Title: CAP: Doxazosin in the Treatment of Co-Occurring PTSD and Alcohol Use Disorders
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# RESEARCH PLAN

## BACKGROUND AND SIGNFICANCE

**Overview.** Since 2001, more than 2.6 million U.S. military personnel have been deployed to Afghanistan and Iraq (IOM, 2014), and an increasing number of Veterans are returning home with posttraumatic stress disorder (PTSD) and alcohol use disorders (AUD). There are substantial gaps in the evidence base regarding the treatment of co-occurring PTSD and AUD, particularly pharmacotherapeutic treatment. This study, which is part of the Consortium to Alleviate PTSD (CAP), directly addresses this research gap by testing the efficacy of doxazosin for the treatment of co-occurring PTSD and AUD among U.S. military Veterans (including National Guard and Reservists). In addition, functional magnetic resonance imaging (fMRI) will be employed pre- and post-treatment to investigate clinically relevant biomarkers as diagnostic and prognostic indicators of co-occurring PTSD and AUD.

**PTSD among Veterans.** PTSD is the most common mental health disorder among Veterans presenting for treatment at VA hospitals (Seal et al., 2007). PTSD is a chronic, debilitating psychiatric condition that may develop after direct or indirect exposure to traumatic events, and it is characterized by: (1) intrusive symptoms (e.g., memories, nightmares); (2) avoidance (e.g., avoiding people, places or situations that are reminders of the event); (3) negative cognitions and mood (e.g., thoughts and feelings related to guilt and shame); and (4) alterations in arousal and reactivity (e.g., trouble sleeping, aggression, exaggerated startle response). Combat and peacekeeping missions over the past decade have been characterized by high levels of exposure to violence, including life threatening patrols and direct fire, witnessing violence, and receiving hostile responses from civilian populations. The majority of military personnel serving in Iraq report being attacked or ambushed (92%); receiving incoming artillery, rocket or mortar fire (89%); being shot at or receiving small-arms fire (95%); or knowing someone who was seriously injured or killed (87%) (Hoge et al., 2007). Exposure to such events has been associated with increased risk for PTSD. Among the general population, the current (past 12 months) rate of PTSD is estimated to be 3.5% (Kessler et al., 2005). In comparison, a large-scale investigation of over 88,000 Veterans serving in the Iraq war found that 16.7% had symptoms of PTSD at six months post-deployment (Milliken et al., 2007). Similarly, among 1,965 OEF/OIF service members across branches of service and rank, and from 24 geographic areas, approximately 15% were estimated to have PTSD (Tanielian et al., 2008). Almost half (45.7%) of military personnel with PTSD remain symptomatic three years later (Smith et al., 2008).

**AUD among Veterans.** Like PTSD, substance use disorders are chronic, debilitating and relapsing conditions. Symptoms of AUD include, for example, drinking more than intended; exhibiting the need for markedly increased amounts of alcohol in order to achieve the desired effect (tolerance); unsuccessful efforts to cut down or quit; cravings to consume alcohol; withdrawal symptoms upon cessation of use; continued use despite having problems caused or exacerbated by alcohol (e.g., depression, liver function impairment, interpersonal conflict); and using alcohol in situations in which it is physically hazardous (e.g., driving a car). Epidemiological data show that rates of substance use disorders are significantly higher among military as compared to civilian populations. Data from the National Survey on Drug Use and Health indicate that approximately 7.1% of Veterans (~1.8 million persons) meet criteria for a current (past 12 months) substance use disorder (SAMHSA, 2007). This rate is almost twice as high as data from the National Comorbidity Survey Replication (*N*=9,282) study, which estimated rates of past 12 months substance use disorders in the general population to be 3.8% (Kessler et al., 2005). Furthermore, examination of substance use disorder rates in Veterans 18–53 years of age reveals a current prevalence rate of 18.2%, which is almost five times as high as the general population (SAMHSA, 2007). AUD is the most common type of substance use disorder among military personnel and Veterans (IOM, 2013). In a recent report by the Institute of Medicine (IOM, 2012) substance abuse in the armed forces was described as a "public health crisis," stemming largely from highly preventative problematic use of alcohol (Bray et al., 2009; Burnett-Zeigler et al., 2011). High rates of binge alcohol use have been observed (21.0%-22.6% in past month; Bray et al., 2010; Wagner et al., 2007), particularly among Veterans serving in the Marine Corps (25.2%) or Army (21.6%) (IOM, 2012). Numerous research documents that deployments and combat exposure are associated with increased rates of binge drinking and alcohol-related problems (Bray et al. 2009; Russell et al., 2014; Spera et al., 2011).

AUD is a significant economic and health burden to our nation's military health care system. In 2011, the DOD examined the relative health care burden among the armed services, grouping all medical encounters into 139 diseases based on ICD-9 codes. The health care burden attributable to a disease was determined by (1) total number of medical encounters (e.g., hospitalizations, ambulatory visits), (2) total number of service members affected, (3) total bed days during hospitalization, and (4) total number of lost duty days. Out of 139 diseases, the health care burden of substance use disorders ranked 7th for medical encounters (395,021 encounters in 2011) and 1st for hospital bed days (53,589 bed days in 2011) (IOM, 2012). Medical problems associated with encounters for AUD included withdrawal and detoxification, alcohol poisoning, liver disease, cardiomyopathy, alcoholic gastritis, and polyneuropathy. Furthermore, data from 2001-2010 revealed that the number of bed days attributable to chronic AUD roughly quadrupled over the 10-year period (IOM, 2012). These findings highlight the critical need for emphasis on the development of effective interventions to reduce the burden and costs associated with AUD. While the VA and DOD have made significant gains toward expanding access to care and increasing the use of evidence-based practices for substance use disorders (VA & DOD, 2009), significant gaps remain and there is an urgent need for the development of more effective treatments.

**Comorbidity of PTSD and AUD**. Extensive literature documents a strong association between PTSD and substance use disorders (Back et al., 2000; Sofuglu et al., 2014; Torchalla et al., 2012; van Dam et al., 2012). Initial reports among military personnel focused on Vietnam Veterans with PTSD, in which up to 84% met lifetime criteria for an AUD (Keane & Kaloupek, 1998). More recently, data from the Department of Veterans Affairs indicate that, among Veterans serving in the Vietnam era or later (N=1,001,996), 41.4% of Veterans with substance abuse were also diagnosed with current PTSD (Petrakis et al., 2011). Of particular relevance to the proposed project, Norman and colleagues (2013) recently examined risk factors for continued substance use problems among 1,599 Veterans at 1-year post separation. The findings demonstrated that higher PTSD symptom scores were a significant predictor of continued substance use problems following military discharge. A number of studies provide evidence suggesting that Veterans with PTSD and AUD often use alcohol to "self-medicate" (Khantzian, 1985) symptoms of PTSD (e.g., to sleep and not remember nightmares, to "numb out" and forget the event, or to socialize with others) (Kehle et al., 2011). In both Veteran and non-Veteran populations, research demonstrates a more complicated clinical course and worse treatment outcomes in persons with comorbid PTSD and addiction, compared to those with either disorder alone (Back, 2010; Ouimette et al., 2003). A series of associated problems are common among individuals with dually diagnosed PTSD and AUD, including medical problems, family dysfunction, homelessness, HIV risk behavior, and poor quality of life (Back et al., 2000, 2014; Blanco et al., 2013; Mills et al., 2014; Ouimette et al., 2003). Veterans with co-occurring PTSD/AUD have poorer treatment outcomes on multiple indices of functioning, including more social and legal problems, suicide attempts, and violence, and they tend to have a longer duration of substance use and undergo more episodes of substance abuse treatment (Ouimette et al., 2003; Young et al., 2005).

**Corticolimbic Circuitry Dysregulation**. Converging research suggests that both PTSD and AUD are associated with impaired prefrontal cortex (PFC) regulation of limbic brain regions, in particular the amygdala (AMY). The AMY plays a crucial role in threat perception, fear conditioning, emotional salience, and heightened memory for emotional events (Pitman et al., 2012). The PFC is responsible for disrupting habitual or compulsive behaviors that are not adaptive (e.g., compulsive alcohol use) (Pitman et al., 2012). Dysregulation of the PFC-AMY circuitry (i.e., lack of "top down" control) likely makes it difficult, therefore, to inhibit or modulate obsessive cognitions such as intrusive trauma-related memories or craving-related thoughts, as well as repetitive behaviors such as compulsive alcohol use (Goldstein & Volkow, 2011). Compared to controls, Veterans and civilians with PTSD exhibit hyperactive AMY and hypoactive medial PFC (mPFC) activity (Huang et al., 2014; Pitman et al., 2012), and significant uncoupling between the mPFC and the AMY during symptom provocation and at rest (Sripada et al., 2012). Of interest, individuals with substance use disorders also demonstrate lower PFC-AMY functional connectivity (Gu et al., 2010). Importantly, in a recent study in cocaine-dependent individuals, attenuated PFC-AMY connectivity was shown to be a marker of early relapse risk (McHugh et al., 2014). Another study found that chronic alcohol use generates long-term plasticity in the mPFC and impair fears extinction, suggesting that alcohol may exacerbate the pathophysiology of PTSD or impair recovery from PTSD (Holmes et al, 2012).

**Noradrenergic Modulation of Corticolimbic Circuitry.** The noradrenergic system plays a key role in stress, and noradrenergic dysregulation has been consistently demonstrated in both PTSD and withdrawal states from chronic alcohol and other substances. The AMY provides bottom-up regulation of the PFC both directly through efferent projections to cortical sensory regions, and indirectly through brain arousal systems including the locus coeruleus that sends noradrenergic drive to regions of the mPFC (Holland et al., 1999). Central noradrenergic tone plays an important role in executive control, cognitive flexibility, selective attention and arousal (Aston-Jones et al., 2005), and increases in noradrenergic activity have been implicated in hyperarousal, flashbacks, and heightened physiologic responses to trauma cues (Southwick et al., 1999). In addition, provocation of the noradrenergic system with the alpha2-noradrenergic antagonist yohimbine increases anxiety and corticolimbic brain activity in Veterans with PTSD, but not controls (Bremner et al., 1997). These data suggest that PTSD is associated with increased central noradrenergic tone. Increases in noradrenergic tone in regions of the extended AMY have been implicated in drug-seeking behavior (Erb et al., 2000). In addition, drug-related cues have been found to increase noradrenergic activity in individuals with addiction (Sinha et al., 2009). These findings strongly suggest that therapeutic interventions targeting the noradrenergic system may help decrease PTSD and AUD symptom severity by decreasing the AMY response to provocation and normalizing corticolimbic connectivity.

**Pharmacologic Treatment of Comorbid PTSD and AUD**. The pharmacologic treatment of PTSD is an area of intense investigation. While many medications have been investigated, only the serotonin specific reuptake inhibitors (SSRIs) have received FDA approval. However, SSRIs are of limited efficacy for the military (Hertzberg et al., 2000; Friedman et al., 2007), as SSRIs are more effective in women than men, and more effective in treating acute as compared to chronic PTSD. Furthermore, there has been little investigation of the pharmacologic treatment of co-occurring PTSD and AUD, and the few studies that have been conducted suggest only a modest response at best (Batki et al., in press; Brady et al., 2005; Foa et al., 2013; Petrakis et al., 2012; Sofuoglu et al., 2014).

Prazosin, a postsynaptic alpha-1 adrenergic receptor antagonist which is FDA-approved for hypertension, has been shown to improve sleep and nightmares in military personnel with PTSD (Raskind et al., 2007, 2013). In addition, a pilot study of 24 alcohol-dependent participants without PTSD found improvement in alcohol-related outcomes with prazosin as compared to placebo (Simpson et al., 2009). In a small (N=30), as yet unpublished placebo-controlled, randomized trial of prazosin for PTSD and AUD, Saxon (Consultant on this project) and colleagues found decreases from baseline to week 6 in the number of standard drink units per week from 80.2 (SE=11.2) to 5.3 (SE=14.5) in the prazosin group, compared to 50.7 (SE=11.2) to 29.6 (SE=11.8) in the placebo group (p=0.004). *Notably, PTSD symptoms did not change significantly in either the prazosin or placebo group in this comorbid sample.* Preclinical data demonstrate attenuation of cocaine-induced reinstatement in rats treated with prazosin (Zhang & Kosten, 2005). A significant limitation of prazosin, however, is its short half-life (2-3 hours) which requires TID (3x/day) dosing.

Doxazosin is a promising candidate to alleviate both PTSD and AUD. Doxazosin also is a selective postsynaptic alpha-1 antagonist and is FDA-approved for the treatment of hypertension. In contrast to prazosin, however, doxazosin has a much longer half-life of 22-30 hours that allows for a once per day dosing. *This significantly enhances the ability of doxazosin to be easily transferred to VA hospital settings and patient populations, and increases its potential for efficacy both as a treatment for PTSD and for AUD.* In a 12-week, open-label pilot trial of doxazosin (8 mg/day) in 12 individuals with PTSD (27% with combat-related PTSD), De Jong and colleagues (2010) found significant reductions in Clinician Administered PTSD Scale (CAPS) total scores by 68% from baseline to week 12, as well as significant improvement in sleep. In a recent, double-blind, placebo-controlled trial (Shorter, Lindsay & Kosten, 2013) in 30 cocaine-dependent Veterans, doxazosin (8 mg/day) was found to increase consecutive weeks of abstinence (cocaine-negative urines) significantly more than placebo (44% vs. 7%). Recent preclinical data also suggest that doxazosin may be an important new approach to the effective treatment of AUD. O'Neil and colleagues (2013) found that treatment with doxazosin resulted in significantly reduced alcohol intake in rats and did not affect locomotor activity. These findings suggest that noradrenergic medications may be effective in reducing PTSD as well as AUD severity and improving treatment outcomes for dually-diagnosed patients. While prazosin has been more widely studied, doxazosin warrants further investigation because its longer half-life suggests possible superior efficacy over prazosin and

makes implementation and adherence more likely if the results of this study support possible efficacy in treatment.

**Pharmacologic and Clinical Properties of Doxazosin.** Doxazosin is a quinazoline compound that is a selective inhibitor of the alpha-1 subtype of alpha-adrenergic receptors. The chemical name is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The molecular formula for doxazosin is $C_{23}H_{25}N_5O_5 \bullet CH_4O_3S$ and the molecular weight is 547.6. Doxazosin is used clinically to treat hypertension and improve urination in men with benign prostatic hyperplasia. Peak plasma levels occur at 2-3 hours after oral administration. Plasma elimination of doxazosin is biphasic, with an elimination half-life of 22-30 hours, which is not influenced by age, renal function or dose. Doxazosin is available in the U.S. as a prescription product for oral use. The most frequently reported adverse reactions include headache (10-14%), dry mouth (2-11%), tiredness (5-12%), dizziness (15%), hypotension (1.7%) and nausea/vomiting (2-4%) (De Jong et al., 2010; Shorter et al., 2013).

## RESEARCH DESIGN AND METHODS

**Overview.** This study is a Stage II double-blind, 12-week, randomized controlled trial of the effects of the alpha-1 adrenergic antagonist, doxazosin (immediate release formulation), as compared to placebo in reducing PTSD symptomatology and substance use severity in Veterans with co-occurring PTSD and substance use disorders (SUD). Participants may also complete neuroimaging scanning sessions prior to and following treatment.

**Subjects.** Participants will be 144 treatment-seeking Veterans with current PTSD and SUD. Subjects taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks or more, based on clinical judgment, before treatment initiation. Primary exclusions include bipolar disorders; previous treatment with doxazosin; adverse reactions to quinazolines or other alpha-1-antagonists; and abnormal liver function tests. Additional inclusion and exclusion criteria can be found in the Human Subjects section.

**Recruitment.** The recruitment sites will be the outpatient Ralph H. Johnson's VAMC and the affiliated Community Based Outpatient Clinics (CBOCs). The primary recruitment clinics will be the Substance Treatment and Recovery (STAR) program which is directed by Karen Hartwell, MD and the Primary Care Mental Health Integration (PCMHI) program, directed by Daniel Gros, PhD. Dr. Back is a Staff Psychologist in the STAR program. We will also place IRB-approved recruitment flyers in prominent locations (a) throughout the Charleston VA hospital, including the PTSD Clinic, Women's Health Clinic, Pain Clinic, Primary Care, and Emergency Department; (b) in affiliated CBOCs; (c) throughout the MUSC hospital, including the Center for Drug and Alcohol Programs, and the National Crime Victims Treatment Center. Further, participants who have consented to be contacted for future research studies will be recruited via telephone screening and/or e-mails using an IRB approved script. These individuals will be referred to us via EPIC; only individuals who have previously agreed to be contacted for research opportunities within their MUSC medical records will be identified. We will place advertisements on social networking sites (e.g., Craig's List, Facebook) and in local newspapers. Once a HIPAA waiver is established, we will send recruitment letters to the veteran list supplied by the VAMC followed by a follow-up phone call seven days after each letter is mailed. Study participants will also have the option to recruit other subjects for the study. If they choose to do so, they will be provided study information to give to other individuals that may be eligible and interested in participating. These individuals will not be identified unless they contact the study staff themselves. For any referrals that result in the successful enrollment of a new subject, the referring participant will receive $10. Participation in this recruitment process will be completely voluntary and will not affect participation in the study.

**General Procedures.** Figure 4 illustrates the study procedures and design. Interested individuals will be screened either by telephone or in person. Individuals who meet inclusion/exclusion criteria will be invited to come into the office for a comprehensive baseline assessment. Potential subjects will be given a full description of the study and asked to read and sign VA and MUSC IRB-approved informed consent forms before any study procedures or assessments are conducted. Ineligible individuals will be referred clinically for treatment. Consent will take place in a private office and will be conducted by trained staff, including the PI, Co-Is, Study Coordinator,

or Research Assistant. Baseline screening will involve further verification of diagnostic conditions (PTSD, SUD), a medical history and physical exam, assessment of concomitant medications, and breathalyzer and urine drug tests. Self-report measures of PTSD, substance use severity and other associated mental and behavioral problems (e.g., depression, anxiety, sleep functioning) will also be assessed at baseline and throughout the trial.

Complete medical evaluations will be conducted at baseline. This evaluation will include: physical examination including neurological examination; vital signs including orthostatic blood pressure and pulse measurements; weight and BMI calculation; and urine β-HCG in women with child-bearing potential. Laboratory testing including complete metabolic panel to include liver function test as well as an electrocardiogram will be conducted at baseline to ensure study eligibility. At other study visits conducted in person or via telehealth/phone, abbreviated assessments and adverse events will be reported and vital signs may also be recorded (e.g., blood pressure). Following the baseline visit, eligible participants may complete a neuroimaging session (described in the Neuroimaging Component section) and will then enter a 12-week, double-blind, placebo controlled medication trial during which they may be seen up to twice weekly for dosing and completion of assessments. Participants may complete another neuroimaging session during the last week of treatment. Then, participants may be seen again for a 6-week, post-treatment follow-up visit.

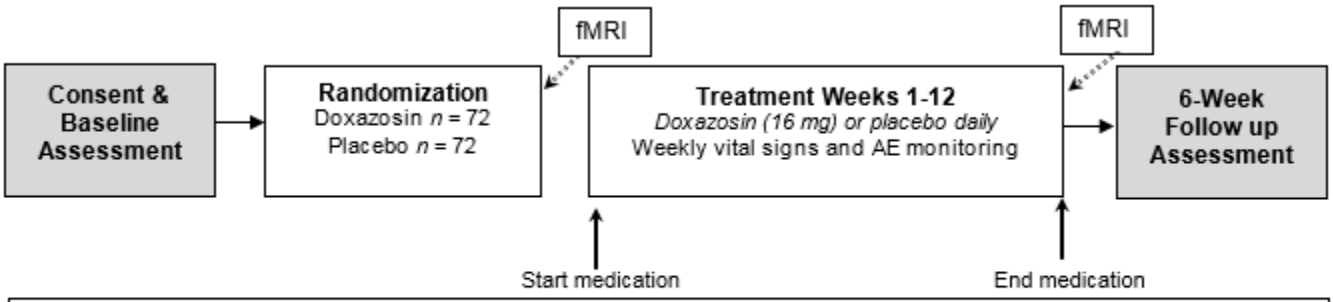


**Figure 4.** Study design overview. Participants randomized to 12 wks of doxazosin (16 mg) or placebo. Up to twice weekly visits during wks 1-12, and a 6-week follow up. Neuroimaging scan prior to treatment initiation and again during week 12 prior to medication discontinuation.

**Telephone Assessment:** Participants in this research study may choose to do some of the weekly study visits via telephone, which may enhance retention by directly circumventing financial, transportation or other barriers associated with traveling to MUSC/VA clinics for in-person appointments. Telephone assessments will be delivered via MUSC/VA approved telephones.

**Study Medication, Dosage, and Administration.** Study medications will be prepared in the Compounding Lab at Plantation Pharmacy 531 Wappoo Rd Charleston SC 29407. Plantation Pharmacy is a licensed Community and Compounding Pharmacy that is inspected regularly by the South Carolina Board of Pharmacy as both a retail pharmacy and a compounding pharmacy. Plantation Pharmacy is also a member of a national compounding supply, support, and education, company called Professional Compounding Centers of America (PCCA). Pharmacy staff involved in preparation of study medication are trained in the science and art of compounding and maintain all licensure and continuing educations requirements as dictated by the South Carolina Pharmacy Practice Act. Study medication and matching placebo will be encapsulated in standard-sized gelatin capsules, and be of sufficient opacity and color so as not to reveal contents inside or disclose any possible difference between placebo and active capsules. Commercially available doxazosin 8 mg tablets supplied by the primary investigators (DAVA 8mg tablets NDC 67253-0383-10) will be utilized as the source for active drug material for all strengths involved in the study. The tablets will be triturated to a fine, uniform powder to provide for the active ingredient source material. Capsule packing statistics been determined for each powdered component in the capsules. Each study capsule will contain 25 mg of riboflavin USP. The remaining volume in each capsule not utilized by active material and riboflavin will be back-filled to proper packing level with an inert filler of dextrose. Placebo capsules will consist of 25 mg riboflavin and be back-filled with dextrose in color-matched, opaque, identically sized capsules. Participants will be randomly assigned to receive doxazosin (target

dose of 16 mg/day) or placebo. This dose was selected based on previous research (Kenna et al., 2015; Rodgman et al., 2015). Side effects and adverse events will be evaluated weekly. Identical matched placebos will be used. Doxazosin will be initiated at 1 mg/day and then titrated up to 16 mg/day as tolerated. Research staff will dispense the study medication or placebo at the weekly visits or by mail. Participants will be instructed to self-administer the study medication or placebo each day, with or without food. Subjects will be maintained at the target dose for 6 weeks (through week 12). A one-week downward titration for safety will occur at the end of week 12 (Kenna et al., 2015). Riboflavin (25 mg) will be administered as a biomarker for medication compliance. Participants who wish to take a multivitamin during the treatment phase of the study will be given a multivitamin that does not contain riboflavin. Treatment assignment will follow a pre-arranged randomization scheme and be carried out by a VA research pharmacist not involved in clinical management of participants (to preserve the double-blind design).

**Subject Compensation.** Participants will receive $40 for the baseline visit. They will be given a $25 bonus if the baseline/first visit is attended as scheduled. They will receive up to $560 for completion of up to twice weekly visits during the 12-week treatment phase. Participants will receive $100 for the 6-week follow-up visit. If participants are eligible and interested in the neuroimaging phase, they will receive $25 for the imaging script visit and $70 for each scanning visit. Thus, the total amount subjects may receive for all visits is $890, or $725 without the imaging phase. Participants who are eligible and interested in the neuroimaging phase, who live more than 60 miles from Charleston, SC, may be eligible to receive $325 additional compensation for each scanning visit for time and travel. For these individuals, the total amount subjects may receive for all visits (including imaging phase) is $1540. Additionally, participants have the option to refer other Veterans to the study. For each referred individual who is enrolled in the study, the referring participant will receive a $10 bonus.

**Assessment Instruments.** The instruments to be used (see Table 1) were selected in consultation with Dr. Brett Litz (Director, CAP Assessment Core) in order to ensure the use of common data elements (CDEs). The use of CDEs across studies is one of the action tasks outlined in the National Research Action Plan (NRSA, 2013); it will allow for more coordinated research efforts and uniformity of instrumentation across CAP-specific projects as well as other PTSD trials conducted nationwide. The use of CDEs will allow investigators to integrate and share data, which will ultimately accelerate understanding of the characteristics and underlying mechanisms of PTSD and co-occurring conditions, such as SUD. Many of the instruments in Table 1 are standardized, widely used, and have been previously used by the investigative team. The primary clinical outcomes include: (1) PTSD symptom severity (CAPS-5 total score) and (2) substance use severity (TLFB).

***General Diagnostic and Inclusion/Exclusion Criteria***

- Demographics and Military Service Characteristics Form**:** This form measures demographics (e.g., race, gender, age, education) and military service information, such as branch and rank.
- Mini International Neuropsychiatric Interview 7.0 (MINI 7.0; Sheehan et al., 1998): The MINI is a standardized structured interview used to assess psychiatric diagnoses. The MINI is similar in sensitivity, specificity, and inter-rater reliability to other more lengthy diagnostic interviews, such as the Structured Clinical Interview for DSM-IV (Sheehan et al., 1998). This instrument will be used to diagnose SUD and will confirm other exclusionary psychiatric diagnoses such as bipolar disorders. The MINI 7.0 will have a modified timeframe (from 12 months to 6 months) to assess current SUD.
- Treatment Services Tracking Form: This form measures the amount of treatment a participant has engaged in. This will measure how many AA/NA meetings, case management appointments, psychotherapy appointments, etc.

***Vital Signs, Adverse Events and Medication Compliance***

- Vital Signs: Orthostatic blood pressure, pulse measurements, weight and body mass index (BMI) calculations will be recorded at baseline, weekly during treatment, and at post-treatment follow-up.
- Adverse Events (AEs): AEs will be assessed at baseline, weekly during treatment, and at follow-up. The type of AE, severity of the AE, duration of the AE, and relationship of AE to study medication will be recorded. The Study Physician (Dr. Hamner) will evaluate and manage, as appropriate, reported AEs. All AEs, serious AEs (SAEs) and Unanticipated Problems Involving Risk to Subjects or Others (UPIRSOs) will be reported to the Consortium, DSMB, and the local IRB according to policies and procedures required by these entities.

- Concomitant Medications: All concomitant medications will be recorded on a standard form throughout the study. Multivitamins supplied by the study will be recorded and inquiries will be made about daily compliance.
- Medication Accountability Log: This is a document describing a one-week schedule recording days of study medicine taken. Returned medication packages will have capsules counted and recorded.
- Patient Blind Questionnaire: This is a document asking the participant which medication he or she believed they received during the medication phase of the study.

**Table 1. Assessment Instruments and Timeline**

| | BSL | Medication Initiation | Medication and Symptom Monitoring | | | | | | | | | | | | F/U |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week → | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 18 |
| Informed Consent | X | | | | | | | | | | | | | | |
| Demographics & Military Service Characteristics Form | X | | | | | | | | | | | | | | |
| History and Physical Examination | X | | | | | | | | | | | | | | |
| Health Questionnaire | X | | | | | | | | | | | | | X | X |
| MINI International Neuropsychiatric Interview (MINI) 7.0 | X | | | | | | | | | | | | | | |
| Adverse Events/Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications Form | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medication Adherence Log | | | 2x | 2x | 2x | 2x | x | x | x | x | x | x | x | 2x | |
| Riboflavin in Urine | | X | | | | X | | | | X | | | | X | |
| Breathalyzer | X | X | 2x | 2x | 2x | 2x | x | x | x | x | x | x | x | 2x | X |
| Urine Drug Screen | X | | X | | | X | | | | X | | | | X | X |
| Pregnancy Test for Female Subjects | X | | | | | X | | | | X | | | | | |
| Clinical Institute Withdrawal Assessment of Alcohol-Revised | X | | | | | | | | | | | | | | |
| Clinician Administered PTSD Scale (CAPS-5) | X | | | | | | | X | | | | | | X | X |
| Life Events Checklist for DSM-5 (LEC-5) | X | | | | | | | X | | | | | | X | X |
| Deployment Risk & Resiliency Inventory-2 (DRRI-2) Combat Experiences and Postbattle Experiences | X | | | | | | | | | | | | | | |
| PTSD Checklist (PCL-5) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Posttraumatic Cognitions Inventory | | X | | X | | X | | X | | X | | X | | X | X |
| Childhood Trauma Questionnaire (CTQ) | X | | | | | | | | | | | | | | |
| History of Head Injuries | X | | | | | | | X | | | | | | X | X |
| Time Line Follow-Back (TLFB) | X | X | 2x | 2x | 2x | 2x | x | x | x | x | x | x | x | 2x | X |
| Alcohol Use Disorders Identification Test (AUDIT)-Self Report | X | | | | | | | | | | | | | | |
| Quick Drinking Screen (QDS) self-report version | X | | | | | | | X | | | | | | X | X |
| Fagerstrom Test for Nicotine Dependence (FTND) | X | | | | | | | | | | | | | X | X |
| Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST) | X | | | | | | | | | | | | | X | X |
| Ethyl glucuronide (EtG) | X | X | | | | X | | | | X | | | | X | X |
| Visual Analog Scale (VAS) | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Health Questionnaire-9 (PHQ-9) | X | X | | X | | X | | X | | X | | X | | X | X |
| Generalized Anxiety Disorder (GAD) | X | | | X | | X | | X | | X | | X | | X | X |
| Veterans RAND 12 Item Health Survey (VR-12) | X | | | | | | | X | | | | | | X | X |
| Brief Inventory of Psychosocial Functioning (B-IPF) | X | | | | | X | | | | X | | | | X | X |
| Self-Injurious Thoughts and Behaviors Interview (SITBI) | X | | | | | | | X | | | | | | X | X |
| Depressive Symptoms Index – Suicide Subscale (DSI-SS) | X | | | X | | X | | X | | X | | X | | X | X |
| Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment short forms | X | | | | | | | X | | | | | | X | X |
| Frequency of Nightmares Questionnaire | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Insomnia Severity Index (ISI) | X | | | X | | X | | X | | X | | X | | X | X |
| Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen | X | | | | | | | | | | | | | | |
| Revised Conflict Tactics Scale (CTS2) | X | | | | | X | | | | X | | | | X | X |
| Addiction Severity Index – Family History Subscale | X | | | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Difficulties in Emotion Regulation Scale (DERS) | | X | | | | | | X | | | | | | X | X |
| Brief Addiction Monitor (BAM) | X | | | | | | | X | | | | | | X | X |
| Treatment Tracking Services Form | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Blind Questionnaire | | | | | | | | | | | | | | X | |
| fMRI Neuroimaging Procedures | ■ | | | | | | | | | | | | | ■ | |
| *BSL=Baseline. F/U = 6-Week Follow-Up.* | | | | | | | | | | | | | | | |

***Trauma History and PTSD***

- Clinician Administered PTSD Scale (CAPS; Weathers, Keane, & Davidson, 2001): The CAPS is a structured diagnostic interview and gold standard for assessing PTSD. It has excellent psychometric properties and diagnostic efficiency. The CAPS for DSM-5 (CAPS-5) was revised to accommodate changes made in DSM-5, reduce administration time, facilitate scoring procedures, and maintain backwards compatibility with the DSM-IV version (Weathers et al., 2013). The CAPS-5 will be administered by an independent evaluators (IE) trained and certified by the CAP Assessment Core and blind to treatment status.
- PTSD Checklist (PCL-5; Weathers et al., 2013): The PCL-5 is a 20-item self-report measure. The PCL-5 is similar in form to the PTSD Checklist (PCL) based on the DSM-IV (Weathers et al., 1993), which has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity. The past month version (assessing symptoms for the past month) will be used at baseline and follow-up sessions while the past week version (symptoms from the past week) will be used for weeks 1 – 12 of treatment.
- Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013): The LEC-5 assesses lifetime exposure to trauma. It includes the list of 16 different events from the original LEC (Gray et al., 2004). In addition, two items screen for military sexual trauma. The primary addition to the LEC-5 is a category involving occupational exposure (e.g., paramedic, police, military, or other first responder"). The psychometric properties of the LEC-5 have not yet been established, however the measure is nearly identical to the original LEC, which has been shown to demonstrate good convergence with the Traumatic Life Events Questionnaire (average kappa = 0.55) and correlate with the Posttraumatic Stress Disorder CheckList (reliability coefficients 0.34 to 0.48), and it demonstrates good test-retest reliability over 7-days.
- Childhood Trauma Questionnaire-Short Form (CTQ-SF; Bernstein et al., 2003): The CTQ is a 28-item self-administered inventory that assesses childhood abuse and neglect. The CTQ-SF is based on a 5-point Likert scale with response options ranging from *Never true* to *Very often true* and contains five subscales including physical, sexual, and emotional abuse, and physical and emotional neglect. The CTQ-SF exhibited good internal consistency with alphas ranging from .81 to .93 in a sample of substance abuse treatment seeking veterans (Bernstein et al., 2003).

***Substance Use***

- Time Line Follow-Back (TLFB; Sobell & Sobell, 1992): The TLFB obtains retrospective self-report of substance use by using a calendar and memory prompts to stimulate recall. Quantity and frequency assessments are made using this instrument (e.g., total number of standard drink units, percent of days using) as well as abstinence (yes/no). TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports. The TLFB will assess consumption of alcohol (standard drink units) and drugs for 60 days prior to starting the study, during the treatment and follow-up phase.
- Alcohol Breathalyzer Test will be used to measure subjects' blood alcohol concentration (BAC) when they come into the clinic. Samples reading >0.01 g/dl will be considered positive.
- Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001): The AUDIT is a 10-item self-report screening measure, developed by the World Health Organization (WHO), with three subscales (alcohol consumption, drinking behavior, and alcohol-related problems). Items are summed for a total score of 40. The AUDIT has good internal consistency (αs = .80-.93) as well as sensitivity and specificity.
- Addiction Severity Index—Family History Subscale; (Cacciola et al., 2007; McLellan et al., 1992): The ASI-Family History Subscale is a standardized, semi-structured interview that provides information regarding family history of drinking and drug use and treatment history.

- Quick Drinking Screen (QDS) self-report version. The QDS (Sobell et al., 2003) will be used to measure alcohol consumption. It consists of 4 items probing frequency and quantity of alcohol consumption. It will be administered in a self-report form. The QDS has been validated against the Timeline Followback daily estimation measure of alcohol use, and it shows good psychometric properties (Roy et al., 2008; Sobell et al., 2003). The QDS's time-frame will be modified to match the "last two weeks" probed by the mandated depression and anxiety instruments for CAP studies (PHQ-9 and GAD-7). Like these other measures, the QDS can be administered frequently throughout CAP trials to track changes in alcohol use.
- Urine Drug Screen (UDS) tests: Monthly urine samples may be collected at in-person office visits tested with a RapidCHECK® Multi-Drug Panel Test, which allows for the detection of THC/Marijuana, Cocaine, Phencyclidine, Opioids, Methamphetamines, Amphetamines, Barbiturates, and Benzodiazepines. The test uses concentrations levels established as standard minimums by the WHO.
- Fagerstrom Test for Nicotine Dependence (FTND). The Fagerstrom (Heatherton et al., 1991) is a 6-item self-report measure that assesses severity of nicotine dependence. Questions probe both quantity of nicotine use (e.g., number of cigarettes per day) and pattern of use (e.g., time to first cigarette in morning). Respondents choose among response options, each of which is assigned a numerical value, with higher numbers corresponding to greater nicotine dependence. Scores on all items are summed to create a severity index (0-2 = very low dependence; 3-4 = low dependence; 5 = medium dependence; 6-7 = high dependence; 8-10 = very high dependence). The Fagerstrom scale has been shown to have high convergent validity with biochemical indices of nicotine use, and the measure has shown acceptable internal consistency (Heatherton et al., 1991). A review of 26 studies of the psychometric characteristics of the Fagerstrom found that it is a reliable instrument for measuring nicotine dependence in diverse settings and populations (Meneses-Gaya et al., 2009).
- Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST). This is a modified version of the Fagerstrom Test that focuses on smokeless tobacco use, whereas the original Fagerstrom focuses exclusively on smoking. Like the FTND, the FTND-ST is a 6-item self-report measure of severity of nicotine dependence that has demonstrated convergent validity with biochemical indices of nicotine use (Ebbert et al., 2006; Ferketich et al., 2007). As on the original FTND, respondents choose among response options, each of which is assigned a numerical value, with higher numbers corresponding to greater nicotine dependence. Scores on all items are summed to create a severity index (range = 0–10).
- Clinical Institute Withdrawal Assessment of Alcohol-Revised (CIWA-Ar; Sullivan et al., 1989): The CIWA-Ar is a widely used, 10-item clinician administered instrument that will be used to assess alcohol withdrawal symptoms. Subjects experiencing significant withdrawal, as evidence by a score of $\geq$ 10, will be assessed by the Study Physician (Dr. Hamner) and referred clinically for medically supervised detoxification.
- Ethyl glucuronide (EtG): The conjugated alcohol metabolite EtG remains positive in urine for several days following cessation and is a useful biomarker of recent drinking in outpatient settings (Dahl et al., 2011). This will be used as the primary biologic assessment of drinking status as breathalyzer tests only assess very recent alcohol use. The assay may be done in the Charleston VAMC laboratory or by research staff on samples collected monthly at in person office visits at week 0, week 4, week 8, week 12 (end of treatment) and 6-week follow-up visit. UDS, breathalyzer and EtG may be used to corroborate self-report. Results will be used to correct discrepant self-reports.
- Visual Analog Craving Scale (VAS): A Modification of the Within Session Rating Scale used in our group's human laboratory studies will be used to assess subjective ratings including craving, stress, and anger. This 100 mm Visual Analogue Scale (VAS) is anchored from 0 (none) to 10 (extreme).
- Brief Addiction Monitor: (BAM; Cacciola et al., 2013) is a 17-item instrument monitoring substance use related behaviors to determine the severity of the individual's problems. The measure has exhibited excellent Cronbach's alpa (approaching or exceeding .70) and excellent test-retest reliability in a sample of 175 patients entering a VA outpatient substance abuse clinic.

***Sleep***

- Frequency of Nightmares Questionnaire (Davis & Wright, 2007): Items assessing nightmare frequency and nightmare disturbance were selected from The Trauma-Related Nightmare Survey (TRNS). Davis and Wright

(2007) report adequate test-retest reliabilities over a 2-week period for frequency of nightmares (r = .64), and disturbance of nightmares (r = .63).

- Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment short forms. The PROMIS Sleep Disturbance and Sleep-Related Impairment short forms (Yu, Buysse, & Germain, 2012) are self-report measures of past-week sleep disturbance and past-week sleep-related impairment, respectively, derived from the larger PROMIS item banks (Buysse et al., 2010). Each short-form measure includes 8 items, with most items (symptoms) scored in intensity from 1 ("not at all") to 5 "(very much"). Each measure has shown strong reliability and construct validity (Yu et al., 2012).
- Insomnia Severity Index (ISI; Morin, 1993): This ISI is a 7-item self-report measure that assesses perceived severity of insomnia. The items sum to produce a total score (range 0–28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = 0.67), the Dysfunctional Beliefs and Attitudes about Sleep (r = 0.55), and sleep diaries (r ranges from 0.32-0.91).
- Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen. To better understand sleep disturbance associated with PTSD and PTSD treatment, the STOP screen (Chung et al., 2008) will be administered to screen for sleep apnea. The STOP is a four-item questionnaire developed and validated in 211 pre-operative surgical patients. Based on the endorsement of 2 or more questions, the sensitivity of the STOP ranged from 66% to 80% as compared with the apnea-hypopnea index (AHI) of polysomnography depending upon the AHI cut-off used. Individuals answering "yes" to 2 or more of the questions will be advised that they may be at risk for having sleep apnea and advised that they may want to speak with their primary care provider to consider referral for an overnight sleep evaluation.

***Depression and Suicidality***

- Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms (Kroenke, Spitzer, & Williams, 2001). It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the diagnostic criteria for DSM MDD. Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The PHQ-9 has high internal consistency (e.g., alpha ranging from .83 to .92; Cameron, Crawford, Lawton, & Reid, 2008), and correlates strongly with other measures of depression (Kroenke et al., 2001).
- Depressive Symptom Index – Suicidality Subscale. The DSI-SS (Metalsky & Joiner, 1997) will be used to assess current suicidal ideation. The DSI-SS is a 4-item self-report measure of suicidal ideation that focuses on ideation, plans, perceived control over ideation, and impulses for suicide. It is being used as a core measure in the Military Suicide Research Consortium. Scores on each item range from 0 to 3, with higher scores reflecting greater severity of suicidal ideation. Instructions will instruct the participants to respond based on the past two weeks. A systematic review of measures of suicidal ideation and behaviors found that the DSI-SS had evidence of excellent internal consistency and concurrent validity (Batterham et al., 2014).
- Self-Injurious Thoughts and Behaviors Interview short. The Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock, Holmberg, Photos, & Michel, 2007) is a structured interview assessing the historical presence, frequency, and characteristics of self-injurious and suicidal thoughts and behaviors. The short form version of the SITBI, with 72 items total if no skip-outs are used (i.e., the patient endorses the initial item in each module), will be administered at baseline by an Independent Evaluator, who will instruct the participants to answer the questions based on their entire lifetime of experience. The SITBI has shown high interrater reliability, test-retest reliability, and concurrent validity (Nock et al., 2007).

***Associated Areas of Functioning***

- Health Questionnaire. The Health Questionnaire measures medical and mental health diagnoses that respondents have received, medical board and disability status, medications taken, and caffeine use. The version of the Health Questionnaires used at follow-ups also probes emergency room use, hospitalizations, mental health treatments, military status changes, and any important new life events or changes since the time of the last assessment.
- Generalized Anxiety Disorder Screener (GAD-7). The GAD-7 (Spitzer, Kroenke, Williams, & Lowe, 2006) will be used to assess generalized anxiety symptomology. This is a 7-item measure that asks participants to rate the frequency with which they have been bothered by anxiety symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant anxiety symptoms (0-4), mild anxiety symptoms (5-9), moderate anxiety symptoms (10-14), and severe anxiety symptoms (>15). Respondents also indicate the degree to which their anxious symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The GAD-7 has been shown to have high internal consistency (e.g., α = .89; Lowe et al., 2008) and has been shown to reliably discriminate between anxious and non-anxious diagnostic groups (Kroenke, Spitzer, Williams, & Lowe, 2010).
- Veterans RAND 12-Item Short Form Health Survey (VR-12): The VR-12 is a 12-item questionnaire that was developed from, and explains 90% of the reliable variance of, the longer VR-36 (Selim et al, 2009). Items assess physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and mental health. The VR-36 has been widely used, distributed and documented in the Veterans Health Administration.
- Brief Inventory of Psychosocial Functioning (B-IPF). This is a 7-item self-report instrument measuring respondents' level of functioning in seven life domains: romantic relationship, relationship with children, family relationships, friendships and socializing, work, training and education, and activities of daily living (Marx, 2013). Respondents indicate the degree to which they had trouble in the last 30 days in each area on a 7-point scale ranging from "0 = Not at all" to "6 = Very much." The B-IPF has demonstrated concurrent validity, and the full 80-item IPF from which it was created has strong test-retest reliability and internal consistency (Marx, 2013).
- Deployment Risk and Resiliency Inventory-2 (DRRI-2): The DRRI-2 (Vogt et al., 2013) is a suite of 17 individual scales that assess key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health. The Combat Experiences and Postbattle Experiences subscales will be used to assess stressful deployment experiences.
- History of Head Injuries (modified Defense and Veterans Brain Injury Center [DVBIC] 3-Item Screening Tool). We will use a modified version of the Defense and Veterans Brain Injury Center (DVBIC) 3-Item Screening Tool (Schwab, Baker, Ivins, Sluss-Tiller, Lux & Warden, 2006; Schwab, Ivins, Cramer, Johnson, Sluss-Tiller, Kiley, Lux & Warden, 2006) that was used in STRONG STAR. This instrument, initially called the Brief Traumatic Brain Injury Screen (BTBIS), was used as the gold standard for the diagnosis of TBI in a sample of soldiers returning from duty in Iraq and/or Afghanistan (Schwab, Ivins, et al., 2006). As recommended by the DVBIC, the 3-Question Screen will be considered positive when the participant endorses an injury (question 1) and altered consciousness (question 2, items A-E) for the worst head injury sustained while deployed. The form was modified for STRONG STAR and now CAP to capture the number of injuries, and to answer question 2 based on the worst injury; the original form does not recognize the possibility of multiple head injuries during deployment. As the 3-Question Screen does not query head injuries prior to deployment, an additional four questions have been added to solicit information about each head injury sustained outside of deployment.
- Conflict Tactics Scale (CTS2): The CTS2 (Straus & Douglas, 2004) assesses five tactics used when there is conflict in the relationships of dating, cohabitating, or marital couples: Physical Assault, Psychological Aggression, Negotiation, Injury, and Sexual Coercion (Straus, Hamby, Boney-McCoy & Sugarman, 1996). In 2004 a revised CTS was developed which includes 20 items, reducing the test administration time to three minutes (Straus & Douglas, 2004. Testing in a sample of 317 undergraduate students from well-educated

parents, the CTS demonstrated alpha reliabilities ranging from 0.79 to 0.95 (Straus, Hamby, Boney-McCoy & Sugarman, 1996).

- Difficulties in Emotion Regulation Scale (DERS): The DERS (Gratz & Roemer, 2004) is a comprehensive assessment of emotion dysregulation which includes six subscales: Nonacceptance (*Nonacceptance of Emotional Responses*), Goals (*Difficulties Engaging in Goal-Directed Behavior*), Impulse (*Impulse Control Difficulties*), Awareness (*Lack of Emotional Awareness*), Strategies (*Limited Access to Emotion Regulation Strategies*), and Clarity (*Lack of Emotional Clarity*). The DERS exhibited high internal consistency (α = .93) and item-total correlations ranged from $r$ = .16 to $r$ = .69.

All diagnostic clinical interviews will be conducted by an IE. IEs participate in four stages of training under the direction of the Consortium Assessment Core: (1) relevant readings, (2) didactic instruction with an expert in the field, (3) mock interviews with co-workers, and (4) co-rating exercises with previously taped assessments. After the completion of training, IEs will engage in weekly calibration exercises to ensure that they continue to meet high quality standards. Any drift in scoring will be identified and corrected in future assessments.

**Behavioral Therapy.** Participants will be given the option to enroll in the Ralph H. Johnson VAMC and affiliated CBOCs *Substance Treatment and Recovery (STAR)* program and receive weekly structured cognitive-behavioral group or individual therapy targeting addiction during the treatment phase. Dr. Back (PI) is a Staff Psychologist in STAR and has used this method of recruitment successfully in a recent DOD-funded pharmacologic trial among Veterans with comorbid PTSD and addiction. STAR group/individual therapy targets relapse prevention and includes topics on, for example, drink refusal skills, cognitive restructuring, coping with cravings, managing anger, and relaxation skills. STAR provides a case manager who assists Veterans with housing, vocational employment, and medical needs. Subjects who cannot commit to the STAR or other VA programs will be given the option to receive 12, weekly individual CBT therapy sessions with a trained Study Therapist. The CBT will target addiction and focus on similar topics covered in the STAR program (e.g., drink/drug refusal skills, coping with cravings and urges to drink, cognitive restructuring, managing anger). Receipt of weekly behavior therapy during the treatment phase will facilitate retention and medication adherence, and ensure that all participants receive adequate psychosocial support, regardless of medication arm. Study Therapists will be Masters or Doctoral level clinicians with experience delivering CBT. They will be trained in the CBT study protocol and receive weekly supervision by Dr. Therese Killeen.

**Neuroimaging Component.** Given the severe negative outcomes associated with co-occurring PTSD and AUD, investigating potential neural circuitry underlying PTSD/SUD as well as neural circuitry involved in positive therapeutic response to doxazosin could be important in guiding future studies targeting this circuitry using other therapeutic agents or treatment modalities. To that end, fMRI data will be acquired at baseline and end-of-treatment on all eligible participants to examine (a) resting state connectivity, and (b) response to trauma, substance, and neutral cues. We will continue to work closely with the CAP Co-Is and Neuroimaging Core, directed by Dr. Peter Fox, to ensure comparability of imaging data acquisition and pre-processing. Scans will be conducted at the MUSC Center for Biomedical Imaging (CBI), which houses a Siemens 3T TIM Trio MRI scanner (Siemens Medical, Erlangen, Germany). The neuroimaging component will involve three visits, each lasting 60-90 minutes and following the same procedures. In visit 1, imagery scripts will be developed according to standardized procedures described by Sinha (Sinha & Li, 2007) and employed in our ongoing research with Veterans. During visits 2 and 3 (see Fig 5), participants will first be screened for metal using a handheld metal detector. Trained staff will position subjects on the scanner bed with foam padding placed around their head to prevent motion. Participants will wear headphones to listen to the audio-recorded scripts. For co-registration and normalization of functional images, a high resolution T1-weighted MPRAGE anatomical image will be acquired with the following parameters: TR = 2100 ms, TE = 4.18 ms, flip angle = 12°, field of view = 256 mm, slice thickness 1.0 mm. The scanning planes will be oriented parallel to the anterior commissure–posterior commissure line. Next, participants will be asked to relax and keep their eyes opened and fixed on a cross-hair for six-minutes while resting state data are collected.

Following the resting state scan, participants will be exposed to trauma, substance and neutral cues. Resting state scans will always occur before trauma and substance cue runs (Fig. 5). We will use a block design

consisting of one 12-minute run. During the trauma cue, participants will hear an audio recording describing their traumatic event. During the blocks of neutral cue, participants will hear an audio recording describing their relaxing scenario. During the substance cue, participants will hear an audio recording describing in detail the last time they consumed alcohol or drugs. To minimize potential carry-over effects, the runs will be counterbalanced so that half of the participants in the placebo group and half of the participants in the treatment group are exposed to the trauma cue first and the remaining participants in each group are exposed to the substance cue first. T2*-weighted gradient-echo planar images (EPI) will be acquired with the following parameters: TR = 2000 ms, TE = 27 ms, flip angle = 76º, matrix 64 x 64, field of view = 23 cm, slice thickness = 3.7 mm with no gap, with 36 slices to cover the entire brain.

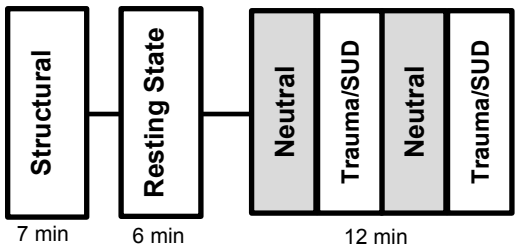


**Fig 5.** Overview of fMRI neuroimaging session. Assessment of (a) resting state connectivity, and (b) response to trauma, alcohol and neutral cues.

**Statistical Analyses**

**General.** Baseline clinical and demographic characteristics will be collected and contrasts performed between treatment groups. Continuous and ordinal characteristics will be compared using a Wilcoxon Rank-Sum test statistic while categorical characteristics will be compared using a Pearson Chi-Square test statistic. All analyses will be performed on the intent-to-treat sample consisting of all randomized subjects.

**Randomization.** The randomization will be stratified by (1) PTSD severity (PCL total score) and (2) AUD severity (AUDIT total score) for a total of four strata. Urn randomization will be employed to balance the randomization assignment with respect to these strata. The purpose of stratification is to distribute these potential prognostic factors equally across treatment groups. To the extent that the stratification variable is predictive, stratifying on it may enhance statistical power to identify treatment effects.

**Power.** This study is powered to estimate the effects of doxazosin on significant reduction in PTSD symptoms at the end of treatment (see Hypothesis 1), and increased abstinence rates at the end of treatment (see Hypothesis 2). Placebo rates of reduction in CAPS scores are conservatively estimated to be 20% (Zohar et al., 2002). In a small pilot study, De Jong et al. (2010) found ~31% reduction in CAPS scores using 4mg doxazosin. A sample of 100 participants will provide 80% power with a .05 type 1 error rate to detect a difference in the reduction of CAPS scores between doxazosin (31±20%) and placebo (20±20%). Placebo rates of drug abstinence are estimated from established double-blind placebo controlled trials. Continuous abstinence from weeks 9-12 is observed in 10-15% of treatment seekers without co-occurring PTSD (Shorter et al., 2013) so we anticipate an attenuated rate of 5-10% in the placebo group. Although there is limited information on the effectiveness of doxazosin in addiction, a sample of 100 subjects (50 in each arm) will provide adequate power to detect an abstinence rate as low as 32% in the doxazosin when the placebo cessation rate is 10% and as low as 23% when the placebo rate is 5%. Due to the nature of the study population, we anticipate ~30% dropout rate; thus the number of subjects randomized is inflated to 144, n=72 randomized to each treatment arm of the study.

Power calculations for the neuroimaging component are based on previous studies of individuals with PTSD or substance use disorders. Based on our previous work and the extant literature, we conservatively estimate that approximately 88/144 will be eligible and volunteer to participate in the neuroimaging component. Of these 88 participants, half (n=44) will be assigned to doxazosin and half to placebo (n=44). Hypotheses 3A and 3B will, therefore, involve the subset of 44 participants who complete the neuroimaging component and receive doxazosin treatment. A recent study of Veterans with PTSD (n=14) as compared to controls (n=15) observed significant differences in PFC-AMY resting state connectivity (Sripada et al., 2012). The effect size for this difference was 0.8 (measured using Cohen's d). Thus, power (1-ß) reaches .80 with a total sample size of N=26 (two-tailed, alpha=.05). Another recent study of cocaine-dependent individuals (N=45) found that

individuals who relapsed (n=24) during treatment had significantly lower PFC-AMY connectivity at baseline as compared to individuals who did not relapse (n=21) (McHugh et al., 2014). The effect size for this reduction was 1.0. Thus, power (1-ß) reaches .80 with only 34 total participants (two-tailed, alpha=.05). The present study is therefore well-powered to test the proposed hypotheses.

**Missing Data.** We will perform attrition analyses on whether participants and dropouts differ on key variables, and whether variables on which they differ interact with treatment to affect outcome measures. As participants will be randomized to treatment, it is unlikely that missing data will produce biased estimates of treatment effect, as observed and unobserved covariates should theoretically be balanced across treatment groups. In addition, in general, less than 10% missing data have little impact on power and do not introduce bias, regardless of the missing data mechanism. Larger proportions of data missing at random (MAR) or missing not at random (MNAR) could potentially bias study findings and reduce power. If the percent missing data are greater than 10%, propensity score methods will be used for data imputation. In the propensity score method, first the distribution of the missing indicator variable given the observed data is modeled to derive a propensity score. Then observations are grouped on these propensity scores and an approximate Bayesian bootstrap imputation is applied to each group.

**Hypotheses.** The hypotheses and statistical approaches for testing each hypothesis are listed below. An experienced biostatistician at MUSC (Nathaniel Baker, Department of Public Health) who has worked with our group for the past five years will collaborate with Dr. Jim Mintz (Director of the CAP Data Management and Biostatistics Core) as needed during the project to ensure consistency across sites with regard to scoring and analysis of dependent measures.

Hypothesis 1: Participants who receive doxazosin, as compared to placebo, will evidence significantly greater reductions in PTSD severity. To test this hypothesis, generalized linear mixed effects models will be employed to assess reduction in CAPS-5 and PCL-5 total scores during the treatment phase. Restricted maximum likelihood (REML) methods will be used to estimate the fixed effects and variance components, and model based treatment effect estimates will be used to construct group level tests over time.

Hypothesis 2: Participants who receive doxazosin, as compared to placebo, will evidence significantly greater reductions in SUD severity. To test this hypothesis, logistic regression analysis will be used to examine rates of abstinence (TLFB, biological tests) during the end of treatment phase (week 9-12). Weekly point prevalence abstinence will be examined using generalized linear models under a generalized estimating equations (GEE) framework. GEE models will allow for examination of differential effects of doxazosin vs. placebo on abstinence over the course of the treatment phase of the study. Weekly abstinence (yes/no) as well as amounts (e.g., standard drink units, dollar amount of substances) will be examined over time to determine if treatment is effective in reducing substance use when abstinence is not achieved.

Hypothesis 3A: PFC-AMY connectivity at rest and in response to trauma vs. neutral cues will predict amount of change in PTSD symptoms (CAPS-5).

Hypothesis 3B: PFC-AMY connectivity at rest and in response to substance vs. neutral cues will predict time to first use of alcohol or drugs (TLFB).

The following preprocessing and analytical parameters will be used to test hypotheses 3A-3B. Preprocessing: Post-acquisition preprocessing and statistical analysis of all of imaging data will be performed using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library). Data will be preprocessed using scripting tools from FEAT. Non-brain signal will be removed using FSL's BET brain extraction. Scans will be corrected for motion using FSL's linear registration and scans will be spatially smoothed using a Gaussian kernel of 8 mm FWHM. Participants with head motion $\geq$ 0.2 mm will be excluded from the analyses [1]. Motion artifacts will be identified and scrubbed from each subject's data. Scans will be spatially co-registered with a standardized anatomical template (Montreal Neurological Institute) using a 12 parameter affine transformation.

fMRI Analysis: Functional connectivity will be measured using a PPI seed-based approach [2]. PPI analyses for resting state, trauma and substance cues will be performed separately. Customized sq. wave forms representing the trauma run (1=trauma block and -1=neutral block) and the substance cue run (1=substance block and -1=neutral block) the duration of each block will be convolved with a double-gamma hemodynamic response function. A mask of the seed region will be made using a 12-mm diameter sphere located in the center

of the amygdala using the MNI coordinates (x, y, z = ±22, 0, -22). The transformation parameters described above will also be applied to the mask. For each subject, the mean corrected and high pass filtered time series of the BOLD signal in the AMY will be extracted and used in a single subject whole brain PPI analysis. The PPI model will include the task vector, time series of the BOLD signal in the AMY, a term representing the positive task x seed interaction, and a term representing the negative task x seed interaction. The first level analysis will generate contrast images of the parameter estimates for each of the four regressors. Voxels will be thresholded at Z>2.3 using a corrected cluster threshold of p=0.05. The contrast images of the parameter estimates of the positive and negative task x seed interactions will be combined for group-level t-tests to identify regions that exhibited altered connectivity with the AMY during the trauma and substance cues as compared to neutral cues. All group-level results will be thresholded at Z>2.3 using a corrected cluster threshold of p=0.05. Separate linear regression tests will be used to test for associations between PFC-AMY connectivity at baseline and improvement in PTSD and SUD symptoms during treatment. Changes in CAPS-5 total scores will be regressed against the parameter estimate obtained from the center voxel from each cluster that exhibited a significant task x seed interaction with the AMY at rest and in response to the trauma cue (Hypothesis 3A). The number of days to first use (TLFB) will be regressed against the parameter estimate obtained from the center voxel from each cluster that exhibited a significant task x seed interaction with the AMY at rest and in response to the substance cues (Hypothesis 3B).

**Problems and Alternative Strategies**. The use of retrospective data is limited by the accuracy of the participants' recall. A partial check on the reliability of data will be provided by using multiple standardized measures, biological tests, and repeated interviews. Doxazosin at 16 mg/day may not reduce PTSD or AUD symptom severity. However, data from the extant literature suggest that this dose and length of treatment is optimal to yield significant reduction in PTSD and SUD symptomatology (Kenna et al., 2015; Rodgman et al., 2015). If no significant differences are observed in total PTSD scores, we will examine symptom subscales. Similarly, if no significant differences are observed in abstinence rates, we will examine additional indices of severity (e.g., percent of heavy drinking days, frequency of substance use). While the primary objective of the current study is to examine the efficacy of doxazosin for the treatment of PTSD/SUD in Veterans, a secondary objective is to utilize neuroimaging methodologies to investigate neural circuitry related to PTSD/SUD comorbidity and positive treatment response in order to inform future research. Doing so will provide substantial neurobiological information to further sharpen research hypotheses to be tested in future investigations and guide future investigations targeting the development of effective treatments for comorbid PTSD and SUD.

**Summary.** This study will provide important information regarding the efficacy of doxazosin in the treatment of one of the most common mental health comorbidities facing our nation's Veterans: PTSD and SUD. If the findings are positive, it will open a new avenue for the treatment of this common comorbidity. The study will also provide important information to elucidate possible mechanisms underlying improved outcomes. The proposed project has the potential to significantly improve the standard of patient care for comorbid PTSD and SUD, advance the comorbidity science in this area, decrease public health expenditures, improve military readiness, and contribute to the overall health of U.S. military personnel, Veterans, and their families.

## HUMAN SUBJECTS RESEARH

### 1. RISKS TO SUBJECTS

Drs. Back, Brady, Moran-Santa Maria, Joseph, Flanagan and Hamner have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. The research team includes two licensed clinical psychologists (Drs. Back, PI and Flanagan, Co-I) and two board certified psychiatrists (Co-Is, Drs. Brady and Hamner) with extensive clinical research experience in posttraumatic stress disorder (PTSD) and substance use disorders. Dr. Moran-Santa Maria (Co-I) also has clinical research experience in posttraumatic stress disorder (PTSD), alcohol use disorders (AUD), and neuroimaging. Dr. Joseph has expertise in neuroimaging. All research activity, informed consents and continuing reviews will be reviewed by the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) and the Ralph H. Johnson VAMC Office of Research

and Development (R&D) committee, in compliance with 45CFR46 before the research is initiated. Continuing review will occur annually.

**Human Subjects Involvement and Characteristics**

A total of 144 adults will be recruited over a 4-year period. The inclusion/exclusion criteria are as follows:

***Inclusion Criteria:***

1. Male or female; any race or ethnicity.
2. Served in U.S. Military – any branch or operation.
3. Subjects must be able to comprehend English.
4. Meet criteria for current (i.e., last 6 months) Substance Use Disorder (SUD) using a modified version of the MINI 7.0 (i.e., must meet DSM-5 criteria for SUD in the past 6 months instead of 12 months).
5. Meet DSM-5 criteria for current (i.e., last month) PTSD.
6. Subjects taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks before treatment initiation. This is because initiation or change of medications during the course of the trial may interfere with interpretation of results.
7. Must consent to random assignment to doxazosin or placebo.
8. Must consent to complete all treatment and follow-up visits.

***Exclusion Criteria:***

1. Subjects meeting DSM-5 criteria for current bipolar affective disorders, as the study protocol may be therapeutically insufficient.
2. Subjects experiencing significant withdrawal symptoms, as evidence by a score of 10 or above on the Clinical Institute Withdrawal Assessment of Alcohol (CIWA). These subject will be referred for clinical detoxification and may be re-assessed for study eligibility after medically supervised detoxification has been completed.
3. Individuals considered an immediate suicide risk or who are likely to require hospitalization during the course of the study.
4. Previous treatment with doxazosin.
5. Subjects on maintenance anxiolytic, antidepressant, or mood stabilizing medications which have been initiated during the past four weeks. If it is determined, based on clinical criteria, that a subject needs to be started on maintenance medications for anxiety, mood or psychotic symptoms during the course of the study, they may be discontinued from the treatment trial.
6. Women who are pregnant, nursing or not practicing an effective form of birth control.
7. Individuals with a history of or current medical illness including unstable angina, myocardial infarction, congestive heart failure or other cardiac condition, hypotension, renal or hepatic disorders, endocrine disorders, prostate or other cancer, pancreatitis, or a seizure disorder.
8. Subjects with abnormal liver function test (LFTs) as evidenced by laboratory findings of SGOT or SGPT greater than two times normal.
9. Subjects with a history of adverse reactions to quinazolines or other alpha-1-antagonists (such as allergic reactions, priapism, hepatitis, angioedema, or intraoperative floppy iris syndrome).
10. Individuals currently taking alpha blockers (terazosin, prazosin), hypnotics/benzodiazepines, atypical antipsychotics (olanzapine, quetiapine, risperidone, clozapine), alpha-2-agonists (Clonidine, methyldopa, tizanidine, guanfacine), conivaptan, boceprevir, idelalisib, PDE-5 inhibitors or alpha-1-antagonists, protease inhibitors (treatment of HIV), oral antifungals, alfuzosin, pazopanib, silodosin, tadalafil, or tamulosin.
11. MRI exclusions: Claustrophobia; tattoos above the shoulders after evaluation by MRI technician; permanent eyeliner or permanent artificial eyebrows; cardiac pacemaker; metal fragments in eye, skin, or body, including shrapnel; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; lifetime history of aneurysm surgery; intracranial bypass, renal, or aortic clips; prosthetic

devices such as middle ear, eye, joint, or penile implants; joint replacements; non-removable hearing aid, neurostimulator, or insulin pump; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires; or any other metal implants.

No special classes of subjects, such as, pregnant women, prisoners, institutionalized individuals, or others will be recruited for this study.

**Potential Risks**

Some participants may experience distress by questions pertaining to their substance use history, trauma or their emotional functioning. All participants will be informed at the outset that the study is voluntary and they may terminate participation at any point. Our past and ongoing research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms. This experience includes substantial research with younger and older adults, active duty service members, OEF/OIF/OND military Veterans, rape victims, victims of other forms of violence (e.g., natural disasters, car accidents), and work on large-scale studies asking questions about similar topics with general population samples. Legal risks arise if individuals are homicidal or suicidal and make these intentions known to project staff, who may then be required to notify authorities and the target of homicidal intent. These risks are outlined in the informed consent documents.

In the event that subjects experience psychological distress secondary to participation, they will be encouraged to telephone the Principal Investigator (PI), Dr. Back, who is a licensed clinical psychologist. They will be given Dr. Back's contact information at the time of consent, as well as resources for local and national 24-hour hotline numbers. In addition, participants will have access to urgent care services at the VAMC. The research team is comprised of licensed clinical psychologists and psychiatrists with extensive experience working with adults who have experienced significant life stressors and drug/alcohol addiction. If assessors or project staff believe that a participant is significantly distressed by participation, the PI will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, the PI will attempt to address all participant concerns and will set up an alternate referral for clinical services outside the project if desired.

If eligible, participants may be asked to complete two neuroimaging scans (functional magnetic resonance imaging; fMRI), which will be conducted at the MUSC Center for Biomedical Imaging (CBI), which is located at 30 Bee Street on the MUSC campus (within 2 blocks of the VA). There are very few potential risks from fMRI itself. There is no exposure to ionizing radiation and the machine and scanning sequences and gradients are approved by the Food and Drug Administration (FDA) for routine clinical use. Individuals who are claustrophobic may experience some anxiety during the scanning procedures. A patient may experience some loud noises during the scanning procedure and there is a mild risk of hearing damage if patients are not given hearing protection. All participants in the study will be given hearing protection. Participants may experience psychological discomfort from undergoing the scanning procedure, such as boredom and fatigue. Ferrous objects in the body that are undetected could move during scans. This could lead to tissue damage and hemorrhage. These risks are outlined in the informed consent document. In our past and ongoing studies utilizing fMRI, we have been able to safely complete imaging procedures without undue distress or negative outcomes. This includes research with military Veterans who have current PTSD and co-occurring substance use disorders.

All medications have potential side effects. Side effects that have occurred in clinical trials with doxazosin include dizziness/fainting, fatigue, headache, shortness of breath, diarrhea, abdominal pain, edema, priapism, and hypotension. Doxazosin can cause floppy iris syndrome during cataract surgery. Participants will be informed of all potential side effects associated with doxazosin and closely monitored each week.

Because participants are U.S. military personnel, absolute confidentiality of research records cannot be guaranteed. We will, however, make all possible efforts to protect the privacy and confidentially of study participants. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures.

**Sources of Materials**

Data will be in the form of structured clinical interviews conducted by trained Independent Evaluators, self-reported questionnaires, medical record review, urine and breath samples, and neuroimaging data that will be obtained specifically for research purposes.

In addition to consenting for this study, participants will be offered participation in the STRONG STAR Repository. The South Texas Research Organizational Network Guiding Studies on Trauma and Resilience, or STRONG STAR, is a multidisciplinary and multi-institutional research consortium funded by the U.S. Departments of Defense (DOD) and Veterans Affairs (VA) to develop and evaluate the most effective early interventions possible for the detection, prevention, diagnosis, and treatment of combat-related PTSD and related conditions in active-duty military personnel and recently discharged Veterans. Under the leadership of the UTHSCSA and based in south-central Texas, STRONG STAR brings together the expertise of a world-class team of military, civilian and VA institutions and investigators and one of the largest populations of active-duty and recently discharged OEF/OIF/OND Veterans in the nation.

The STRONG STAR Repository is approved by the UTHSCSA IRB, which also reviews research for the STVHCS, and has received Central VA approval as a tissue bank maintained at the UTHSCSA. The STRONG STAR Repository is a large comprehensive database of information, biological specimens and neuroimages related to the identification, assessment, and treatment of PTSD and related conditions in our active duty and retired veterans of combat operations. All information entered into the Repository will be extracted from primary datasets collected as part of IRB-approved studies, including this study, being conducted and /or supported by the projects of the CAP. A unique, sequential alpha-numeric ID is assigned to each participant at the time of recruitment into this study. However, all repository data will be identified with a different code number that can be cross linked to the original study code only through records maintained by the Data Management and Biostatistics Core. Data, biological specimens and images constitute the STRONG STAR PTSD Repository. Participation in the repository is completely voluntary and entirely optional which means that a potential participant's willingness to participate in the repository has no influence upon their eligibility to participate in the primary study they have either already enrolled in or are considering enrolling in. At the conclusion of this study, participants who signed the consent to have their specimens and data placed in the STRONG STAR Repository will be maintained under the IRB-approved Repository protocol. Biological specimens and information from study participants who declined participation in the STRONG STAR Repository will be permanently de-identified (i. e., all PHI will be deleted from the study data bases) and the de-identified blood and information placed in the Repository for future use.

## 2. ADEQUACY OF PROTECTION FROM RISK

**Recruitment and Informed Consent**

Participants will be primarily recruited from the Ralph H. Johnson VAMC and affiliated CBOCs' Substance Treatment and Recovery (STAR) program. Dr. Back (PI) is a Staff Psychologist in the STAR. Potential study participants will be told about the study at STAR intake, the program orientation session, and at weekly group therapy meetings, and provided with a telephone number to call and receive more information. IRB-approved flyers and brochures describing the study and providing contact information will be placed in each of the STAR group therapy rooms, in each of the STAR clinician and case manager offices, and in the STAR program waiting room. We will also post IRB-approved recruitment flyers in prominent locations in other VA hospital clinics (e.g.,

internal medicine, women's health, PTSD clinic, pain clinic, emergency department) and other satellite clinics within the Charleston VAMC catchment area. The research team has used these methods successfully in the past to recruit Veterans to various clinical protocols.

While recruitment will be primarily from the STAR, we will also place IRB-approved recruitment flyers in prominent locations in affiliated community based outpatient clinics (CBOC) and throughout the MUSC hospital, including the Center for Drug and Alcohol Programs, and the National Crime Victims Treatment Center.

The research team and all of the study staff have completed (or will complete upon hiring) the Miami Collaborative IRB Training Initiative (CITI) course and its associated tests in research ethics. Informed consent (IC) will be collected at the study research offices, in a private and interruption-free enviornment. The PI, Co-Is, Study Coordinator, or other trained research staff will obtain IC. The IC form will outline: a) the sponsponsorship of the study; b) the nature, purpose and procedures of the study; c) the voluntary nature of participation (i.e., participation is not required; participation can be discontinued at any time); d) the duration of the study; e) potential risks and discomforts, as well as benefits of participation; f) that all information will be kept confidential subject to the provisions of the state and federal law; g) compensation; and h) alternative treatements. The IC form will specifically review the potential for psychological distresss, and the risks associated with fMRI and doxazosin that may occur as a result of study participation. The IC form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. The IC form will include emergency contact information for the PI (Dr. Back). Any questions pertaining to the study or consent process will be answered fully. Potential participants will not be required to make a decision to participate at the initial contact, though that possibility will be available. If participants wish to discuss study participation with their family and/or significant others, they will be encouraged to do so. Participants will be informed that they can discontinue their participation in the study at any time and that this decision will not influence the care they receive at the VAMC or MUSC clinics. Consent will be documented by the signature of the participant on the IC document, accompanied by the signature of the individual obtaining the consent. Participants will be given a copy of the informed consent. Research staff will document the informed consent process in the medical record of the participant.

**Protection Against Risk**

We will take careful precautions to maintain confidentiality for all participants, using procedures that we have successfully employed in similar previous as well as ongoing studies with Veterans. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). All study data related to psychological outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be no linkage between a participant's identity and their responses. There will be only one master list of participants (again, not linked to any participant responses) which will be kept locked separate from all data and will be available only to the PI, Co-Is and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or RA's research office) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Specifically, access to de-identified study data will be limited to named project investigators, the Study Coordinator, sponsor audit personnel, VAMC R&D auditors, and MUSC IRB auditors. Neuroimaging data will be stored on a secure password protected server maintained by MUSC's Center for Biomedical Imaging (CBI). Only Drs. Back, Joseph, and Moran-Santa Maria will have access to the files on the secure CBI server. The PI, Co-Is and study personnel have completed (or will complete upon hiring) a certified program of instruction in the protection of human subjects in research, such as the VA website tutorial or the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human subjects will be completed on an annual basis, in compliance with VA and MUSC regulations.

In addition, a Research Monitor has been selected for the present study. The Research Monitor, Dr. Robert Malcolm, M.D, will oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the Human Research Protection Office (HRPO).

Risks associated with assessment include the possibility that participants might be upset by questions pertaining to trauma, alcohol or drug use, or their emotional functioning. The research team will closely monitor for any increase in distress at every treatment visit. Substance use, PTSD, anxiety and depression symptoms will be monitored weekly using standardized measures in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening PTSD, substance use and depression symptoms and to discuss these with the research team. All participants will be informed at the outset that they may terminate participation at any point. If a participant becomes upset in-between visits, he or she will be encouraged to contact the Study Coordinator, his or her case manager at the VA, and/or Dr. Back. If a participant needs or desires immediate attention, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document provides direction to contact the study staff during office hours and/or the Emergency Room at any time for worsening of symptoms.

Our past research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among adult participants. This experience includes substantial research with younger and older adults, military service members, rape victims, victims of other forms of violence, and work on large-scale studies asking questions about similar topics with general population samples. In addition, it includes Veterans with alcohol, cocaine, marijuana and/or opioid use disorders. In the event that participants experience extreme psychological distress secondary to participation, they will be encouraged to telephone the PI. In addition, they will have access to urgent care services at the Charleston VAMC and CBOC locations. Any adverse events occurring among randomized participants will be reported to the PI, who will then report these adverse effects in writing to the VA R&D Committee, MUSC IRB, and the study sponsor per protocol (see the Data Safety and Monitoring Plan at the end of this section for more details). The research team is comprised of licensed clinical psychologists and psychiatrists with extensive experience working with adults who have experienced significant life stressors and addiction. If project staff believes that a participant is significantly distressed by participation, the PI will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, the PI will attempt to address all participant concerns and will set up an alternate referral for counseling for those who desire it from outside the project. All participants will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress as a potential outcome of participation. If necessary, they will be asked to complete a safety plan and agree to call the project staff or 911. However, if safety is in question in the minds of any project staff, the Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit will be dispatched to the participant’s home to assure safety. In our NIH and DoD-funded clinical trials of comorbid PTSD and substance use disorder treatment provision, we have not had any problems related to participation that could not be safely resolved with these methods.

A portion of the history and physical examination for participants at affiliated CBOC locations may be performed via telemedicine, if necessary. Research staff at the CBOC will take vital signs, including orthostatic blood pressure and pulse measurements, each week. In addition, all participants will receive an electrocardiogram at baseline and a complete metabolic panel to include liver and renal function tests to ensure study eligibility. A medical clinician on the research project may meet with the participant via telemedicine to assess medical and related history (e.g., social, surgical, family history) and review of systems. Whenever the history and physical

examination is conducted in part utilizing telemedicine we will include two additional steps to ensure patient safety and determine eligibility to enroll in the study: 1) a study physician will review the CPRS records to identify any potential medical or other exclusions, and 2) the research staff will view alert and/or call the participant's primary care doctor and ask if they have any concerns with the individual participating in the doxazosin study. The study medication (doxazosin) is an approved agent with a long safety record; thus, we do not anticipate any problems utilizing telemedicine to complete part of the history and physical examination. Furthermore, it is expected that only a small proportion of history and physical examinations will occur via telemedicine. However, because telemedicine is different than the standard of care, we have decided to add in these additional measures to ensure patient safety.

All relevant study staff will be required to complete the CBI's MRI safety training class. The course is taught by an American Registry of Radiologic Technologists registered technician. The staff will be trained about safety in the MRI environment, and how to screen oneself and others. The staff will also have knowledge of safety procedures for entering the scanner facility, safely removing participants from the scanner, when and how to quench the magnet and basic emergency procedures including emergency contact information. Standard operating procedures for emergency situations are located on-site. The MRI technician and Drs. Joseph and Moran-Santa Maria (Co-Is) are authorized to operate the equipment and will be present or available during the scanning sessions. Although there are no known risks of MRI scanning to a developing fetus at 3.0 T, the possibility that risks could be discovered in the future cannot be ignored. Therefore, urine pregnancy tests will be used to exclude pregnant women from study participation. A careful metal screening history will be taken from each participant to assess the possibility of metal devices/implants and will be reviewed by the PI, MRI technician and/or clinical staff who have had extensive training and experience with MRI safety. If the screening yields information that raises a question of safety, the participant will be asked to provide the appropriate documentation (i.e., film) before they are allowed to participate. In addition, participants will be asked to empty their pockets and will be screened with a hand-held ferromagnetic-detector wand. Participants will wear earplugs and/or sound-dampening headphones to decrease the intensity of the scanner noise. Prior exposure to pictures of the scanner, getting into the mock scanner, and seeing others in the scanner, often reduces psychological discomfort or identifies people for whom scanning is not appropriate.

Subjects will have weekly contact with study staff while receiving doxazosin, which will allow for frequent monitoring of side effects. Standing and sitting/supine blood pressure may be recorded at weeklyvisits. Subjects will be taught about potential side effects of doxazosin and will be closely followed by psychiatrists (Drs. Hamner and Brady), a physician assistant, and other members of the research team. The instrumentation used for physiological recordings meets all safety standards for non-invasive recordings, and participants are located out of reach of any AC-powered devices in the laboratory. Our research group has extensive experience administering medications to and monitoring clinical populations including Veterans with comorbid PTSD and substance use disorders (i.e., alcohol, cocaine, marijuana and opioid use disorders).

Research Monitor. The Research Monitor, Robert Malcolm, MD, will oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

## 3. POTENTIAL BENEFITS OF RESEARCH TO SUBJECTS AND OTHERS

Potential benefits of participation in this study may include a reduction in PTSD and AUD/SUD symptoms. However, there is no guarantee or promise that participants will receive any benefit from participation in this study.

## 4. IMPORTANCE OF KNOWLEDGE TO BE GAINED

The potential benefits of the knowledge to be gained from the proposed study are considerable. Since 2001, more than 2.6 million service members have deployed in support of combat operations in Afghanistan and Iraq. One of the signature injuries from these operations is PTSD. Various reports of the post-deployment health-related needs estimated that 20% of Veterans returning from deployment will have symptoms of PTSD or related behavioral health conditions, including AUD. This study proposes to test doxazosin in the treatment of co-occurring PTSD and AUD. The plans for monitoring risk as described above warrant the conduct of this study for the knowledge that may reasonably be expected to result.

## 5. DATA SAFETY AND MONITORING (DSM)

A Data Safety and Monitoring Plan (DSMP) for STRONG STAR and CAP studies has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in this study. Recruitment and safety data are monitored according to the schedule established by the monitoring board. Quality control and assurance of data entered into the database is discussed above as part of Protections Against Risk. Missing data will be considered as part of the plan for statistical analysis. Depending upon the source of funding, the DSMP for this study will be advised by either the VA Data Monitoring Committee structure or the STRONG STAR and CAP Data Safety Monitoring Board (DSMB). The board will meet every 6 months once the first participant is consented, but may be called at any point if needed for unexpected AEs, etc.

Summary of the Protocol: This application proposes to test the feasibility and efficacy of doxazosin, as compared to placebo, in reducing PTSD and AUD severity among U.S. military Veterans. The primary outcomes of interest include: 1) alcohol use severity and PTSD symptomatology; 2) measures of associated mental and behavioral health problems; and 3) fMRI measures of functional connectivity.
Trial Management: The study will be conducted and managed in the Ralph H. Johnson VAMC Mental Service Line.

Data Management and Analysis: Data will be entered by trained research assistants directly into a computer using standard database software provided by STRONGSTAR-CAP. Neuroimaging data will be stored and analyzed on the CBI's password protected server. Data will be reviewed on an ongoing basis to ensure that data integrity is maintained. Quarterly audits of at least 10% of data entry will be completed in collaboration with the Data Management and Biostatistics Core (Dr. Jim Mintz, Director). A detailed data analysis plan is outlined in the Statistics Analysis section of the Research Plan.

Regulatory Issues: All unexpected Adverse Events (AEs) will be reported to the PI (Dr. Back), who will then report these AEs in writing to the VA R&D Committee and the MUSC IRB within ten working days. AEs are reportable if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Serious AEs (SAEs) will be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to the study sponsor, VA R&D Committee, and the MUSC IRB. All AEs are reviewed weekly by the PI, and annually or more by the Data Safety Monitoring Board (DSMB), VA R&D Committee, and MUSC IRB. AEs and SAEs occurring during the course of the trial among participants randomized to study condition will be collected, documented, and reported in accordance with protocol and IRB

and VA R&D Committee reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. The Research Assistant or Study Coordinator will identify any potential AEs during the course of the study from participant self-report and administration of assessments and procedures. This information will be provided to the PI (Dr. Back) and Study Physician (Dr. Hamner), who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE: An Adverse Event (AE) is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the study that may or may not be related to study participation. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, OR requires intervention to prevent one of the above outcomes.

Documentation and Reporting: Any clinical study event that is judged to be an AE will be recorded on the AE Form during the course of the study. The PI and/or Study Coordinator will ensure this information is captured during every study visit. Whenever a study participant has reported any AE, the study coordinator discusses the event immediately with the PI (if possible while the study participant is there) who must evaluate the event. If the AE is not serious, the information is recorded, managed medically as appropriate, and the event is followed until resolution. SAEs are also recorded on the AE Form, managed medically as appropriate, and the event is followed until resolution. In addition, the PI reviews all completed AE forms for determination of SAE that require reports to the Sponsor. The PI informs the Sponsor immediately of knowledge of a SAE. All information available on the event (hospital records, lab tests, discharge summaries, etc.) is forwarded to the Sponsor so they can determine whether the SAE is unexpected or associated and the reporting outcome of the SAE. As additional information becomes available on the SAE, it should be forwarded to the Sponsor. All SAE reports shall be sent to the VA R&D Committee and MUSC IRB within 24 hours of learning of event occurrence.

AEs/SAEs are documented and reported as per protocol and VA requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are documented on AE Logs and additional relevant AE information, if available, will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study.

When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified within 24 hours of the site's initial notification of the SAE:

a) The Principal Investigator and the Study Physician will provide oversight, consultation, assessment and documentation as appropriate of the SAE.
b) The research staff will notify the VA R&D Committee and the MUSC IRB, and complete the AE report form in conjunction with the PI. Both committees meet monthly. Communication with the VA R&D and MUSC IRB is through email, memos, official IRB forms, and online reporting.
c) The data safety monitoring board members.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the sponsor as appropriate.

All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

Trial Safety: The potential risks and benefits and methods to minimize these risks are outlined above. Protocols for reporting AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration. Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by participant's physicians and other medical providers will be referred directly to PI.

DSM Plan Administration: The PI (Dr. Back) will be responsible for monitoring the study. In close collaboration with the CAP Data Management and Biostatistics Core leadership, Dr. Back and the on-site statistician (Nathaniel Baker) will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSM report will be filed with the R&D, IRB and sponsor on a yearly basis, unless greater than expected problems occur. The report will include subject characteristics, retention and disposition of study subjects, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.

Data Sharing Plan: The data collected from study participants, including PHI, will be entered into and securely stored in the STRONG STAR-CAP database on a secure UTHSCSA server by a member of the study research team under a signed Data Use Agreement between Ralph H. Johnson VA and UTHSCSA. Terms of the Data Use Agreement data have been reviewed and approved by VACO and found to meet VA security compliance standards. Electronic data will be stored, managed, and analyzed by the Data Management and Biostatistics Core staff of the STRONG STAR-CAP Consortium. The overall study PI and named collaborators will have access to identifiable data through the STRONG STAR-CAP website and UTHSCSA server.

A *STRONG STAR Repository* has been established to enable the STRONG STAR-CAP Consortium to store data for future use. As part of a separate protocol that will be submitted to the Ralph H. Johnson IRB for review, participants will be offered participation in this *Repository*. Participation in the repository is completely voluntary; a potential participant's willingness to participate in the Repository has no influence upon their eligibility to participate in the primary study they have either already enrolled in or are considering enrolling in. At the conclusion of this study, participants who signed the consent to have their PHI placed in the STRONG STAR Repository will have their PHI maintained under the IRB-approved Repository protocol at UTHSCSA. Data from study participants who decline participation in the STRONG STAR Repository will be permanently de-identified (i. e., all PHI will be deleted from the study data bases) at the time of study closure with the Ralph H. Johnson VA IRB. The de-identified data will be transferred to the STRONG STAR Repository for future use.

In brief, sharing of data through the Repository is governed by the University of Texas Health Sciences Center at San Antonio (UTHSCSA) IRB-approved repository protocol and STRONG STAR-CAP Consortium standard operating procedures. This repository has been approved by the VA. All requests from outside the Consortium for data are reviewed and approved by the Consortium leadership and investigators. Once approved, only de-identified data are released under an IRB-approved research protocol and signed Data Sharing Agreement between the Consortium and the recipient investigator. Use of the data collected specifically as part of the proposed study would need the approval of study PI as a Consortium investigator before any data would be released to outside investigators.

## *6.* INCLUSION OF WOMEN AND MINORITIES

Both male and female participants will be recruited. There will be no exclusion based on race or ethnicity. Participants will be recruited without preference for gender, race, ethnicity or socio-economic status. Based on previous VAMC data (Magruder et al., 2005), we estimate that approximately 40% of the sample will be comprised of African Americans. We also will include female participants; however, the percentage of female participants in our catchment area is low (<8%). Thus, while we do not anticipate a large number of female participants, we do predict that a significant minority will be enrolled.

## 7. INCLUSION OF CHILDREN

Children will not be included.