 above, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Data Element(s)	MHS	Non-MHS Systems	MHS Hard Copies
1. Names	☑	☑	☐

2. Postal address with only town, city, state and zip code	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☑	☑	☐
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☑	☑	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐
6. Telephone numbers	☑	☑	☐
7. Fax numbers	☑	☑	☐
8. Electronic mail addresses	☐	☐	☐
9. Social Security numbers (SSNs)	☑	☑	☐
10. Medical record numbers	☑	☑	☐

11. Health plan beneficiary numbers	☐	☐	☐
12. Account numbers	☐	☐	☐
13. Certificate/license numbers	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

The study will use social security numbers to abstract data from electronic health records.

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the

rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ◉ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ○ Waiver/alteration of HIPAA Authorization is being requested

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Study personnel will have access to participants' medical records during the period of study participation and for 30 days after study completion or early discontinuation. Records will be reviewed to monitor for changes in health, adverse events, any laboratory results, and completion status of the treatment program. Laboratory results may include urine toxicology screens performed as part of the participant's treatment. Other than the labs listed as being done at screening visit and the GGT that will be obtained at baseline and weeks 8, 13, and 19, no clinical labs will be done as part of the study.

Approximately 7 ml of blood will be drawn for liver function tests (AST, ALT) at the screen visit. Other clinical labs (chemistry panel, and complete blood count) at the screen visit, if clinically indicated. If the additional labs are drawn, a total of 15 ml of blood will be drawn at the screen visit. Urine will be collected at the screen visit for routine urinalysis, if clinically indicated. A urine sample for urine pregnancy test will also be collected at the screening visit from women of childbearing potential.

Blood samples (approx. 10 ml each) will be collected at baseline and at weeks 8, 13 and 19 for PEth and GGT measurement.

All samples will be used in their entirety for the testing specified. No samples will be stored for future research.

All information collected at study visits will be recorded on standardized case report forms. Forms will be labeled with study code number only. Code numbers will be assigned sequentially and will not include participant initials or any other identifiers. Case report forms (coded without identifying information) will be stored on shelves in a locked room in the VA Puget Sound Mental Illness Research and Education Center (MIRECC) offices. The CRFs are needed at VA Puget Sound because the data from the CRFs is entered by VA Puget Sound staff and because VA Puget Sound is the study coordinating center.

Source documents (research charts, which may contain identifying information) will be maintained in locked cabinets within a locked room at VA Puget Sound in the MIRECC offices. (Offices are currently located at the Seattle division in Building 1, Rooms B22 and B25.) Only those people on the approved protocol will have access to the secured documents. Research charts must be stored at VA Puget Sound because the bulk of the study staff are located at VA Puget Sound. Participants are asked to call the medical providers at VA Puget Sound if they have an adverse event, and are instructed to call the study coordinators at VA Puget Sound if they need to cancel or reschedule an appointment.

Providers for this study are located in offices at JBLM, Madigan clinics, and VA Puget Sound. If at any time access to a research chart that is stored at VA Puget Sound is required, such information may be faxed to the PI. The study team will meet on a weekly basis to discuss study participants and any study concerns ensuring the PI is continually informed regarding all current participants.

All documents will be stored in compliance with record storage policies at VA Puget Sound. The files will be hand carried in locked boxes or containers between JBLM and VA Puget Sound in a HIPAA-compliant secured container and will only be accessible to the persons named on the protocol. The Database Manager will provide database design and maintenance and any required computer programming. VA Puget Sound and the VA Northwest Network MIRECC will provide maintenance of computer hardware and software at VA Puget Sound. Initial and second data entry will be performed regularly at VA Puget Sound by a Research Assistant under the supervision of the Database Manager. The Database Manager will

generate reports of data discrepancies. The Research Assistant under the supervision of the Study Coordinator and Data Manager will be responsible for rectifying data entry errors on a regular basis. Data will be analyzed using Statistical Package for Social Sciences (SPSS) software. Database maintenance includes nightly backup of hard drives and storage of backups at a secure location off-site. Only personnel having the correct user name, password, and signing on from a computer with the appropriate IP address will have access to the database.

Disposition of Data: Case report forms will be stored indefinitely in a locked room accessible only to MIRECC investigators and staff at VA Puget Sound, Seattle division (currently Building 1, Rooms B22 and B25). The Data Managers and Biostatistician will not have access to the link between study code numbers and participant identities. The Project Leader and Study Coordinator will maintain the password-protected link between study code numbers and participant identities. This document will be stored on the VA Research server in a workgroup that is only accessible to approved personnel. The VA Research server is FIPS 140-2 compliant.

Because a Records Retention Schedule approved by National Archives and Records Administration is required to destroy Federal records, and because at this time there is not such a schedule for VA research records, we must retain data pending approval of such a schedule. Therefore, all study data, including the link between participant identities and study code numbers will be maintained until we have permission to destroy them or until data analysis is complete (whichever comes later).

At that time, the code list will be destroyed in compliance with Federal Guidelines in force when the records are destroyed (currently outlined in 44 USC3302§1228.5). The electronic code list will be destroyed in compliance with Federal Guidelines (Currently national Archives and Records Administration rules and National Institute of Standards and Technology 800-88 guidelines for Media Sanitization) and all study data will become anonymous. Anonymous study data will be kept indefinitely.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

This study does not bank data or specimens for future research.

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

Primary Outcome Measures: Analysis of the primary outcomes will follow the ITT principal. For the each of the two outcomes, a linear regression model with covariates that include treatment group, the stratifying variables, and baseline value of the outcome will be used to compare the prazosin and placebo groups at 13 weeks. In addition, we will conduct a repeated measures analysis using data from the two points of follow-up (8 and 13 weeks). The repeated measure analysis will be conducted by comparing response profiles between prazosin and placebo groups. An initial comparison will be conducted using the general estimating equations (GEE) method of Liang and Zeger,[91] which allows all observed data points for each participant. Secondarily, an analysis of covariance (ANCOVA) rate of change analysis will be done as a confirmatory or sensitivity analysis. Stratifying variables will be included as covariates in each model since they are factors in the stratification. It is anticipated that a retrieved dropout strategy will

result in a limited number of missing observations. For the GEE analysis no imputation strategy is required. For the ANCOVA analysis the missing data patterns will be evaluated between the treatment groups. If the patterns are similar and the magnitude of missing data is small, a conventional last observation carried forward (LOCF) imputation will be performed. If the amount of missing data is substantial and/or the patterns of missingness disparate, as an alternative to the traditional ANCOVA, the summary statistic method of Dawson[92] will be employed. This method has been shown to be robust to non-ignorable missingness. The approach summarizes the response profile using a least square slope, and stratifies on the missing data pattern. We will also run analyses to assess the interactions between treatment group and gender.

A completers analyses will be done in a similar fashion for the primary outcome measures, using only the cases that remained on protocol throughout the 13-week study drug period.

Secondary outcome measures: All secondary outcome measures (PSQI, CAPS, PCL-M, SIP, and biological markers) will be analyzed in a manner similar to that described above for the primary outcome measures. (We will also perform exploratory analyses in a similar manner on the CAPS symptom clusters and individual CAPS items to generate hypotheses about differential responsiveness to prazosin for AUD relative to response of individual PTSD symptom clusters/symptoms).

Procedures to minimize missing data: Although all efforts will be made to complete study visits in person, it may be necessary to obtain assessments by telephone. Attempts will be made to reach the participant by telephone. The following actions will be attempted (as appropriate per visit schedule): 1) adverse events will be assessed by telephone, 2) assessments shall be completed by telephone interview with the raters, 3) self-rated measures will be done by mail using prepaid envelopes, and 4) dispensing of study drug shall be done by traceable shipment. No-show, missed visits and actions taken will be documented in the study record.

11.2 Sample Size:

Sample Size Estimation: The power analysis is based on two types of preliminary data: the results of Dr. Simpson's study of prazosin for reduction of alcohol use in persons with AUD without PTSD and the preliminary results of our study of prazosin for combat trauma PTSD in active duty SMs without AUD in which we obtained the PACS. There were 19 completers in Dr. Simpson's pilot study. Standard drink units in the final month of the study drug period were 30.3 ± 32 (mean ± SD) (N=10) in the prazosin group and 62 ± 58 (N=9) in the placebo group (F=1.50, p=0.012). There were 53 completers in the prazosin study for combat trauma PTSD in active duty SMs. The difference (delta) in PACS scores were -2.6 ± 5.8 (N=27) vs. -0.3 ± 3.3 (N=26) in the prazosin vs. placebo groups, respectively, t=-1.74, p=0.04 (one-tailed).

We used these preliminary data to power for both the primary outcome measures, the alcohol use calendar (similar to the Time Line Followback from Dr. Simpson's Interactive Voice Response [IVR] Standard Drink Units [SDU] data) and the PACS (from Dr. Raskind's data). Using the SDU data gives us 97% power, 2-tailed at alpha=0.05 with a sample size of 60 in each group (total N=120). Using the PACS data gives us 76% power, 2 tailed, at alpha=0.05, and 85% power, one tailed, at alpha=0.5, with the same sample size. We have conservatively powered because Dr. Simpson's used IVR methodology and data were from persons with AUD without PTSD, and Dr. Raskind's were from Service Members with PTSD without diagnosed AUD, to power adequately for not only Hypothesis 1 for prazosin efficacy for AUD, but also Hypothesis 2 to determine the effects of PTSD diagnosis on response to prazosin for treatment of AUD.

Assuming an approximately 40% dropout rate, we will randomize 200 participants to have 120 study completers.

11.3 Total number of subjects requested (including records and specimens):

300

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

randomize 200 on a 1:1 ratio prazosin or placebo

11.5 Please provide a justification for your sample size

11.6 Data Analysis Plan:

Statistical Analysis: Baseline comparability between treatment groups will be evaluated with respect to entry criteria, as well as demographic characteristics and baseline symptoms and assessment measure scores. We will use summary statistics and graphical techniques, such as box plots, to compare the baseline characteristics of treatment groups. Prior to conducting the main analyses, we will do checks via *t*-test and Chi-square to evaluate whether the randomization procedures resulted in groups with meaningful differences with regard to demographic factors such as age and ethnicity, AUD and/or PTSD symptom severity, subjective impressions of alcohol's reinforcing effects, and alcohol craving (PACS). Should we identify significant differences on any of these parameters, they will be taken into account statistically through covariation procedures. Since randomization will be blocked on assignment to the stratifying variables, we do not anticipate differences across conditions in those variables. We will also evaluate whether there are systematic differences (again via *t*-test and Chi-square) with regard to the individual characteristics noted above among those randomized that do and do not complete the study. In addition, we will generate summary descriptive statistics for each of these different subgroups and the overall sample.

Secondary analyses: In addition to the major analyses designed to address the study aims, the following secondary analyses will also be conducted:

Treatment retention: Between group comparisons via Chi-square will be conducted to determine whether the prazosin condition was more likely to complete the medication phase of the study. Study completion will be operationalized such that study completers will have attended at least 10 of the 14 interim study visits and the visit at 13-weeks when study participation is completed. We will also use t-test to compare the number of study visits attended overall by the two groups.

Study drug compliance: We will report descriptive statistics for pill counts to determine adherence. We will use t-tests to compare medication compliance across the two study conditions. Since prior work shows that individuals on active medication with 80% or greater medication adherence have superior outcomes to non-adherent individuals,[93] participants who achieve ≥ 80% adherence will be defined as adherent.

Adverse events: Descriptive statistics regarding the number, severity, and types of adverse events reported by participants in the two conditions will be generated. Depending on the types of between group differences (e.g., type vs. severity vs. number) detected, if any, significance testing via t-test or Chi-square will follow.

12.0 Participant Information

12.1 Subject Population:

Participants will be 300 consented, 200 randomized SMs with concurrent AUD with or without PTSD. Specific Inclusion and Exclusion criteria for these participants are described in detail below. All participants will be in stable medical health. Racial, ethnic, and gender distribution of the participants is expected to mirror that of SMs being treated in the DBH clinics from which they will be recruited; i.e., 70% Caucasian, 21% African American, 6% Asian American/Pacific Islander, 3% Native American; Hispanic ethnicity 10%; 10% women, 90% men. Because the proposed study specifically addresses treatment of AUD in active duty SMs, all participants will be over the age of 21.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34
- ☑ 35-44
- ☑ 45-54
- ☑ 55-64

- [x] 65-74
- [x] 75+

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [x] Wounded Warriors
- [x] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [x] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

You must also consider the requirements of 32 CFR 219.111(b).

12.5 Inclusion Criteria:

Order Number	Criteria
1	Male or female active duty personnel over the age of 21 with a current DSM-IV diagnosis of Alcohol Abuse or Dependence or a current DSM-V diagnosis of Alcohol Use Disorder
2	Recent alcohol consumption: more than 14 (women) or 21 (men) drinks per week for at least 2 weeks in the past 60 day period OR at least 2 days of heavy drinking in the past 60 day period (4 or more drinks for women and 5 or more drinks for men)
3	Good general medical health (*see Exclusion Criteria)*

4	Women of childbearing potential must agree to abstain from sexual relations that could result in pregnancy or use an effective method of birth control acceptable to both participant and the study clinician during the study. Men are not required to use contraception during the study.
5	Concomitant use of naltrexone and/or Antabuse must be stable for 2 weeks prior to Baseline.
6	Capacity to provide informed consent
7	English fluency

12.6 Exclusion Criteria:

Order Number	Criteria
1	Current diagnosis of opioid, methamphetamine, cocaine, marijuana, or other illegal substance dependence or abuse.
2	Signs or symptoms of alcohol withdrawal at the time of initial consent
3	Current diagnosis of schizophrenia, other psychotic disorder, manic phase of bipolar disorder, or cognitive disorder.
4	Suicide attempt or suicidal ideation with intent in the past month.
5	Significant acute or chronic medical illness, including unstable angina, recent myocardial infarction, history of congestive heart failure, preexisting hypotension (systolic <100) or orthostatic hypotension (defined as a systolic drop > 20mmHg after two minutes standing accompanied by lightheadedness or syncope); insulin-dependent diabetes mellitus; chronic renal or hepatic failure, acute pancreatitis, Meniere's disease. Liver function tests more than 5 times the upper limit.
6	Concomitant use of trazodone (due to increased risk of priapism). There will be a two week trazodone washout period before the baseline visit
7	Concomitant use of an alpha-1 blocker medication or insulin
8	Use of prazosin in the 4 weeks prior to Baseline
9	History of prazosin sensitivity/allergy
10	Not suitable for study per the clinician's judgement
11	Participants who use erectile dysfunction (ED) medications (avanafil, sildenafil, tadalafil, or vardenafil) will be asked to abstain from ED drug use during the study titration phase and then may use ED drugs at one-half the customary dose during study participation
12	Use of bodybuilding/weightlifting supplements with vasodilator properties

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Participants will be recruited from SMs DBH treatment programs including Substance Use Disorders Clinical Care (SUDCC). No participant will be excluded based upon race, ethnicity, or gender. Racial, ethnic, and gender distribution of the participants is expected to mirror the demographics of SMs undergoing treatment in the DBH. SMs enter these programs from multiple referral sources: self-referral, command direction, medical referral, etc.
The number of SMs referred to the standard outpatient alcohol treatment programs is approximately 150 per month for pure AUD without concomitant use of other drugs of abuse (e.g., marijuana, cocaine, methamphetamine, DMA, and opiates). The average age is 24 with a range of 21-55 years. The racial composition is 70% Caucasian, 21% African American, 6% Asian American/Pacific Islander, 3% Native American. The Hispanic ethnicity of the referred population is 10% Hispanic, 90% non-Hispanic. Gender composition is 10% women, 90% men.
We will not enroll any members of "special vulnerable populations." Although SMs may have command requirements to complete the clinical outpatient JBLM assignment to the SUDCC programs, command pressure to participate in this research study will be strictly avoided. If a participant becomes incarcerated for longer than one day after the Baseline, the participant will be discontinued from the study. Participants who have been discontinued from the study during the screening phase (e.g., do not currently meet inclusion/exclusion criteria) may be re-screened at a later date. Those discontinued following randomization will not be eligible for re-enrollment.

13.2 Compensation for Participation:

Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation and may not exceed $50 per blood draw. They may not receive any other payment or non-monetary compensation for participation in a research study unless they are off duty or on leave during the time they are participating in the protocol.
Participants will be compensated with a $50 gift card per blood draw (up to five blood draws total, up to $250 value). They will receive a $50 gift card after each visit at which a blood draw is performed (screen, baseline, weeks 8, 13 and 19).

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

Formal psychiatric and medical screening: After written informed consent is obtained, a formal screening visit will be performed. At this visit, basic demographic information will be obtained (gender, age, racial and ethnic identification, and educational attainment). Military/deployment history will be collected and reviewed. Medical records will be reviewed for medical/psychiatric diagnoses, recent treatment, lab results, and medications.

Participants will be interviewed using the Structured Clinical Interview for DSM-IV (SCID-IV) to document DSM-IV diagnosis of Alcohol Abuse or Dependence and to rule out exclusionary psychiatric disorders. The Clinician-Administered PTSD scale (CAPS) will be completed to confirm PTSD diagnosis (used as a stratifying variable) and for baseline measure of PTSD severity.

Medical screening will include review of medical history and medications, and screening physical exam. Blood pressure (BP) and heart rate (HR) will be measured after the participant has been seated or lying down for at least 10 minutes and again after the participant has been standing for 2 minutes (seated/supine and standing BP and HR). Approximately 7 ml of blood will be drawn for liver function tests (AST, ALT). Clinical labs (chemistry panel and complete blood count) will be drawn if clinically indicated. If the additional labs are drawn, a total of 15 ml of blood will be drawn at the screen visit. A routine urinalysis will be done if clinically indicated. Twelve-lead EKG will be obtained if clinically indicated (i.e., history of cardiac disease, arrhythmia, or symptoms of potential cardiac origin such as chest pain).

Female participants of childbearing potential will have a urine pregnancy test. Pregnant or nursing women are not eligible for study participation. Women of childbearing potential must agree to abstain from sexual relations that could result in pregnancy or use an effective method of birth control acceptable to both participant and the study clinician during the study. Men are not required to use birth control during the study.

13.4 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

The study will be explained to eligible participants by one of the approved study personnel in a private setting. DBH personnel will not conduct the initial consent visit.
Potential participants will be given ample opportunity to read the consent form and will be encouraged to ask questions. If the potential participant wishes to have a relative or friend present during the consent process, we will accommodate the potential participant. If a potential participant wants to take the consent home for further consideration before agreeing to participate, he or she will have that opportunity.
Written informed consent/HIPAA authorization will be obtained from participants. The signed consent form and a note documenting consent will be placed in the participant's research record.

The following elements will be discussed with the potential participant:

- The purpose and objectives of the study
- The length of the study
- Any potential risks, discomfort and inconvenience
- The importance of following study procedures
- The importance of compliance with all assessments and study visits
- The possibility of the need for unscheduled visits
- Randomization – there is a 50/50 chance of being randomized to either treatment (active medication or placebo)
- Participation is entirely voluntary and the participant may withdraw from the study at any time without loss of benefits to which he/she may otherwise be entitled
- Alternative treatments
- Provisions for keeping study data confidential and exceptions to confidentiality
- Adverse events are treated at no cost to the participant

Care will be taken to assure that each participant's current treatment and future services and benefits are not contingent on participation in this or any research study. The voluntary nature of research study participation will be emphasized. The participant must sign the informed consent/HIPAA authorization form before any study procedures are performed.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A
○ Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Study Discontinuation or Termination: If the participant is not able to tolerate a minimum dose of 3 mg /day of placebo/prazosin, he or she will undergo early termination and all week 13 assessments will be performed; the participant will be referred to his/her primary mental health care provider for further management. Reasons for early discontinuation or withdrawal will be recorded.

Participants may be discontinued prematurely from study treatment to manage deterioration of clinical status. Specifically, dangerousness toward self or others or emergence of acute psychiatric symptoms necessitating hospitalization will result in discontinuation from the study. If at any time during the study, psychiatric symptoms become markedly increased resulting in severe participant distress or presenting immediate danger to self or others, the participant will be discontinued from the study. In case of need for increased level of care or emergent care, study personnel will provide a warm hand-off to DBH personnel. DBH personnel will assume responsibility for arranging appropriate care.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Risks of study drug: There are no known absolute contraindications to prazosin. In clinical trials of prazosin, the most frequent adverse reactions were: dizziness (10%), drowsiness (8%), headache (8%), lack of energy (7%), weakness (7%), palpitations (7%), and, nausea (5%). Less frequent adverse reactions (1-4%) reported in clinical trials were: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency, blurred vision, reddened sclera, epistaxis, dry mouth, and nasal congestion. Fewer than 1% of patients have reported the following (causal relations sometimes not established): abdominal discomfort or pain, liver function abnormalities, pancreatitis, tachycardia, paresthesias, hallucinations, pruritus, alopecia, lichen planus, incontinence, impotence, priapism, tinnitus, diaphoresis, fever, positive ANA titre, and arthralgia.
Rare but serious side effects (less than 1% of people who take prazosin)

- A potentially dangerous side effect of prazosin is priapism (a painful erection of the penis in men and a similar condition in women that lasts for hours). Participants will be instructed to seek medical attention if this side effect is experienced and if it lasts longer than 4 hours.
  Less likely side effects (less than 4% of people who take prazosin):
- problems with the digestive system (such as vomiting, diarrhea, constipation, and indigestion)
- drop in blood pressure when standing up, fainting
- vertigo (loss of balance)
- shortness of breath
- depression
- nervousness
- rash
- edema
- increased urinary frequency
- blurred vision and reddened eyes
- dry mouth
- nasal congestion and nose bleeds
  Likely side effects (less than 10% of people who take prazosin)
- nausea (4.9%)
- palpitations or abnormal heart beat (5.3%)
- weakness (6.5%)
- lack of energy (6.9%)
- drowsiness (7.6%)
- headache (7.8%)
  More likely side effects
- dizziness and/or lightheadedness (10.3%)

Prazosin may cause syncope. In most cases this is believed to be due to excessive postural hypotension although occasionally the syncopal episode has been preceded by severe tachycardia with heart rates of 120-180 beats per minute. Syncopal episodes have usually occurred within 30-90 minutes of the initial dose. The incidence of the syncopal episodes is 1% if the initial dose is 2 mg or more. Clinical trials suggest that syncopal episodes can be minimized by starting with a dose of 1 mg and slowly titrating up to the final dose, as we are doing in this study.
In post-marketing experience, Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients who are taking or have taken alpha-1 blockers. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique to reduce the surgical risk of IFIS. If a patient needs to have cataract surgery, he/she should tell his/her eye surgeon that he/she may have taken prazosin in a research study.
Prazosin should not be taken concurrently with trazodone. Potential participants who are taking trazodone for sleep and who are willing to discontinue will be washed out before starting this study.
Care should be taken when alpha-1 blockers are combined with erectile dysfunction medications. We will be following VA pharmacy prescribing guidelines regarding these medications. Erectile dysfunction medications will not be allowed during the titration period. Once stable dose has been reached, participants will be allowed to use ED drugs at half the usual clinical dose.

Participants will be monitored at each visit for adverse events. Any adverse event will be managed by the study team as clinically appropriate. If necessary, a participant will be referred for treatment of an adverse event. Adverse event reporting will begin after the dispensing of the first dose of study drug. All events reported prior to dispensing of the first dose of study drug shall be part of the participant's health history.

Risks of Questionnaires and Assessments: The interviews and questionnaires may cause participants to focus their attention on traumatic experiences and as a result may produce transient subjective distress or to increase the symptoms of PTSD. There are also sensitive and potentially embarrassing questions regarding alcohol use and whether the participant has had any DUIs. Our study team has experience in conducting interviews and administering these questionnaires to persons with and without PTSD.

Risks of Loss of Confidentiality: There is a risk of loss of confidentiality. We will take all due care so that responses to questionnaires are not commingled with patient medical records. Source documents (which may contain identifying information) will be maintained in locked cabinets within a locked office. Source documents and case report forms will be stored separately. The paper documents will be stored in compliance with record storage policies at VA Puget Sound. Electronic records are in restricted-access folders (only the study team is able to access the folders) on the VA Puget Sound server.

Risks of blood draw: Having blood drawn might cause some discomfort. Removal of blood by a needle and syringe may cause pain or bruising at the site of the needle stick. There is also a slight risk of infection where we insert the needle. Some people may become dizzy or faint when they get their blood drawn.

14.2

Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Protection against adverse effects of prazosin: Participants will undergo screening evaluation including review of medical and psychiatric history, physical examination and 12-lead ECG (if clinically indicated). Seated/supine and standing BP and HR will be monitored at each in-person study visit.

Women of childbearing potential must have a negative urine pregnancy test at screen and within one week of starting study drug. Female participants must agree to abstain from sexual relations that could result in pregnancy or use an effective method of birth control acceptable to both participant and the study clinician during the study in order to be eligible. Women who are nursing will not be eligible for study participation. Any woman who becomes pregnant during the course of the study will be discontinued from the study but will continue with customary AUD treatment or treatment with her DBH provider.

Risks of medication side effects will be minimized by starting at a low dose and titrating up to the maximum dose over a period of weeks, by maintaining frequent contact with study participants, and by performing safety assessments on a regular schedule. As a further precaution, male participants will be advised to sit on the toilet for urination during the first week of dose titration.

Vital signs, including orthostatic BP and HR, will be performed at all in-person study visits. Systolic and diastolic BP and HR will be obtained following at least 10 minutes of seated/supine posture and then repeated following 2 minutes of standing. Occurrence of lightheadedness, dizziness on standing, palpitations, drowsiness, headache, nausea, nasal congestion, peripheral edema, and other adverse effects will be rated by a study clinician. For vital signs parameters, unacceptable side effects will include seated/supine hypotension (seated/supine systolic BP<90) and clinically meaningful orthostatic hypotension ($\geq$ 20 mmHg drop in systolic BP accompanied by lightheadedness or syncope).

Safety procedures specific to the war zone trauma population: Participants will be discontinued from the study to manage marked deterioration of clinical status or if the study clinician determines the participant is not stable enough to continue participation. For example, psychiatric symptoms become markedly increased resulting in severe participant distress, dangerousness toward self or others or emergence of acute psychiatric symptoms necessitating hospitalization. Study termination will be followed by a warm hand-off to DBH personnel. DBH personnel will assume responsibility for arranging appropriate care. A study clinician will be on call at all times to receive telephone calls from participants regarding any adverse events; participants will be provided with a 24-hour emergency contact number.

Participants are asked about suicidal ideation at each visit. If endorsed, participants will be assessed as to their level of risk and the level of care required to keep themselves or others from harm. If a participant requires inpatient treatment in order to prevent harm or is found to have symptoms of disorganized thought processes secondary to psychosis, DBH personnel will be notified immediately to assist with appropriate triage and referral.

Protection against risk of loss of confidentiality: Confidentiality is strict. All case report forms (CRFs) will be stored by participant code and no identifying information will be included with CRFs. Study records and data will be kept in a secure location as described below or on restricted-access, password-protected servers. Identifiable information will not be stored with study data. Only the persons named on the Madigan and VA Puget Sound IRB applications will have access to the source documents and original research data. Data will not be revealed to insurance companies or other individuals or organizations.

Exceptions to confidentiality: The study team will have access to participant medical records from initial consent until 30 days beyond the end of participant study participation to monitor for adverse events and treatment progress. Participant endorsement of illegal substance use, and any self-harm, suicidal or homicidal disclosures will be shared with DBH personnel. Results of the screening labs and GGT testing will be placed in the participants' AHLTA record and will be available to any of the participant's other Army health care providers or any health care providers to whom a participant releases his/her medical records.

14.3
Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

All study information will be recorded on standardized case report forms (CRFs). CRFs will be labeled with study code number only. Code numbers will be assigned sequentially and will not include participant initials or any other identifiers.

Data will be stored on a secure VA server with restricted access. Only the persons named on the Madigan and VA Puget Sound IRB applications will have access to the source documents and original research data. Data will not be revealed to insurance companies or other individuals or organizations. The code list will be stored on a VA Puget Sound server in a restricted-access folder, which is only accessible by persons named on the protocol. The VA Puget Sound server complies with current Federal standards.

Identifying information will be kept in the participants' paper study source document file. The research files will be transported the same day from JBLM, a Joint Commission compliant records storage facility, to the VA Puget Sound Seattle, a Joint Commission compliant records storage facility. The research files will be transported in HIPAA compliant secured containers by selected members of the study staff and will only be accessible by IRB approved study staff. No research records will be left unattended or unsecured overnight off-site of either JBLM or VA Puget Sound Seattle medical treatment facilities. The research charts and case report forms must be stored at VA Puget Sound because most of the study personnel are located there and must be able to contact participants when necessary to schedule appointments and in case a participant reports an adverse event. Participants are instructed to call VA Puget Sound staff in these cases. Providers for this study are located in offices at JBLM and VA Puget Sound. If at any time information contained in a participant's research chart is required, it can be faxed to the PI. As the study providers are located at multiple locations, the study team will meet on a weekly basis to discuss study participants and any study concerns. This will help the PI to be continually informed regarding all current participants. The files should be most accessible to those who are most likely to respond to the participant needs.

The lead study coordinator, site investigator and overall PI are all responsible for ensuring the continued security of the research records.

14.4
Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Through participation in this research, all participants will receive additional monitoring and visits in addition to their customary treatment for AUD. Participants will get thorough medical and psychiatric assessments, which may benefit them by providing them information about these assessments. It is possible that participants in the prazosin group will experience additional benefit resulting in reduced alcohol use and decreased PTSD symptoms. Society at large will benefit if improved treatments for AUD are discovered through this research.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

SMs engaged in DBH treatment programs who have reported alcohol issues will be asked if they are willing to speak to a research team member about potential participation in the study. If the individual agrees, the staff member will make the referral by contacting the research team. Study personnel will give a brief overview of the study and ask whether the individual is still interested. For individuals who want to learn more, and who meet basic prescreening inclusion criteria, an appointment will be scheduled with a trained investigator who will explain the study in detail and obtain written informed consent as described below. Potential participants who self-refer to the study will be given information about the study and DBH alcohol treatment options.

The study will be explained to eligible participants by one of the approved study personnel in a private setting. DBH personnel will not conduct the initial consent visit.
Although SMs may have command requirements to complete the clinical outpatient JBLM assignment to the SUDCC programs, command pressure to participate in this research study will be strictly avoided.

All study visits occur in private clinic spaces.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

It is possible that participants in the prazosin group will experience additional benefit resulting in reduced alcohol use and decreased PTSD symptoms.

Participants will be monitored at each visit for adverse events. Any adverse event will be managed by the study team as clinically appropriate. If necessary, a participant will be referred for treatment of an adverse event.

At the study termination or the week 13 visit, all participants will be offered a follow-up appointment with a DBH provider or clinical health care providers. The blind will be broken at participant termination visit regardless of participant trial completion. (All raters will remain blind and will not be informed of any instances of breaking the blind).

We recognize that not breaking the blind for each participant until all participants have completed the protocol is ideal. However, the appropriate and safe method of initiating open-label prazosin by necessity differs depending on the study drug received in the double-blind study (prazosin or placebo).

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ○ DSMP
- ◉ DSMB
- ○ Both
- ○ Not Applicable

Describe the composition of your DSMB and how frequently it meets. Explain who will be responsible for ensuring data accuracy and integrity, how often interim data be reviewed - and by whom - and who will perform aggregate analysis of data and adverse events.

In addition to a Research Monitor (described below), a DSMB will be established for this study. The DSMB will consist of two psychiatrists who each have had extensive experience with performance and safety monitoring of clinical trials in psychiatric patient populations. The DSMB will review the Adverse Symptom Checklist performed at each study visit as well as results from the PCL-M, PHQ-9, and SIP. In addition, the DSMB will review compiled vital signs measurements for each participant and will review reasons for study termination for any participant who discontinues the study before completion. Data reviewed by the DSMB will be unmasked with respect to treatment group assignment (the unmasking will be performed by a person not otherwise connected with this study and the study investigators will remain blind). The DSMB will be provided with interim analyses of safety and efficacy data every six months after enrollment of the first participant. The Chair of the DSMB will generate a report of the review, including a recommendation for continuing or terminating the trial. Copies of these 6-month reviews will be sent to the study PI, the IRBs at VA Puget Sound and MAMC, and the VA Puget Sound Research and Development Committee. Upon request, the IRBs will also have access to study safety data at any time during the study.

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Serious adverse events (SAEs), both expected and unexpected, will be reported to the Principal Investigator (PI), or if not available, another clinician investigator immediately upon discovery. SAEs will be reported to the Madigan IRB/DCI within two business days of event discovery via memorandum in IRBNet. The research monitor will be notified of the submission. A copy of the report will also be sent to the VA Puget Sound IRB within five business days of the discovery of the event, per VA guidelines.

Unexpected, but not serious, adverse events, which the PI determines are related or possibly related to research participation, will be reported to the Madigan IRB/DCI within two weeks of event discovery. The research monitoineligibler will be informed of the event.

Unanticipated problems involving breach of confidentiality or HIPAA violation or any other risk to the health or welfare of participants that the PI determines are related or possibly related will be reported to the Madigan IRB/DCI within two weeks of event discovery. The research monitor will be informed of the event.

Expected adverse events, which are not serious and possibly related to research participation, will be reported to the Madigan and VA Puget Sound IRBs on the annual report.

All other adverse events or problems that the PI determines are unrelated to research participation will be reported to the Madigan IRB/DCI with the annual report.

All reports to the Madigan IRB/DCI will occur by memorandum submitted in IRBNet. A summary of all above reports will be sent to the Madigan and VA Puget Sound IRBs with the annual report.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

☐ Are drug(s) in this research being used in accordance to the approved labeling?
☑ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** prazosin **Generic Drug Name:** **Investigational Drug Name:**	Yes	Yes	

Trade Drug Name:	prazosin
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Teva

Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	N/A
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	This study will be conducted using the drug, prazosin, which has been approved by the FDA for the following indication(s): treatment of hypertension. Pursuant to AR 40-7, paragraph 4-12, "Use of an Approved Drug for an Unapproved Indication," this study does not require the acquisition of an IND number from the FDA. All conditions listed in this paragraph as "a-e" are met by this clinical investigation. Additionally, Department of Health and Human Services "Investigational Use of Marketed Products" guidelines, dated February 1989, indicate an IND number is not required in the conduct of this study. (a) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor intended to be used for any other significant change in the labeling for the drugs. (b) The drugs undergoing investigation are lawfully marketed as prescription drug products, and the investigation is not intended to support any other significant change in the advertising for the drug products. (c) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug products. (d) The investigation is conducted in compliance with the requirements for human use review and informed consent set forth in AR 40-38. (e) The drug is not represented in a promotional context as being safe or effective for the purposes for which it is being investigated.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	1 mg to 20 mg
Frequency:	3 times/day
Route of administration:	oral
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Madigan IND pharmacy packaged in blister cards
Indication(s) under Investigation:	Alcohol Use Disorders
Where will the drug be stored	Madigan IND pharmacy
Drug Storage Restrictions (including temperature, etc.):	

Administration Instructions:	drug taken by mouth 3 times per day
Possible Untoward Effects, Their Symptoms & Treatment:	In clinical trials of prazosin, the most frequent adverse reactions were: dizziness (10%), drowsiness (8%), headache (8%), lack of energy (7%), weakness (7%), palpitations (7%), and, nausea (5%). Less frequent adverse reactions (1-4%) reported in clinical trials were: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency, blurred vision, reddened sclera, epistaxis, dry mouth, and nasal congestion. Fewer than 1% of patients have reported the following (causal relations sometimes not established): abdominal discomfort or pain, liver function abnormalities, pancreatitis, tachycardia, paresthesias, hallucinations, pruritus, alopecia, lichen planus, incontinence, impotence, priapism, tinnitus, diaphoresis, fever, positive ANA titre, and arthralgia. Prazosin may cause syncope. In most cases this is believed to be due to excessive postural hypotension although occasionally the syncopal episode has been preceded by severe tachycardia with heart rates of 120-180 beats per minute. Syncopal episodes have usually occurred within 30-90 minutes of the initial dose. The incidence of the syncopal episodes is 1% if the initial dose is 2 mg or more. Clinical trials suggest that syncopal episodes can be minimized by starting with a dose of 1 mg and slowly titrating up to the final dose, as we are doing in this study. In post-marketing experience, Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients who are taking or have taken alpha-1 blockers. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique to reduce the surgical risk of IFIS. If a patient needs to have cataract surgery, he/she should tell his/her eye surgeon that he/she may have taken prazosin in a research study.
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	N/A
Contraindications and Interactions, If Known:	There are no known absolute contraindications to prazosin. Prazosin should not be taken concurrently with trazodone. Potential participants who are taking trazodone for sleep and who are willing to discontinue will be washed out before starting this study. Care should be taken when alpha-1 blockers are combined with erectile dysfunction medications. We will be following VA pharmacy prescribing guidelines regarding these medications. Erectile dysfunction medications will not be allowed during the titration period. Once stable dose has been reached, participants will be allowed to use ED drugs at half the usual clinical dose. Use of bodybuilding/weightlifting supplements with vasodilator properties when combined with prazosin may cause priapism.
Investigators Authorized to Prescribe:	Colin Daniels, Kris Peterson, Kim Hart, Rebecca Hendrickson, David Hoff, Cynthia Mayer, Elaine Peskind, Murray Raskind, Garth Terry

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

Serious adverse events (SAEs), both expected and unexpected, will be reported to the Principal Investigator (PI), or if not available, another clinician investigator immediately upon discovery. SAEs will be reported to the Madigan IRB/DCI within two business days of event discovery via memorandum in IRBNet. The research monitor will be notified of the submission. A copy of the report will also be sent to the VA Puget Sound IRB within five business days of the discovery of the event, per VA guidelines.

Unexpected, but not serious, adverse events, which the PI determines are related or possibly related to research participation, will be reported to the Madigan IRB/DCI within two weeks of event discovery. The research monitoineligibler will be informed of the event.

Unanticipated problems involving breach of confidentiality or HIPAA violation or any other risk to the health or welfare of participants that the PI determines are related or possibly related will be reported to the Madigan IRB/DCI within two weeks of event discovery. The research monitor will be informed of the event.

Expected adverse events, which are not serious and possibly related to research participation, will be reported to the Madigan and VA Puget Sound IRBs on the annual report.

All other adverse events or problems that the PI determines are unrelated to research participation will be reported to the Madigan IRB/DCI with the annual report.

All reports to the Madigan IRB/DCI will occur by memorandum submitted in IRBNet. A summary of all above reports will be sent to the Madigan and VA Puget Sound IRBs with the annual report.

18.5 Sponsor (organization/institution/company):

☐ N/A

If applicable, provide sponsor contact information:

DoD CDMRP--USAMRMC
Brittanē Foy
Human Subjects Protection Scientist
General Dynamics Health Solutions (GDHS)
Human Research Protection Office (HRPO)
Office of Research Protections (ORP)
U.S. Army Medical Research & Material Command (USAMRMC)
Fort Detrick, Maryland
Email: Brittane.S.Foy.CTR@MAIL.MIL
Phone: 301-619-2286 or DSN 343-2286
Fax: 301-619-7803 or DSN 343-7803
Mailing Address:
Commanding General
U.S. Army Medical Research and Material Command
ATTN: MCMR-RPH/Brittane Foy
810 Schreider Street
Frederick, Maryland 21702-5012

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

○ Registration is not required
○ Registration pending
◉ Registration complete

"NCT" number:

NCT02226367

19.2 Defense Technical Information Center Registration (Optional):

◉ Registration is not required
○ Registration pending
○ Registration complete

20.0

References and Glossary

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20.2 Abbreviations and Acronyms: