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Doxazosin for the treatment of co-occurring PTSD and alcohol use disorder: Design and methodology of a randomized controlled trial in military veterans

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ABSTRACT

Posttraumatic stress disorder (PTSD) and alcohol use disorders (AUD) are two of the most common mental health disorders affecting civilians as well as military populations. If left untreated, individuals with co-occurring PTSD/AUD are at increased risk for developing other mental health problems (e.g., depression, anxiety), physical health problems, reduced resiliency and military readiness, and vocational and social impairment. Substantial gaps in the treatment of co-occurring PTSD/AUD exist and there is a critical need to develop more effective pharmacological treatments. The current study addresses this gap in the literature by testing the efficacy and safety of doxazosin, a long-acting and selective alpha-1 adrenergic antagonist, as compared to placebo in reducing PTSD and AUD severity among U.S. military veterans. Noradrenergic dysregulation has been implicated in the development and maintenance of PTSD and AUD, and pilot studies examining doxazosin in PTSD-only or AUD-only samples have shown promise. This is the first study, however, to evaluate doxazosin in a comorbid PTSD/AUD sample. This paper describes the rationale, design and methodology of a randomized, double-blind,

Abbreviations: AMY, amygdala; AUD, alcohol use disorder; BAM, Brief Addiction Monitor; BP, blood pressure; CAP, Consortium to Alleviate PTSD; CAPS-5, Clinician-Administered PTSD Scale for *DSM-5*; CIWA, ArRevised Clinician Institute Withdrawal Assessment of Alcohol; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition*; EPI, gradient-echo planar images; FDA, U.S. Food and Drug Administration; fMRI, functional magnetic resonance imaging; HIV, human immunodeficiency virus; IRB, Institutional Review Board; MINI, Mini International Neuropsychiatric Interview; MPRAGE, magnetization-prepared rapid gradient-echo; MRI, magnetic resonance imaging; MUSC, Medical University of South Carolina; OCDS, Obsessive Compulsive Drinking Scale; PCL-5, PTSD Checklist for *DSM-5*; PFC, prefrontal cortex; PPI, psychophysiological interaction; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitors; TLFB, Timeline Follow Back; USP-grade, meets or exceeds requirements of the United States Pharmacopeia; VA, U.S. Department of Veterans Affairs; U.S., United States

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placebo-controlled trial of doxazosin (16 mg/day) delivered over 12 weeks among military veterans with current PTSD and AUD. In addition, functional magnetic resonance imaging (fMRI) is applied at pre- and post-treatment to investigate the underlying pathophysiology of comorbid PTSD/AUD and identify prognostic indicators of treatment outcome. This study is designed to accelerate research on co-occurring PTSD/AUD and provide empirical evidence to inform clinical practice.

1. Introduction

Military veterans are at increased risk of developing of posttraumatic stress disorder (PTSD) and substance use disorders (SUD) [56]. In comparison to the general population, rates of PTSD are almost 5 times higher, and rates of SUD are approximately twice as high among veterans [29,65,67]. Furthermore, extensive literature documents the frequent co-occurrence of PTSD and SUD [63,69,70]. Initial reports among military personnel focused on Vietnam veterans with PTSD, in which up to 84% met lifetime criteria for an alcohol use disorder (AUD) [27]. 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% with SUD meet criteria for current PTSD [43]. A series of associated problems are common among individuals with dually diagnosed PTSD and SUD, including medical problems, family dysfunction, homelessness, HIV risk behavior, and poor treatment outcomes [6,34,36,39,45,46].

Despite the frequency and severity of co-occurring PTSD and addiction, there are substantial gaps in treatment, particularly pharmacotherapeutic treatment. The studies conducted to date have examined a variety of medications (e.g., sertraline, topiramate, naltrexone, *n*-acetylcysteine) with modest therapeutic effects observed and significant room for improvement [4,9,14,44,63]. The noradrenergic system has been implicated in PTSD, withdrawal states from chronic substance use, and in response to substance-related cues [21,25,31,61], suggesting that therapeutic interventions targeting the noradrenergic system may represent a promising avenue for the treatment of comorbid PTSD and SUD. Previous studies have examined the use of prazosin, an alpha-1 noradrenergic blocker approved by the U.S. Food and Drug Administration (FDA) for hypertension and benign prostatic hyperplasia, in the treatment of PTSD, AUD and comorbid AUD/PTSD. The findings have been mixed with some studies showing significant reduction in AUD symptoms [15,59,60] and reduction in PTSD symptoms, particularly nightmares, sleep disruption and daytime hyperarousal symptoms [18,50,52], while other studies find no significant differences in prazosin vs. placebo for AUD or PTSD symptoms [41,49]. Several studies suggest that pre-treatment blood pressure may represent a biomarker to help identify who will respond favorably to prazosin, or potentially other alpha-1 blockers [48,74].

Doxazosin is another alpha-1 noradrenergic antagonist that is approved by the FDA for the treatment of hypertension and benign prostatic hyperplasia. Doxazosin and prazosin have the same chemical structure, with the central element being a piperazine ring. However, there are several advantages of doxazosin in comparison to prazosin [28]. For example, doxazosin has a significantly longer half-life of approximately 22 h (vs. 2–3 h half-life of prazosin). The longer half-life allows for a once-per-day dosing, rather than twice or thrice daily dosing, which is generally preferred by patients and promotes medication adherence [73]. The slower onset of action also reduces the risk of first-dose postural hypotension as compared to prazosin [17,30] and doxazosin has no significant effect on blood pressure among normotensive patients, which further reduces the risk of hypotensive side effects [26]. Unlike other alpha-1 blockers, doxazosin can be taken at any time during the day, with or without food, which further promotes medication adherence [30].

Two small studies provide initial support for doxazosin's safety and therapeutic effects on PTSD. In a 12-week, open-label pilot trial (N = 12 civilians and veterans) of doxazosin (8 mg/day) in individuals with PTSD, De Jong et al. [13] found significant pre-to post-treatment reductions (baseline = 77 vs. end of treatment = 53) on the Clinician Administered PTSD Scale (CAPS; [72]). Depression severity, as measured by the Montogmery-Asberg Depression Scale [77] also significantly decreased from baseline to end of treatment (score at baseline = 25 vs. end of treatment = 19). More recently, a small randomized controlled study (N = 8 male veterans) demonstrated that doxazosin (16 mg/day) was effective in significantly reducing self-report PTSD symptoms as measured by the PTSD Checklist – Military Version (PCL-5; [7,71]) and a trend for reduction on the CAPS hyperarousal scale was observed [54,55]. However, both studies are limited by small samples sizes and require replication with larger samples.

Several early trials have also examined doxazosin in individuals with SUD. In a 10-week, randomized controlled trial of 41 individuals with AUD, Kenna et al. [28] found that doxazosin (16 mg/day) was associated with significantly lower reductions in drinks per week, heavy drinking days, and craving among individuals with high family history density of alcoholism. In a secondary analysis of the same data set (N = 41), Haass-Koffler et al. [20] examined the role of pre-treatment standing blood pressure (BP) as a moderator of doxazosin's effect on AUD severity and found that patients with high pre-treatment BP had the most favorable AUD outcomes. Other clinical studies in patients with cocaine use disorder [58] as well as preclinical studies [37] suggest that doxazosin may help reduce SUD severity.

The current study is the first study to evaluate doxazosin among individuals with co-occurring PTSD/AUD. This paper describes the design and methodology of an ongoing randomized controlled trial (RCT) to evaluate doxazosin in reducing PTSD and AUD severity among a sample of military veterans. While the primary focus of the study is the medication trial, we are also employing functional magnetic resonance imaging (fMRI) at pre- and post-treatment to further investigate the underlying pathophysiology of PTSD/AUD and identify potential prognostic indicators of treatment outcome.

1.1. Research objectives and hypotheses

This project is one of 11 nationwide research projects supported by the Consortium to Alleviate PTSD (CAP), which is part of a National Research Action Plan jointly issued in 2013 by the U.S. Department of Defense, Department of Veterans Affairs (VA), Department of Health and Human Services, and Department of Education. The overall aims of the CAP are: (1) develop and evaluate effective treatments for PTSD and comorbid conditions, such as alcohol and drug use disorders, in military service members and post-9/11 veterans; and (2) identify the biological causes of PTSD and changes in those biomarkers that are associated with treatment outcomes. More information about the CAP is available at www.ConsortiumToAlleviatePTSD.org.

The primary research objective of the current study is to address the gap in the evidence base regarding pharmacologic treatment of co-occurring PTSD and AUD by comparing doxazosin (16 mg/day) versus placebo in reducing PTSD symptomatology and alcohol use severity in veterans with co-occurring PTSD/AUD. There are three main hypotheses that pertain to changes in outcomes of interest during the treatment phase (weeks 1–12). Hypothesis 1 proposes that participants who receive doxazosin, as compared to placebo, will evidence significantly greater reductions in PTSD severity at week 12, as measured by the Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) ([72]a) and the PTSD Checklist for *DSM-5* (PCL-5) ([72]b). Hypothesis 2 is that