# Title Page

**TITLE:** RCT TARGETING NORADRENERGIC STRESS MECHANISMS IN ALCOHOLISM WITH DOXAZOSIN

**PI NAME AND INSTITUTIONAL AFFILIATION:** JOHN J. CURTIN; UNIVERSITY OF WISCONSIN, DEPARTMENT OF PSYCHOLOGY

**PROTOCOL VERSION DATE:** 11/07/19

**COORDINATING CENTER IDENTIFICATION (IF APPLICABLE):** N/A

**CO-INVESTIGATORS (IF APPLICABLE):**

DR. CRAIG W BERRIDGE

DR. ALEKSANDRA ZGIERSKA

**STUDY COORDINATORS:** SUSAN SCHNECK

**FUNDING SPONSOR:** NIAAA

**CLINICALTRIALS.GOV IDENTIFIER**: NCT02989493

# Table of Contents

## Project Summary and Abstract

Current pharmacotherapy for alcohol and drug addiction yields relatively low probability for attaining long-term recovery. The recent dramatic reduction in R&D by the pharmaceutical industry for novel medications to treat psychiatric conditions, particularly substance use disorders, provides a strong impetus to “repurpose” currently available compounds that may be effective treatment alternatives. Orally available, brain-penetrant $\alpha$1-noradrenergic (NE) receptor antagonists are widely used to treat hypertension. Additionally, $\alpha$1-NE antagonists are increasingly used to treat post-traumatic stress disorder (PTSD), consistent with the well-documented role of NE in mediating multiple behavioral and physiological processes in stress. Stress is a significant contributor to alcohol/drug relapse. Stress-related reinstatement is a well-validated animal model of addiction and $\alpha$1-NE antagonists reduce relapse in this animal model. NIAAA Director George Koob has made strong calls for translational research on stress-mechanisms in humans. This preclinical evidence in animals suggests the use of $\alpha$1-NE antagonists may be useful in relapse prevention including stress-related relapse. To test this hypothesis, we propose two complementary preclinical and clinical objectives in humans:

1. To translate the preclinical evidence from animal models to stress-induced relapse in humans via direct pharmacological antagonism of the NE system in abstinent alcoholics with doxazosin, an $\alpha$1-NE blocker.

2. To screen the efficacy of doxazosin to target stress-related relapse mechanisms in abstinent alcoholics as a cost-effective first step to repurpose this $\alpha$1-NE antagonist for relapse prevention in addiction.

These two objectives will be accomplished in a randomized controlled trial (RCT) of recently abstinent alcoholics, to examine the efficacy of 8 mg doxazosin (vs. placebo, between-subjects) on stress reactivity and clinical outcome measures (e.g., heavy drinking) during an 8 week treatment period. We assess doxazosin’s impact on stress-related relapse mechanisms using a well-validated human model of stressor reactivity (NPU task) at baseline (pre-treatment), and after 4 weeks and 8 weeks of treatment. The NPU task has strong translational ties to both methods and measures from the preclinical literature in animals. This task has demonstrated reliable, robust effects of drug administration and drug deprivation in drug dependent users. As such, it serves as an attractive early surrogate endpoint post-treatment to assess treatment efficacy and examine stress mechanisms. Repurposing existing pharmaceutical agents has recently been promoted by NIH director, Francis Collins, as a research priority. Tom Insel and others have strongly advocated for the development and use of early surrogate endpoints in clinical research. This project aligns well with the NIMH RDoC focus on dimensions of observable behavior and neurobiological measures in psychopathology research. This project also anticipates changes at NIMH to capitalize on simultaneous examination of mechanism and outcome in RCTs.

## Specific Aims

Current pharmacotherapy for alcohol and drug addiction yields relatively low probability for attaining long-term recovery. The recent dramatic reduction in R&D by the pharmaceutical industry for novel medications to treat neuropsychiatric conditions, particularly substance use disorders, provides a strong impetus to repurpose currently available compounds that may be effective treatment alternatives[1,2]. Orally available, brain-penetrant α1-noradrenergic (NE) receptor antagonists are widely used to treat hypertension and related conditions. Additionally, α1-NE antagonists are used in the treatment of post-traumatic stress disorder (PTSD)[3], consistent with the well-documented role of NE in mediating multiple behavioral and physiological processes in stress[4]. Stress is a significant contributor to relapse[5,6]. Stress-related reinstatement is a well-validated animal model of addiction[7–9] and α1-NE antagonists reduce relapse in this animal model[10]. Additional evidence suggests that NE contributes to drug- and cue-related reinstatement/relapse[9,11]. This preclinical evidence in animals suggests the use of α1-NE antagonists may be useful in relapse prevention including stress-related relapse[12–15]. To test this hypothesis, we propose two complementary preclinical and clinical objectives in humans.

1. To translate the strong preclinical evidence from animal models to stress-induced relapse in humans via direct pharmacological antagonism of the NE system in abstinent alcoholics using doxazosin, an FDA-approved α1-NE antagonist.

2. To screen the efficacy of doxazosin to target stress-related relapse mechanisms in abstinent alcoholics as a cost-effective first step to repurpose this α1-NE antagonist for relapse prevention in addiction[16–18].

These objectives will be accomplished by between-subject, double-blind placebo-controlled administration of a therapeutic dose of doxazosin (8 mg/day) to recently abstinent alcoholics for 8 weeks. We assess doxazosin's impact on stress-related relapse mechanisms using a well-validated human model of stressor reactivity (unpredictable shock threat in the NPU task[19]) at baseline, 4 weeks and 8 weeks post-treatment. The NPU task has strong translational ties to both methods and measures from the preclinical literature in rodents and non-human primates[20,21]. This task has demonstrated reliable, robust effects of drug administration and drug deprivation in drug dependent users[22–26]. As such, the NPU task serves as an attractive early surrogate endpoint to examine stress mechanisms. Clinical outcome measures (heavy drinking days) will be measured throughout the 8-week medication period. To accomplish our two objectives, we pursue two specific aims:

**AIM 1: Examine effects of a therapeutic dose of doxazosin on responses to unpredictable stressors in NPU task.** The aim is to obtain preliminary evidence via a laboratory surrogate endpoint to repurpose doxazosin for the treatment of stress-induced relapse mechanisms in alcoholism. **PREDICTIONS**: Following four and eight weeks of therapeutic dosing, doxazosin (8 mg vs. placebo, between-subjects) will selectively reduce response to unpredictable (vs. predictable) stressors indexed by physiological defensive reactivity (startle potentiation) in abstinent alcoholics.

**AIM 2: Examine effects of a therapeutic dose of doxazosin on early clinical outcome measures.** The aim is to obtain additional evidence via clinical outcome measures to repurpose doxazosin for the treatment of stress-induced relapse mechanisms in alcoholism. **PREDICTIONS**: Following eight weeks of therapeutic dosing, doxazosin (8 mg vs. placebo, between-subjects) will decrease heavy drinking days during the medication treatment period.

## Background and Significance

### A1. Drug Addiction, Norepinephrine, And Unpredictable Stressors

Stressors are potent instigators of relapse to drug use in clinical research with abstinent drug dependent humans and preclinical relapse models (i.e., stressor-induced reinstatement) in rodents[5,7]. In rodents, brain norepinephrine (NE) levels are elevated in response to both discrete stressors[27–32] and drug deprivation[9,33]. In humans, plasma and CSF NE-metabolite levels are elevated during alcohol deprivation[34–36] and in response to acute stressors[37–39], suggesting similar NE involvement in drug withdrawal and stressor response in humans.

In rodents and non-human primates, manipulations that increase central nervous system (CNS) NE levels (e.g., yohimbine, NET inhibitor, NE injections) increase drug-seeking behavior across a wide class of drugs including alcohol[40], nicotine[41], cocaine[42–44], heroin[45], and methamphetamine[46]. Although all three central noradrenergic receptor classes (post-synaptic $\alpha$1 & ß; autoreceptor $\alpha$2) are implicated in the etiology of addiction, $\alpha$1-NE receptors may be particularly impactful on stress-induced relapse and drinking/drug use outcomes more generally. Doxazosin and prazosin, which are selective noradrenergic $\alpha$1-NE receptor antagonists, reduce baseline alcohol consumption[47], particularly in alcohol-preferring genetic strains of rats[48–51]. Noradrenergic $\alpha$1-NE antagonists block escalation of drug-seeking behavior in rodent models of dependence for alcohol[47], cocaine[52], opioids[53], and nicotine[54]. Chronic prazosin treatment concurrently reduces anxiety-like behavior and alcohol intake in rodents[55]. Most critically, systemic administration of $\alpha$1-NE antagonists blocks reinstatement of alcohol self-administration that is induced by unpredictable footshock stressors or directly increased NE via yohimbine[10]. Based on this and other preclinical evidence, primarily from animal models, $\alpha$1-NE antagonists have obvious treatment potential for reducing stressor-induced relapse in alcohol and other drug addiction. However, clear translation of this preclinical evidence from animals on the role of $\alpha$1-NE in stress-induced relapse among human abstinent alcoholics requires explicit manipulation of the NE system during stressor exposure. Thus, one important translational aim of the proposed research is to manipulate the NE system via eight week treatment with 8mg/day doxazosin (an $\alpha$1-NE receptor antagonist) and confirm its impact on response to stressors in human alcoholics with a sensitive and precise laboratory stressor task that putatively engages this NE system.

Unfortunately, “stress” remains ill-defined and inconsistently operationalized in both preclinical and clinical research on drug addiction in humans. Research on stress responding implicates central nervous system, endocrine, and peripheral biological systems that produce changes in affect, arousal, and attention[56–59]. However, research is rapidly accruing to suggest that the CNS negative affect component of the stress response, and more specifically, acute response to a subset of stressors that are unpredictable (vs. predictable), may provide a critical mechanism to account for stressor-induced relapse among drug dependent rodents and humans[7]. These unpredictable stressors (i.e., ambiguous or otherwise ill-defined, low probability, temporally imprecise stressors) appear to produce phenomenologically distinct responding via partially separable neural mechanisms relative to predictable stressors (i.e., well-defined, high probability, imminent stressors)[20]. Critically, the NE system has been selectively implicated in response to unpredictable rather than predictable stressors[20]. Moreover, unpredictability is a cardinal feature of the typical stressors that humans experience in their daily lives (e.g., uncertain job/financial security, unpredictable interpersonal conflicts, legal problems, inconsistent social support, illness/death of self or family) and these types of stressors often instigate relapse. As such, examination of NE mechanisms in stress-related relapse requires measures in tasks that can parse unpredictable vs. predictable stressors.

### A2. Startle Potentiation During Stressor Exposure

Programmatic affective neuroscience research has relied heavily on startle potentiation as a primary measure of defensive system activation to parse the neural mechanisms involved in response to unpredictable vs. predictable stressors. In addition, the use of startle potentiation to index affective response to stressors among

rodents, non-human primates, and humans has provided an important animal-human translational bridge in this research[21,60,61]. As such, we have detailed knowledge of the neurobiology of the startle response and its potentiation[21,61–63]. Startle potentiation also can be measured with minimal disruption of task-related processes and reduced influence by demand characteristics than measures under volitional control (e.g., self-report).

In preclinical rodent models, startle potentiation during unpredictable stressors has strongly implicated NE and corticotropin-releasing factor (CRF) sensitive pathways through the lateral divisions of the central amygdala (CeA) and bed nucleus of the stria terminalis (BNST)[20,64,65]. In contrast, distinct pathways through the medial division of the CeA appear responsible for startle potentiation during predictable stressors[20,66,67]. A large corpus of research implicates CRF as a critical mediator of the stress response, particularly to unpredictable stressors[20,68], and NE is a powerful modulator of extrahypothalamic CRF[69–71]. In rodents, $\alpha$1-NE agonists elicit stress-related behaviors (e.g., decreased exploratory behavior) and $\alpha$1-NE blockade reduces stress-induced changes in behavior[70]. Specifically, $\alpha$1-NE antagonists reduce startle potentiation in rodents due to stressor exposure[72], direct manipulations of CRF[69], and other stress-relevant neurotransmitter systems (e.g., dopamine[73]). Baseline startle response in prospectively predicts subsequent voluntary alcohol intake and preference[74], representing a translational marker of risk prediction. In humans, the startle response is potentiated by pharmacological challenge that elevates NE levels via yohimbine in healthy controls and particularly in drug dependent populations[75,76]. However, the effect of an $\alpha$1-NE antagonist on startle potentiation has not been examined in humans to date. Thus, startle potentiation during unpredictable stressors represents 1) a psychophysiological index of heightened response to stressors, 2) is sensitive to CNS NE system activation in rodents, 3) has well known neurobiological substrates in rodents, and 4) and can be assessed in rodents, non-human primates, and humans, positioning it as an attractive translational measure.

**A3. The No Shock, Predictable Shock, Unpreditable Shock (NPU) Task**

Research in affective neuroscience has relied extensively on cued stressor (e.g., threat of electric shock) tasks to explicate psychological and neurobiological mechanisms involved in the negative affective response to stressors in animals and humans. Christian Grillon at NIH has developed a cued-stressor task called the “No Shock, Predictable Shock, Unpredictable Shock” (NPU) task to carefully contrast response to unpredictable vs. predictable stressors[19,77]. Predictable shock conditions involve administration of 100% cue-contingent, imminent electric shock. Unpredictable shock conditions involve temporally and probabilistically uncertain administration of shock. Startle potentiation during unpredictable shock (relative to no-shock blocks) provides the primary measure of negative affective response to stressors that in rodents engages both NE system activity and elicits etiologically relevant behaviors for addiction (i.e., stressor-induced reinstatement). This task represents a direct translation of methods and measures used in rodents to parse the neural mechanisms involved in response to unpredictable vs. predictable stressors[20,66]. Dr. Curtin’s (PI) laboratory has successfully used this task with humans in a number of studies to date[22,24,78,79]. We will use startle potentiation in this task in the proposed research as an assay of an early surrogate endpoint to assess treatment efficacy (**AIM 1**).

**A4. Preliminary Evidence**

Recent research from Curtin’s lab (R03 AA13422; R01 AA15384; R01 DA033809; R36 DA022373; P50 DA19706) provides compelling evidence that 1) unpredictable stressors in the NPU and related tasks potentiate the startle response, 2) anxiolytic drugs robustly and selectively reduce startle potentiation during unpredictable (vs. predictable) stressors, and 3) drug deprivation or abstinence robustly and selective increase startle potentiation during unpredictable (vs. predictable stressors).

Moberg & Curtin (2009) demonstrated that a moderate dose of alcohol (target BAC= 0.08%) selectively reduced startle potentiation during unpredictable but not predictable threat of electric shock in the NPU task (see red box in left panel of Figure 1)[22]. In other research, Curtin and colleagues demonstrate similar selective

effects of varying doses of alcohol on unpredictable stressors when unpredictability was established via manipulation of the timing[78], probability[24], intensity[79], and location[80] of the threat. In the more recent of these studies[79,80], self-reported negative affect was also measured and it displayed comparable selective effects of alcohol during unpredictable stressors. Similarly, benzodiazepines also selectively reduce startle potentiation to unpredictable stressors[81]. These studies provide evidence that startle potentiation in the NPU and related tasks that manipulate stressor unpredictability provide a sensitive index of the effects of pharmacological agents on negative affective response to stressors.

In a parallel line of research, Curtin and colleagues have demonstrated that drug deprivation or abstinence selectively increases startle potentiation to unpredictable (vs. predictable) stressors. For example, Moberg & Curtin (2012)[26], demonstrated that alcoholics in early (1-8 weeks) abstinence displayed selectively increased startle potentiation during unpredictable (vs. predictable) shock threat relative to matched controls (see red box in right panel of Figure 1). Similarly, cigarette smokers displayed elevated startle response selectively during unpredictable stressors (vs. predictable stressors) after 24-hours of nicotine deprivation compared to non-deprived smokers[23]. Heavy daily marijuana smokers showed significantly increased startle potentiation during unpredictable stressors after three days of marijuana deprivation relative to non-deprived smokers and non-smoker controls[25]. These studies demonstrate that selectively elevated startle potentiation during unpredictable stressors provides an objective, non-invasive physiological assay of the effects of drug deprivation and abstinence across alcohol and other addictive drugs.

This human data, in combination with ample evidence from rodent models on NE and startle potentiation during unpredictable threats[20,69,82,83], support our use of a manipulation of the NE system via an $\alpha$1-NE antagonist (doxazosin) in the NPU task to advance translational research to target mechanisms for novel pharmacological treatments of stress-induced relapse in humans (**Preclinical objective 1; AIM 1**). In addition, the body of preclinical evidence on startle potentiation during unpredictable stressors in animals and humans supports the use of the NPU task as an early surrogate endpoint, which combined with clinical outcome measures, can be used to provide preliminary evidence of the efficacy of doxazosin as a treatment to reduce stress-induced relapse (**Clinical objective 2; AIMS 1-2**). Validation of doxazosin's effects on NPU task via clinical outcomes would lay the groundwork for using the NPU task to screen (e.g., surrogate endpoint) for future drug development (e.g., CRF-antagonists) prior to moving to larger/longer and more expensive clinical trials.

**Figure 1: Alcohol Administration and Deprivation on Startle Potentiation in the NPU Task**
Recent research from Curtin's laboratory has established that administration of a moderate dose of alcohol (BAC= 0.08%) selectively reduces defensive response to unpredictable stressors measured by startle potentiation in the NPU task (see red box in left panel; Moberg & Curtin, 2009). In contrast, alcoholics in early abstinence (1-8 weeks) display selectively exaggerated defensive response to unpredictable stressors (see red box in right panel; Moberg, & Curtin, 2012)


We believe this preliminary evidence also establishes that Curtin's laboratory has the expertise necessary to recruit clinical samples of alcohol and other drug dependent users, precisely manipulate and measure stress, and safely administer drugs in the laboratory. Curtin's lab has the infrastructure to conduct clinical trials. His current R01 (DA033809) examines the impact of treatment with nicotine replacement therapy on stress mechanisms in smokers (via NPU task) and their predictive utility regarding smoking cessation. Curtin has recruited Co-Is and consultants with complementary expertise in randomized controlled trials and clinical and research administration and management of α1-NE antagonists in humans and rodents (see publications and grant support from biosketches of Berridge, Zgierska, Ahearn, and McKee). Of note, Dr. Ahearn has extensive experience conducting RCT with α1-NE antagonists as the site PI for a multi-center national VA cooperative study to evaluate the efficacy of prazosin as a treatment PTSD related nightmares in combat veterans.

## A5. Novel Treatments For Stress And Alcoholism Via Ne System

A number of FDA-approved pharmaceutical compounds that have effects on the central NE system have been clinically available for decades, primarily for their peripheral effects for the treatment of hypertension and related cardiovascular health issues. These drugs all effectively reduce the effects of NE by either blocking the α1 (e.g., doxazosin, prazosin) or β (e.g., propranolol, carvedilol) receptors on the post-synaptic neuron or activating the pre-synaptic α2 autoreceptor (e.g., clonidine, lofexidine) to inhibit further NE release. There is mounting preclinical evidence that all three classes of receptors are intricately involved in the stress response and also are critical mechanisms for stress-induced relapse in addiction. Indeed clonidine is recommended as a second-line medication for tobacco cessation[84] and widely used to treat the physical withdrawal syndromes of alcohol and opioid withdrawal[85]. However, due to the side effect profile (e.g., sedative effects), clonidine is often not well tolerated as a long-term maintenance medication[84,86–88]. Similarly, propranolol is commonly used off-label to treat somatic symptoms of performance anxiety, but recent work has yielded mixed evidence for the treatment of other stress-related disorders such as PTSD[89,90]. Thus, although there is strong preclinical evidence to support the investigation of all three classes of drugs as treatments, α1-NE antagonists (e.g., doxazosin, prazosin) appear to be the most promising candidate class for therapeutic effects on stress-related relapse.

For example, prazosin, a highly selective (Ki=0.12–0.31)[91,92] α1-NE receptor antagonist, has become the focus of a promising body of research on the treatment of post-traumatic stress-disorder (PTSD) and alcoholism[93,94], which are frequently comorbid and share a common feature of heightened stress-reactivity. Over the past decade, Raskind and colleagues have led a series of clinical trials that demonstrate prazosin is an effective treatment of hyperarousal, sleep-disturbances, and global functioning among patients with PTSD[3,95–98]. During the course of these studies they anecdotally observed that individuals with both PTSD and alcoholism also stopped or reduced their alcohol use. Encouraged by these findings, Simpson, and colleagues (2010)[12] conducted a small (N = 24) Phase 2 randomized clinical trial for alcohol dependence and found that prazosin (up to 16 mg/day for 6 weeks) reduced the drinks per day and number of days drinking in the final weeks of treatment.

In another small trial (N = 17), Fox and colleagues (2012)[13] demonstrated that among treatment-seeking alcohol dependent adults, prazosin (16 mg/day for 4 weeks) reduced self-reported alcohol craving and negative affect in response to guided imagery exposure to stress. This is the first evidence in humans implicating α1-NE in stress-induced relapse in addiction. However, this surrogate endpoint of stress-related imagery reactivity has less direct ties to preclinical rodent models of stress reactivity than our model of startle potentiation in the NPU task. Furthermore, the primary outcome measures were self-reported negative affect and measures of peripheral nervous system activation (e.g., cortisol, ACTH). Although there has been considerable interest in the field regarding abnormalities in HPA axis functioning among human drug dependent individuals, George Koob and others have provided compelling evidence that CRF and NE pathways within the central nervous system, rather than the periphery, are the key mediators of stress-induced relapse mechanisms[7,68]. Startle potentiation during unpredictable stressors provides a measure that has stronger direct ties to CNS stress system activity in the extended amygdala, which mediates relapse in preclinical rodent models[7,20].

These initial positive findings in humans[12,13] have generated substantial excitement in the field that α1-NE antagonists, including prazosin and doxazosin, may represent novel treatments for alcohol dependence[99,100]. In particular, α1-NE antagonists may provide longer term adjunct therapy (i.e., maintenance up to several years or longer) to support relapse prevention in the face of stressors. α1-NE antagonists are not contraindicated with first line treatments for alcohol dependence and in fact prazosin has been found to increase the effectiveness of naltraxone in reducing alcohol consumption in rodent models[101]. As further evidence of this excitement for α1-NE antagonists for treatment, NIAAA has recently funded two larger RCTs (N = 120-150) to investigate the efficacy of prazosin for alcoholism treatment (Clinical Trials: NCT00762710 & NCT00585780).

**A6. Why Repurpose Doxazosin?**

As the preliminary evidence of prazosin's efficacy has mounted over the past few years, attention is now poised to shift to another, perhaps even more promising α1-NE receptor antagonist, doxazosin. Doxazosin has a similar chemical structure to prazosin, but has a more favorable clinical profile for alcoholism treatment. Importantly, doxazosin has a significantly longer half-life (16-22hrs[102]) compared to prazosin (2-3hrs[103]). Therefore, doxazosin only requires once/daily dosing as opposed to 2-3x/day dosing of prazosin. This is not insignificant, as medication compliance represents a major obstacle in treatment of substance use disorders. Both medications have been used for decades with millions of patients demonstrating good safety profiles and generally well tolerated side effects. Furthermore, in normotensive adults doxazosin can be used at morning or night and has minimal hypotensive effects (particularly compared to prazosin)[104,105], increasing its utility in clinical practice. Of practical importance, doxazosin is available in generic formulation and therefore affordable.

A nascent body of research has begun to support the use of doxazosin for the treatment of PTSD, alcoholism, or other drug dependence. In 2013 Rasmussen and colleagues provided the first preclinical evidence that

doxazosin reduces alcohol drinking in alcohol-preferring rats[51]. De Jong and colleagues demonstrated that 8 mg doxazosin improved PTSD symptoms in a small (N=12), open label trial[106]; currently being followed up in the VA system (NCT01959022). Doxazosin (4-8 mg/day) reduced subjective pleasure associated with acute cocaine administration[107] and increased the number of cocaine-negative urine screens (vs. placebo) in a pilot treatment study[108]. Our consultant, Dr. Sherry McKee, is currently conducting a trial examining the effects of 4 mg or 8 mg doxazosin (vs. placebo) on surrogate endpoints for stress-induced smoking lapse behavior (using a lab model not suitable for alcoholics; NCT01730846). There is also one ongoing NIAAA-funded Phase 2 RCT of 16mg/day doxazosin treatment for alcoholism that is investigating clinical outcomes broadly, but not mechanisms of change or stress-relevant processes specifically (NCT01437046).

Our application builds on the animal and human preclinical evidence of the role of $\alpha$1-NE mechanisms in stress-related relapse, promising evidence of prazosin's treatment efficacy, clear practical clinical advantages of doxazosin relative to prazosin, and nascent but encouraging evidence with doxazosin. We believe our Phase 2 clinical trial of doxazosin focused on an early surrogate endpoint of unpredictable stressor reactivity (i.e., 4 week NPU task), with complementary clinical outcomes (i.e., heavy drinking measures), is well timed to be highly impactful (**Clinical objective 2; AIMS 1-2**). We believe that the parallel pursuit of mechanism (**Preclinical objective 1; AIM 1**) in this application further increases the potential impact of this research.

## Innovation

This research is innovative in its tight translation of research findings from animal models to the examination of human addiction etiology and treatment ("bench to bedside") using tasks (NPU task), measures (startle potentiation), and manipulations ($\alpha$1-NE antagonist) that have been used in almost identical form in both animals (rodents, non-human primates) and humans[20]. Cross-species translational research is common, but often done with methods that are so divergent across species that successes and failures alike are difficult to interpret unambiguously. This is not the case with the research proposed in this application. Although the animal preclinical evidence for NE stress mechanisms is well established, direct manipulation of this system in humans via administration of an $\alpha$1-NE antagonist is innovative.

This research is innovative in its simultaneous pursuit of both preclinical animal to human translation of mechanism and human preclinical to clinical translation of this mechanism to treatment. This allows us to simultaneously use our intervention ($\alpha$1-NE antagonist) as a treatment for alcoholism (**AIM 2**) while also probing for mechanisms in the etiology of alcoholism with respect to neuroadaptations in the stress system resulting from chronic alcohol use[7] (**AIM 1**). This approach anticipates changes that NIMH Director Tom Insel will implement for future RCTs funded by NIMH[109–111], but which remain uncommon in addiction research.

This research is also innovative in its use of a laboratory surrogate endpoint to screen drug efficacy (AIM 1). David Kessler, former FDA Commissioner, has observed that the considerable advances in AIDS research can be attributed, in part, to the development of "surrogate endpoints" such as HIV viral load that index treatment effects in randomized clinical trials far earlier than the obvious clinical endpoint of survival duration. Kessler and others (e.g., Insel, Hyman) have strongly advocated the development of such surrogates for other diseases: measures that index effects that are linked with ultimate outcomes, but that can be obtained relatively quickly and inexpensively[1,17,112,113] (**AIM 1 & 2**).

Our use of startle potentiation during unpredictable stress in the NPU task is also consistent with the "Fast Fail Trials (FAST)" initiative[114] at NIMH that seeks to identify new or repurposed compounds that merit more elaborative testing concomitant with efforts to identify targets in the brain for the development of additional

candidate compounds. Compounds that are found to engage a target in the brain and alter an indicator of brain function advance quickly for additional evaluation.

Insel also clearly argues that given substantial cuts in R&D budgets for new psychiatric drugs at most major pharmaceutical companies the near term outlook of novel molecular targets is grim[1,2]. Therefore, it is critical to take advantage of existing compounds with proven safety record acting on neurotransmitter systems that have been implicated in the etiology of psychiatric disorders. Repurposing existing pharmaceutical agents has recently been promoted by NIH director, Francis Collins, as a research priority[1,115,116]. The current proposal is one clear example of this theme to screen doxazosin for repurposing for the treatment of stress-induced relapse in alcoholism (**AIM 2**).

Our focus on startle potentiation to unpredictable and predictable stressors that can be measured along a continuum from normal to abnormal aligns well with the current paradigm shift advocated by the NIMH's Research Domain Criteria (RDoC). Briefly, RDoC calls for a dimensional approach to studying the roots of human behavior at multiple levels of analysis that cuts across DSM diagnostic categories[1,117–120]. Our proposed research examines individual differences defined within the Negative Valence System (i.e., acute threat/fear to predictable stressors and potential threat/anxiety to unpredictable stressors) using a task recommended by the NIMH workgroup[121]. Furthermore, we index these dimensions across levels of analysis (neurotransmitter, physiology, self-report, drinking behavior). Although this task is used to study abnormal processes in abstinent alcoholics, it exemplifies an approach to evaluate stress-reactivity dysregulation that spans not only multiple addictive drugs (e.g., tobacco, marijuana, opiates); but likely other disorders (e.g., PTSD) that may share a common neuroadaptation that manifests as a heightened stress response.

# Research Design & Methods

## C1. Brief Overview

Recently abstinent (1-8 weeks) alcoholics will be recruited to participate in an eight-week double-blind, randomized placebo-controlled trial (RCT) examining the effects of an $\alpha$1-NE antagonist (doxazosin) on the defensive (physiological) response to stressors using a well-validated animal-human translational stressor task (NPU task). Study Visit 1 provides a pre-treatment baseline assessment of participants' NPU task stress-sensitivity prior to doxazosin/placebo administration. Next, participants are randomly assigned between-subjects to initiate an 8-week dose escalation schedule up to 8 mg maximum doxazosin dose or placebo as they continue their efforts to abstain from alcohol. After four weeks (Study Visit 2) of treatment, participants will return to complete the NPU task again, and at both four weeks (Study Visit 2) and eight weeks (Study Visit 3), to assess clinical outcomes. These visits allow for evaluation of the effect of a therapeutic dose of doxazosin on the early surrogate endpoint of stress-reactivity (unpredictable shock threat in NPU task; Visit 2; **AIM 1**) and proximal clinical outcomes (heavy drinking days; Visits 2 & 3; **AIM 2**).

## C2. Participants and Recruitment Sites

**Participants**: We will recruit abstinent alcoholics (38% female) aged 18-65 years. Participants will meet criteria for Alcohol Use Disorder with at least moderate severity ($\geq$4 DSM-5 criteria) and be at least one but no more than eight weeks abstinent from alcohol use at Screening Visit, and still abstinent at Visit 1. Participants who are eligible at screening but lapsed at Visit 1 will be rescheduled when they are again at least 1 week abstinent. Participants will be excluded if they have a lifetime history of severe and persistent mental illness (SPMI; e.g., bipolar disorder, schizophrenia, suicidal ideation or psychosis) or current substance use disorder and is not currently pursuing abstinence (other than alcohol or nicotine). Participants with co-morbid Axis 1 disorders will be included unless they are using medications that affect the startle response or contraindicate doxazosin use.

Participants must be able to read and write in English and have normal or corrected-to-normal vision and hearing. Participants will be excluded for: color blindness as task stimuli include colored geometric shapes; use of current medications acting directly on the noradrenergic system (e.g., clonidine, propranolol); any medical condition or concomitant medication that contraindicates the administration of doxazosin or electric shock. Women must test negative for pregnancy in a urine screen at all interim study visits, agree to use a reliable form of birth control, and may not be breastfeeding during the study. See Appendix for full eligibility criteria.

**Recruitment sites:** We plan to recruit participants from 5 local treatment sites across two large healthcare centers: Access Community Health Centers and Journey Mental Health Center. Curtin has pre-existing connections with both centers as recruitment sites in other funded research (R01 AA024391). These sites were selected to support recruitment of a diverse set of patients, adequate patient flow for study recruitment, and patient access to the study site. Journey Mental Health Center provided treatment to approximately 1500 patients with alcohol use disorder in 2013. Access Community Health provided treatment to approximately 3000 patients with alcohol or other substance use disorder in 2013. We will also be doing community recruitment by posting information in places likely to be seen by the target population. This would include locations such as Alcoholics Anonymous meetings and buses and online sites like Facebook and Craigslist. We will also recruit participants via advertisements on television and radio stations.

## C3. General Procedures

All study visits, with the exception of the screening visit, will take place in the Clinical Research Unit (CRU) outpatient unit at the University of Wisconsin Hospital (see letter of support from CRU). All participants will complete a total of three outpatient study visits in addition to the screening visit (see Table 1 for outline of procedures).

At the screening visit, which will take place at the Addiction Research Center offices, general laboratory procedures and risks and benefits will be explained to the participants and informed consent will be obtained. Inclusion/exclusion criteria will be confirmed using interviews conducted by a bachelors- or master-level clinical psychologist (under direct supervision of a licensed clinical psychologist), a urine pregnancy test (females only), blood pressure and heart rate, and self-report questionnaires (Medical Screening Questionnaire) (see Appendix C). Participants will complete the CIWA-Ar; if the participant is currently symptomatic of alcohol withdrawal, Study Visit 1 will be scheduled at least one week in the future. The psychologist will confirm alcohol use disorder diagnosis, establish that the potential participant is free from severe and persistent mental illness and current suicidal ideation, and document any other current Axis I disorders by administering the Structured Clinical Interview for DSM Disorders-Research Version (SCID-RV; see letter of support from Dr. Burk). The SCID-RV interviews will be audio recorded to permit clinical supervision and inter-rater reliability. These recordings will be deleted immediately after review.

At Study Visit 1 (CRU), participants will provide a breath sample to verify an initial blood alcohol concentration (BAC) of 0.00 (Alcosensor IV; Intoximeters, Inc.). Participants will complete the CIWA-Ar; if they are currently symptomatic of alcohol withdrawal, Study Visit 1 will be rescheduled at least one week in the future. The provider will conduct a medical history/exam and review current medication. Medical staff will collect orthostatic vital signs, a blood sample for lab tests, and a urine sample to verify no pregnancy (females only). The provider will also conduct an ECG (see further details about safety procedures in Protection of Human Subjects section). Participants will then complete a variety of self-report batteries, for post hoc individual differences analyses (see Appendix A).

Study staff will then prepare the participant for the NPU task with the application of physiological sensors. Next participants receive a series of shocks of increasing intensity (7 mA maximum) to assess their subjective tolerance threshold as per standard procedures from our laboratory[22,128]. Their subjective maximum tolerated shock from the screening visit is used during the NPU tasks at both Visit 1 and Visit 2 to minimize individual differences in subjective pain tolerance. Next participants complete the NPU task (see below). After the NPU task, participants will be randomly assigned to drug group (doxazosin vs. placebo; between-subjects) in a stratified blocked schedule by sex using urn randomization procedures[129,130]. The randomization and double-blind will be implemented and maintained by the UW Pharmaceutical Research Center (see letter of support), which is located in the same building as the CRU. All participants are told that they will receive either doxazosin or placebo during the study, but neither the participants nor the research staff will be aware of the group they are randomized to receive. Participants who are off study and were consented under a previous protocol which promised unblinding will still be unblinded, via phone contact after their last visit.

Participants will take the first study medication dose at home that evening after Study Visit 1 (Treatment Day 1). Staff will call participants on Day 2 to confirm initial compliance and monitor any adverse events. Participants continue 8 weeks of treatment including an 18-day escalating dose schedule up to a therapeutic dose (8 mg) of doxazosin (or placebo; see Doxazosin Dosing Schedule below). Additionally, participants will attend four medical monitoring visits during the first month of treatment (see below).

Participants will return after 4 and 8 weeks of treatment (Study Visit 2 & 3) to complete a timeline-follow-back (TLFB) procedure to assess drinking since the previous visit to index drinks per days to asses heavy drinking days for this 8 week treatment period. At 4 weeks (Study Visit 2) we will again assess stress-reactivity in the NPU task. If participant reports a binge-drinking episode one week or less prior to Study Visit 2, staff will administer the CIWA-Ar. If participant is currently symptomatic of alcohol withdrawal, Study Visit 2 will be rescheduled. In addition, at both visits participants complete breath and self-report tests as outlined above and detailed in table below. Upon completing their final study visit all participants will be debriefed and receive their final study payment.

Participants receive partial compensation at each Study Visit; they receive $320 for study procedures (approximately 16.5 hrs across screening visit, three study visits and four medical monitoring visits), and up to $200 in bonuses: $25 for attending their first hospital visit, $25 for keeping all their original appointments, $25 for being on time to all their hospital visits, $25 for medication compliance (at least 90%), and $100 for attending all visits and completing all study procedures. Total compensation is therefore up to $520  If participants are deemed not eligible at the screening session they will be paid $25 at that time.

| Table 1: Overview of Study Procedures and Timeline **CATEGORY** | **PROCEDURE** | **Screening Visit** | **STUDY VISIT 1** | **MONITORING VISITS** | **STUDY VISIT 2** | **STUDY VISIT 3** |
|---|---|---|---|---|---|---|
| **TREATMENT DAY:** | | **DAY 0** | **DAY 1** | **DAY 6, 10, 14, 18** | **DAY 29** | **DAY 57** |
| **SCREENING** | | | | | | |
| Eligibility | Consent | X | | | | |
| | Inclusion/exclusion criteria - self-report | X | | | | |
| | Inclusion/exclusion criteria - medical | | X | | | |
| Lab chemistry | Blood chemistry (Chem-12: CBC, TSH) | | X | | | |
| Pregnancy test (females only) | In-stream pregnancy test | X | | | | |
| | Urine analysis pregnancy test | | X | X | X | |
| Medical history/exam | Medical history | | X | | | |
| | Concomitant medications | | X | | | |
| | Physical exam | | X | | | |
| | Vital signs | | X | X | | |
| | ECG | | X | | | |
| Psychiatric evaluation | SCID | X | | | | |
| Self report assessment battery | Self report (Qualtrics) battery | X | X | | | |
| **SAFETY & COMPLIANCE** | | | | | | |
| Study visit monitoring | Vital signs; Adverse events | | X | | X | X |
| Treatment monitoring | Monitoring visits: Adverse events; vitals | | | X | | |
| | Staff phone calls: Adverse events | | | | Day 2, 36, 43, 50 | |
| Medication compliance | Phone call reminder | | | X | X | X |
| | Pill counts; self-report | | | X | X | X |
| | Review of smart caps logs (opening times/dates) | | | X | X | X |
| Behavioral intervention | Brief motivational intervention (following NPU task) | | X | | X | On lapse |
| Acute craving (for study release) | Desire for Alcohol Scale (following NPU task; repeat as needed) | | X | | X | |
| **OUTCOMES** | | | | | | |
| Stress reactivity | Startle potentiation and self-report negative affect in NPU task | | X | | X | |
| | Perceived Stress Scale | | Past week | Past week | Past week | Past week |
| Alcohol use | Blood alcohol concentration (via breath test) | X | X | X | X | X |
| | TLFB (continuous abstinence, days drinking/week, drinks/day) | | Since last visit | Since last visit | Since last visit | Since last visit |
| Craving | Penn Alcohol Craving Scale | | Past week | Past week | Past week | Past week |

p

## C4. Doxazosin Dosing Schedule

| TABLE 2 | TREATMENT DAY | DISPENSATION DAY (mg/capsule) | DAILY DOSE |
|---|---|---|---|
| TREATMENT | 1 - 5 | Day 1: Study Visit 1 (1 mg) | 1 mg qd |
| | 6 - 9 | Day 6: Monitoring Visit 1 (2 mg) | 2 mg qd |
| | 10 - 13 | | 4 mg qd |
| | 14 - 17 | | 6 mg qd |
| | 18 - 28 | Day 18: Monitoring Visit 4 (4 mg) | 8 mg qd |
| | 29 - 56 | Day 29: Study Visit 2 (4 mg) | 8 mg qd |
| TAPER | 57 | Day 57: Study Visit 3 (6 x 1 mg) | 6 mg qd |
| | 58 | Day 58 (4 x 1 mg) | 4 mg qd |
| | 59 | Day 59 (2 x 1 mg) | 2 mg qd |
| | 60 | Day 60 (1 x 1 mg) | 1 mg qd |

All doxazosin and matched-placebo capsules will be prepared and blinded by the University of Iowa Pharmaceuticals, randomized by the UW Pharmaceutical Research Center and distributed through the UW CRU. Half the participants (N=80) will receive doxazosin and half (N=80) will receive a matched number of placebo pills daily for 8 weeks of treatment. The target therapeutic dose (8 mg doxazosin) will be achieved after an 18-day dose escalation schedule. Medication will be distributed across 6 visits. Participants will be provided 3-5 days of extra pills of their current dose at each distribution to provide flexibility in missed appointments; however, participants will not receive their next escalated dose until they attend an in-person visit. On study completion all participants will taper off doxazosin (or placebo) over 5 days using a protocol successfully employed by our consultant Dr. McKee in a recently completed smoking cessation trial. Participants who withdraw from the study will be tapered using the same protocol. There are no adverse effects with rapid cessation that may occur in other noradrenergic drugs (e.g., propranolol rebound hypertension)[131].

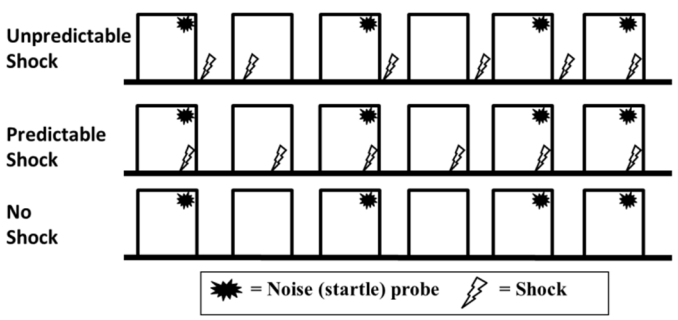
## C5. Medical Monitoring And Medication Compliance

Participants' safety will be evaluated by the study staff and medical staff via measurement of vital signs and self-report of medication side effects, adverse events, medication compliance and alcohol use at each of the three Study Visits (Day 1, 29, 57). Study staff will call participants on Day 2 to monitor (via self-report) adverse events and initial compliance with taking the first pill on Day 1. In addition, participants will attend four additional Medical Monitoring Visits at the UW Hospital the day of each dose escalation (Day 6, 10, 14, 18) for similar evaluation. As such, participants are evaluated in person prior to each dose escalation and at 4 weeks and 8 weeks into treatment.

Participants will complete safety check-ins weekly between Study Visit 2 and 3 (Day 36, 43, 50) to evaluate safety via self-report of medication side effects, adverse events, medication compliance, and alcohol use. These check-ins can occur via phone call or electronic survey according to participant preference. For participants who opt for electronic surveys, study staff will follow-up via phone if the participant reports side effects or problems or if the participant does not complete the survey. While we anticipate that subjects will tolerate study medication well, should participants experience adverse medication side effects, titration will be stopped at the highest tolerable dose. Maximum achieved dose will be included as a covariate in preliminary statistical models.

Medication compliance will be facilitated and increased by several complementary methods. First, participants will receive automated reminders sent daily to their cell phone. These messages will remind them to take their study medication and can be sent via SMS text-message. These prompts also remind participants to contact study staff if they have any side effects or barriers to compliance. This strategy has been successfully implemented in previous addiction trials[12,132,133]. Medication bottles will also be equipped with a medication event monitoring system (smart caps). Smart caps are reusable and provide a time stamped medication use/bottle access. They also provide a programmable visual and auditory reminder of administration time to increase compliance. At all medical monitoring and study visits medication compliance will be assessed by study staff via pill count and download of smart caps logs.

**C6. NPU Stress-Reactivity Task**




Participants view a series of colored square "cues" on a computer in a blocked design[19,22]. There are three block types: No Shock (N), Predictable Shock (P), and Unpredictable Shock (U). Each type of shock block is presented twice and the no shock blocks are presented three times, with blocks counterbalanced both within- and between-subjects (e.g., 2 block orders: PNUNUNP, UNPNPNU). All blocks include 6 cues presented for 5s in the center of the computer monitor separated by a variable inter-trial-interval (ITI; mean 15s, range 10-20s). Electric shock is administered .25s prior to cue offset during every cue in the Predictable shock blocks so that the appearance of the cue 'predicts' that the shock will occur in a few seconds. Electric shock is administered at pseudo-random times during both cues and ITIs in the Unpredictable shock blocks so that the occurrence of the shock is completely unpredictable by the participant. Six electric shocks are administered in each Predictable and Unpredictable shock block. No electric shock occurs during the no-shock blocks. Participants are verbally informed of the cue-shock contingencies to ensure robust block differences. The task lasts approximately 20min.

The primary dependent measure in the NPU task is startle potentiation. The eye-blink startle response is elicited with a binaurally presented acoustic startle probe (50ms, 102dB white noise with near instantaneous rise time). Startle probes occur at 4.5s post cue-onset on a random subset of 4 cues in every block. Serial position of startle probes across the three block types (No Shock, Predictable Shock, Unpredictable Shock) is counterbalanced within-subjects. Electromyogram (EMG) activity to the startle probes is recorded from two Ag-AgCl sensors placed according to published guidelines beneath the eye over the orbicularis oculi muscle[134]. Electromyogram activity is sampled at 2000Hz with an online bandpass filter (1-500Hz) using NeuroScan Grael bioamplifiers (Compumedics USA, El Paso, TX). Offline processing includes a high-pass filter (4$^{th}$ order 28Hz Butterworth filter), creating epochs from 50ms pre-probe to 250ms post-probe, signal rectification and smoothing (30Hz lowpass filter). The startle response is quantified as the peak amplitude 20-100ms post-acoustic probe onset relative to a 50ms pre-probe baseline. Startle potentiation during cues is calculated separately for unpredictable and predictable blocks as the difference between response to probes during shock and no-shock blocks. After the NPU task, participants retrospectively report their negative affective state during each block type (Post-Experimental Questionnaire, PEQ). We recently found this self-report measurement is sensitive to the anxiolytic effects of alcohol[79,80].

**C7. Brief Motivational Interventions**

At Study Visits 1 and 2 all participants will receive standardized 30 min psychosocial support sessions focused primarily on motivational enhancement therapy (MET) for relapse prevention[135–137] and treatment compliance provided by BS, MS or PhD level clinicians (see letter of support from Dr. Burk). For clinical supervision purposes, the MET sessions will be audio recorded; these recordings will be deleted immediately after review. Brief motivational enhancement therapy and related interventions have been demonstrated to affect drinking behavior across a variety of treatment provision settings from primary care to specialty addiction treatment clinics[137–139]. The primary purpose of including MET is to improve clinical outcomes related to alcohol abstinence in all research participants. There are likely to be secondary benefits; MET may also increase medication compliance and decrease study attrition.

The provision of MET to all research participants also provides additional risk reduction regarding our use of the NPU task. It is unlikely that the NPU task would substantially affect craving and/or relapse risk after release from the monitored medical setting. The NPU task represents a robust laboratory stressor but it is no more

stressful than other common everyday stressors. Moreover, it is punctate and terminates with the conclusion of the task, unlike many other life stressors. Nonetheless, brief MET during each study visit initiated after the NPU task provides an additional safeguard against increased craving and/or relapse risk following the NPU task. In addition we will provide an additional 30 minutes of MET at any study visit if relapse is reported and the participant requests counseling. We also measure participants' self-reported craving on arrival at the CRU and immediately prior to release. Participants are required to return to their baseline levels of craving before release (see Protection of Human Subject).

**C8. Plan for Intoxicated Participants**

Participants who arrive intoxicated to any study visit, including potential participants who arrive intoxicated to the screening, will be questioned about their method of transportation. If the participant affirms that they are not driving themselves (walking, public transportation, driven by a friend) they will be permitted to leave with no further intervention.

If the participant affirms that they drove themselves, we will offer to call a cab or a friend to drive them. If this offer is declined, we will suggest that they should stay in the CRU or ARC until their BAC registers below 0.03. This release criterion has been used for many years in our other UW research that involves alcohol administration to research participants. As such, it seems equally appropriate for release for an ineligible participant who has self-administered their own alcohol. By way of comparison, a BAC of 0.08 is considered per se evidence of impairment from alcohol and with a BAC of > 0.05 alcohol impairment can be considered a contributing factor when accident or injury occurs.

If the participant declines to stay and indicates they plan to drive themselves, we will tell the participant that we will call the campus police so that the participant can make a more informed decision about what course of action to take. If the participant continues to indicate they plan to drive, we will call the campus police if the participant is driving away and provide information about the possibility of an impaired driver in the vicinity. We will not reveal the participant's name to the police in order to protect their confidentiality.

## Statistical Analysis:

**Planned Data Analysis for Specific Aims**

Analyses for quantitative and dichotomous dependent measures will be accomplished within either General or Generalized (binomial family with logit link function) Linear Models, respectively, using R[140]. In the sections below, we briefly describe the primary factors in statistical models to evaluate each Specific Aim. All models will include number of days abstinent at Visit 1 as an interactive between-subjects regressor to evaluate if drug effects and outcomes are comparable across alcoholics who vary in their previous duration of abstinence (1-8 weeks) on study initiation, although this has not moderated the effects on NPU task in our preliminary studies. Numerous individual difference measures (e.g., sex, mood/anxiety disorder comorbidity, tobacco use, trait affect, alcohol dependence severity, other treatment) are available to add to these models as interactive between-subject regressors in secondary analyses to evaluate possible individual difference moderators of drug effects.

**AIM 1:** Unpredictable startle potentiation from the NPU task at 4 weeks will be analyzed in separate general linear models controlling for baseline NPU responses (Visit 1) with repeated measures on Condition (unpredictable vs. predictable shock). A between-subjects regressor for Treatment (8 mg doxazosin vs. placebo) will be included. Aim 1 predictions will be supported by significant Treatment X Condition interactions with doxazosin producing selectively larger reduction in startle potentiation during unpredictable relative to predictable shock.

**AIM 2: Any heavy drinking (coded yes vs. no dependent if the participant reported any days** where they consumed >4 drinks per day in men/ >3 drinks per day in women during the medication period) will be analyzed in a generalized linear models with a between-subjects regressor for Treatment (8 mg doxazosin vs. placebo). To be conservative, this analysis will be pursued as an intent to treat (ITT) analysis. Aim 2 predictions will be supported by significant Treatment effects with doxazosin producing selectively lower proportion of participants reporting any heavy drinking. This outcome is measured at Visits 2 & 3 and can be obtained even if the participant arrives with positive BAC.

**Timeline**

This project will be completed within five years of its funding. This goal is reasonable given our team's expertise in conducting both randomized controlled trials and psychophysiological laboratory research working with drug administration, community participants, and stress reactivity. Based on prior recent experience with a similar population of alcoholics who completed multiple laboratory visits, we anticipate that 85% of participants who complete the first visit will return to complete the study. We can complete up to five study visits per week and expect to average approximately 3 study visits per week to account conservatively for no-shows, failed eligibility criteria, equipment failure, and other data loss. We anticipate completing data collection in 4 years, allowing time at the beginning of the grant period for set-up and final pilot testing and the end of the grant period for manuscript preparation.

# Protection of Human Subjects

## D1. Risks to the Subjects

**Human Subjects Involvement and Characteristics**. Alcohol dependent participants (age 18-65 years old) in early abstinence (at least 1 week but no more than 8 weeks since last alcohol use) will be recruited for the study. The ethnic background of the study participants will reflect the demographics of our recruitment sites. No one will be excluded from participation in the study because of minority group membership. Participants must be able to read and write in English.

On arrival at the Addiction Research Center space in Brogden Hall for the screening visit, participants will be provided with and asked to sign a consent form that details all procedures involved. An in-stream urine pregnancy test will be performed if potential subject is female. This test will not be recorded in any identifiable record but merely used to determine eligibility.

Psychological/behavioral screenings and diagnostic assessments are performed by bachelors or graduate level clinicians (doctoral students in clinical psychology) from the Psychology Research and Training Clinic (PRTC) and supervised by a licensed PhD level clinical psychologist. The PRTC provides fee-for-service structured interviewing and diagnostic assessment for research protocols (see letter of support from Dr. Linnea Burk, director of PRTC). The diagnosis of alcohol use disorder will be established by administration of the research version of the Structured Clinical Interview for DSM-5 (SCID[146,147]).

On arrival at the Clinical Research Unit (CRU) in the University of Wisconsin Madison Hospital for the first study visit all participants will complete medical screening that will include review of medical history, review of medications, and screening clinical exam conducted by the provider. Medical staff will conduct clinical assessment to determine vital signs (including sitting and standing blood pressure and heart rate determinations). Twelve-lead ECG will be obtained in all participants. Laboratory evaluation will include chemistry panel comprehensive metabolic profile (Chem-12, assessing kidney and liver function, glucose level and electrolyte status), complete blood count (CBC), and thyroid stimulating hormone (TSH). All study visits will include blood alcohol concentration (BAC) breath-testing. A pregnancy test for women of childbearing potential will occur at all visits with the exception of Visit 3. This is not needed at Visit 3 as tapering the dose, which would be the response to a positive pregnancy test, will happen at this visit for all subjects.

Clinical assessment, clinical exam, and all other medical and medication screenings and monitoring will be conducted by medical staff. ECG interpretations will be confirmed by the study physician. All measures are reviewed by study staff to ensure that participants can safely use doxazosin and participate in the study. Specifically, participants will be excluded for FDA contraindications for doxazosin. All women of childbearing potential will be required to agree to use a study-approved method of birth control or abstinence to prevent pregnancy during the course of the study. Medically-related issues, if needed, will be discussed by the research staff and medical staff with a designated study physician who will be timely available via pager or cell phone.

Exclusion criteria are divided into three broad categories of Medical, Psychiatric/Behavioral, and Medications/Therapies. These criteria are all implemented to protect human subject safety, except where noted with an asterisk (*) denoting scientific/theoretical reasons. See Appendix C (Eligibility Criteria Checklist) for detailed description of eligibility criteria, assessment measures and assessors.

**Medical exclusion**

- Past or current coronary artery disease, cerebrovascular accident, unstable angina, history of myocardial infarction, history of congestive heart failure.
- Current chronic renal or hepatic insufficiency, pancreatitis, immunosuppressive therapy, diabetes, or cancer with systemic effects or therapy.
- Meniere's disease, benign positional vertigo, or narcolepsy.

- A pre-existing hypotension (systolic blood pressure < 100 mmHg) or hypertension (systolic blood pressure > 160 mmHg) or orthostatic hypotension (systolic blood pressure drop > 20mmHg or diastolic blood pressure drop >10mm Hg after two minutes standing) and report of dizziness, lightheadedness, unsteadiness or other problems (nausea, blurry vision) after two minutes standing from seated position.
- Tachycardia >100 beats/minute.
- Heart rate <56 beats/minute.
- Heart rate 56-59 beats/minute AND clinical judgment from study physician that heart rate would preclude a safe participation for the potential participant
- Moderate hepatic impairment assessed via liver enzyme tests.
- Electrocardiogram abnormalities indicates concerns of cardiac function, as determined by study physician's clinical over-read.
- Allergy or previous adverse reaction to doxazosin or other $\alpha$1-NE antagonist.
- Scheduled or reported plans for cataract surgery prior to study completion [Excluded due to risk of Floppy Iris Syndrome].
- Currently symptomatic of alcohol withdrawal. CIWA-Ar Score $\geq$10, or positive for any "visual, auditory or tactile disturbances" or for "orientation and clouding of sensorium".
- Discharged from inpatient treatment for alcohol use disorder or alcohol detoxification within past 7 days.
- Currently medically unstable.
- *Current treatment for chronic pain condition. [Excluded because brief electric shocks are administered during NPU stress-reactivity task].
- *Uncorrected auditory/vision problems. [Excluded because primary measure in NPU stress-reactivity task relies on eyeblink reflex to acoustic startle probe].
- *Color blindness. [Excluded because colored images identify critical differences between predictable, unpredictable, and no-shock conditions in the NPU stress-reactivity task.]
- Other self-reported acute or unstable illness, in the opinion of the study team, would preclude a safe and reliable study participation.

**Medical exclusion (Females Only)**

- Women of childbearing potential with self-reported current pregnancy, positive or undetermined pregnancy test results, do not agree to use a study-approved form of birth control until after study completion (see below), or who are breastfeeding will be excluded.

Definition: Women of childbearing potential are females who have experienced menarche and do not meet the criteria for women **not** of childbearing potential. Women **not** of childbearing potential are females who are permanently sterile (e.g., hysterectomy, bilateral oophorectomy) or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

Definition: Acceptable birth control is defined as the following methods of contraception: abstinence; hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy of partner and tubal ligation; "single" barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) with use of spermicide; or "double barrier" method of contraception (e.g. male condom with diaphragm, male condom with cervical cap).

**Psychological/Behavioral exclusion**

- Self-reported lifetime diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder NOS, Bipolar Disorder (with manic episode), borderline personality disorder, or any neurocognitive disorder that may impair a reliable, safe participation.
- Any current active substance use disorder for which the potential participant is not currently pursuing abstinence, other than alcohol or tobacco.
- Blood alcohol concentration above 0.00.

**Medications/Therapies exclusion**

- Currently prescribed or used within past week: doxazosin or other $\alpha$1-NE antagonist (e.g., prazosin, terazosin).
- Currently prescribed or used within past week: sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) will not be permitted during the study because of increased risk of hypotension in combination with $\alpha$1-NE antagonists. [Increased risk of hypotension in combination with alpha1-NE antagonists].
- Currently used daily or used within past week: alpha1 agonists (e.g., midodrine, metaraminol, oxymetazoline, phenylephrine). [Excluded because these medications directly alter alpha1 noradrenergic neurotransmission.] Note: these cold medicines and nasal decongestants require rescheduling of Study Visit 1 or Study Visit 2 if used within 72 hours of visit; otherwise, they are non-exclusionary.
- Currently used daily or used within past week: benzodiazepines (e.g., diazepam, chlordiazepoxide, lorazepam, clonazepam, alprazolam), zolpidem (Ambien), zaleplon (Sonata), zopiclone (Imovane), eszipclone (Lunesta), dozapin (Silenor).
- Males only: Currently prescribed and used daily or within past 2 weeks: Trazodone.
- *Currently prescribed or used within past week: substances with stimulant properties (e.g., d-amphetamine, methylphenidate) or alternative medications with stimulant properties (e.g., ephedra, pseudophedrine). [Excluded because these medications directly alter CNS noradrenergic neurotransmission.]
- *Currently prescribed or used within past week: beta-blockers (e.g., propanolol), $\alpha$2 agonists (e.g., clonidine, guanfacine, dexmedetomidine), and SNRI anti-depressants (e.g., venlafaxine, duloxetine, atomoxetine, viloxazine). [Excluded because these medications directly alter CNS noradrenergic neurotransmission.]
- *Currently prescribed or used within 2 weeks: Disulfiam (Antabuse). [Excluded because may alter noradrenergic neurotransmission.]

**Sources of Research Materials**. All research materials obtained from participants will be collected directly from them. They will consist exclusively of self-reports, medical evaluations and records of psychophysiological responding. There will be no use of archival records or other such data.

**Potential Risks.** The potential physical risks involved in this study can be grouped in seven categories outlined below

**1. Skin irritation from sensor application or gel**: It is possible that either the sensor gel or the application process may produce some skin irritation and/or redness.

**2. Auditory harm or discomfort from startle probes**: The risk of physical harm is very low but some participants may find the startle probe uncomfortable.

**3. Physical or psychological harm from electric shock**: The risk of physical harm is very low but participants may vary to some degree in how distressing they find the electric shock.

**4. Non-negative pregnancy test**: There is a possible risk that a participant may become upset from an unexpectedly non-negative pregnancy test result. An additional risk is that pregnant women using alcohol place fetus at risk for adverse effects and themselves at risk of placement in custody to protect the fetus.

**5. Side effects from study medication (doxazosin):** The most common side effects associated with doxazosin are drop in blood pressure, dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea. Orthostatic hypotension and syncope (i.e., fainting) can occur in some individuals. Alpha1-NE antagonists have been associated with the so-called “first-dose phenomenon” whereby the possibility of fainting is higher after the first dose in 1% of the population. Syncope risk is increased with dehydration, especially when moving from lying or seated to standing. It is also possible that orthostatic hypotension and syncope could occur after the first dose following increase in dosage, or if therapy with the drug is interrupted.

One rare but serious side effect is priapism, which is a painful penile erection sustained for hours, that can lead to permanent impotence/erectile dysfunction if not promptly treated. The prescribing information for doxazosin suggests that this risk occurs less than once every several thousand people.

**6. Confidentiality failure**: The questionnaires and psychophysiological measures to be used in the proposed research are generally of a benign nature. However, some self-report questionnaires yield sensitive information regarding alcohol use. If confidentiality is broken the information collecting in this study could have unanticipated or untoward consequences for the participant's reputation, employability, or legal status.

**7. Alcohol craving following stressor exposure**: Participants are exposed to a stressor task (the NPU Task) during study visits 1 and 2. It is possible that this stressor could elicit mild, brief alcohol craving in study participants.

**D2. Adequacy of Protection against Risks:**

In this section, we outline the protections in place to reduce the risk associated with the risks identified in D1.

**1. Risks from sensor application**: In addition to warning the participants of these risks, research assistants will attend multiple training sessions, including direct practice with sensor application, prior to being cleared to attach sensors to research participants. They will also be trained to ask participants to inform them of any discomfort so they can adjust or stop the procedure. Additionally, the alcohol pads are the same as those used in hospitals or other health facilities so it is likely the participants have experienced them, and the exfoliant is no different than ones from a drug or beauty store. The sensor gel used is similar in salt concentration to human perspiration, reducing the possibility of this risk.

**2. Risks from Startle probes**: At a maximum of 105dB, the intensity of these stimuli is safely below levels at which there might be any risk of pain or physical damage as established by OSHA and NIOSH guidelines. Specifically, risk associated with noise exposure is reduced in the current experiment by limiting noise intensity to 105dB, limiting total noise exposure time to no more than 5s, and using broad spectrum noise (i.e., white noise). The portion of the experiment in which white noise bursts will be delivered to participants will last approximately 30 minutes. During this period, participants will be exposed to no more than 75 50-millisecond bursts of white noise for a total of 3.75s seconds of exposure. The noises will be delivered via Sennheiser HD-280 headphones. The signal will be calibrated with a slow response meter with A-weighting (B&K sound level meter model 2203). The signal presented for calibration will be 5 sounds in length.

The OSHA recommended limit for noise exposure at 105 dB is no more than 1 hour/day (OSHA section 1910-95). According to the more conservative National Institute for Occupational Safety and Health (NIOSH) guidelines (http://www.cdc.gov/niosh/98-126.html), workers should not be exposed to 105 dB for more than 4 min and 43 sec per 8 hour day. As such, the exposure in the current experiment is far under the more conservative limit recommended by NIOSH. By comparison, noise levels in small music venues (e.g., bars) often exceed 105 dB, and noise levels at rock and roll shows often exceed 115 dB. Participants are occasionally in these environments for more than 1 hour. An additional safety factor is that "white noise" is being employed. White noise is full spectrum, so there is no single frequency with concentrated energy. This acts as further protection to the subject by preventing the focus of energy to a limited area of the basilar membrane in the subject's cochlea.

**3. Risks from Shocks**: There is no reason to believe that the magnitude of this distress exceeds that normally encountered in everyday life. Moreover, participants are forewarned that they will receive these electric shocks during the experiment and that they can terminate their participation without prejudice at any time during the procedure.

The risk of physical harm associated with the administration of electric shock is minimal. The shock parameters and procedures have been used in previous work that has been conducted in Dr. Curtin's lab over the past 20 year and other laboratories at other institutions (e.g., see Grillon et al., 1997, 2012 from the NIH).

The shocks will have an intensity ranging from 0.5 to 7.0 milliamperes and duration of 200 milliseconds. The shocks will be delivered via finger electrodes placed on the index and pointer fingers of their hand. These electrodes are specially-designed to prohibit the possibility of connecting to fingers on opposite hands.

A complex digital input to the shock unit is required to trigger shock administration. This prevents unintended shock administration in the event of computer failure. Moreover, the shock unit is current-limited and designed to automatically shut-off if current is administered for longer than 1000ms. The shock unit has two levels of optical isolation from connections to the computer and the subject will be isolated from any AC current source at all times.

**4. Risks from non-negative Pregnancy test**: The experimenters who conduct these tests will be specifically trained to handle the possibility of such outcomes by noting the conclusiveness of negative results, but also stressing the ambiguity of non-negative outcomes. They would be ready with specific advice about where to get more precise follow-up testing and about how to get counseling if desired. Inasmuch as the pregnancy test is the equivalent of a health screening, it could be construed as a benefit rather than as a risk because non-negative results--although potentially distressing--could promote early, informed and thus more favorable health decisions than might be possible if knowledge of the pregnancy were obtained later.

To avoid collecting information on illicit drug or alcohol use from pregnant women, a pregnancy test will be administered at the beginning of the screening visit prior to the SCID substance abuse module. If a woman's pregnancy test turns out to be positive, she will be considered ineligible for participation and no further testing (e.g., SCID) conducted. This test will be repeated at all study visits with the exception of Visit 3. Women are required to maintain an effective form of birth control throughout their study participation. As such, onset of pregnancy during the study period is low.

**5. Risks from study medications**: Half of the participants (N = 80) will take doxazosin for 8 weeks on an 18 day escalating dose schedule consistent with recent doxazosin studies with cocaine[108] and tobacco dependent samples (see Research Strategy Section). Participants will be made aware of the common side effects of doxazosin before they consent to participate in the study. It should be noted that doxazosin has been FDA-approved and widely used clinically for forty years by millions of people worldwide.

Study staff will have direct contact with participants on 10 occasions during the 8-week study period to assess for any adverse events, medication side effects, and answer questions about treatment. This includes three Study Visits (Day 1, 29, 57), four Medical Monitoring Visits (Day 6, 10, 14, 18) and four Safety Check-ins via phone or electronic survey (Day 2, 36, 43, 50). All study visits will be conducted in the University of Wisconsin-Madison Hospital CRU under medical supervision. A registered nurse will be present in the CRU during all study visits to monitor for drug side effects and provide appropriate medical attention. Orthostatic vital signs will be checked by CRU-RN at all study visits. Any participants experiencing significant side effects will be withdrawn from the study and provided medical attention from the study nursing staff and/or physician as needed. Adverse events will be monitored, and “stopping rules” will be applied if needed (see Stopping rules).

Participants will be educated about potential side effects of doxazosin and ways to mitigate risk. For instance, to reduce the risk of syncope upon standing from bed in the morning, participants will be instructed to slowly sit up and stay on the edge of their bed for 5 minutes before standing following the initial doses of doxazosin. Additional instructions will encourage participants to keep well-hydrated and urinate while sitting down rather than standing. They will be strongly discouraged from driving or operating heavy machinery within 24 hours of the first dose, or at any dose escalation.

It will be recommended that participants continue to take doxazosin before bed, however clinical research has shown that doxazosin is safe to take in morning or evening and with or without food. Doxazosin is not sedating nor are there concerns of rebound hypertension following rapid cessation of use that occur with other noradrenergic agents, such as clonidine[131].

If symptoms of hypotension (such as dizziness) are reported, the participant will be encouraged to increase fluid intake if a negative fluid balance may be playing a role. If hypotension is noted in the CRU settings, the medical staff, upon the study physician orders, is able to place a peripheral venous access and administer IV fluids, such as normal saline, that can provide an effective treatment for orthostatic hypotension.

Participants will be encouraged to continue whatever treatment for alcohol use they were receiving prior to study enrollment throughout the duration of the study. They will be instructed that the study medication is not approved as pharmacotherapy for their alcohol use disorder and therefore will not substitute for their existing treatments and other supports. Participants will be instructed to contact the study staff immediately if they experience any adverse events during these 8 weeks. The study physician will make medical recommendations as appropriate to handle the adverse events. The UW Pharmaceutical Research Center will break the drug blind to inform the participant and study physician if a situation arises where this information is critical to providing appropriate medical care.

Doxazosin in usual medical practice is used to treat high blood pressure and urinary retention associated with benign prostatic hyperplasia; these indications have been associated with certain practices for medication initiation and titration that are optimized for these conditions. In this study, doxazosin is used as an alcohol relapse prevention pharmacotherapy. In this context, the considerations for optimal dosing take into account the risk-benefit ration of a given dose and its titration protocol versus, potential benefits of doxazosin therapy. Research documents the overall safety and superior results of the titration protocols similar to the proposed one, when compared with a slower-titration protocol or placebo for relapse prevention (or improving outcomes) among individuals with substance use disorders ([108,148], https://clinicaltrials.gov/ct2/show/NCT01730846). In addition, the risk of alcohol relapse is highest in the first 3 months after stopping drinking in alcohol dependent adults, suggesting that effective interventions, when implemented early in the recovery, have the best potential to prevent relapse. Therefore, both evidence and conceptual framework derived from a natural history of alcohol dependence suggest an increased benefit of the proposed, previously-tested titration schedule in alcohol dependent adults, compared to a slower titration, typical in hypertension or BPH. Although the potential benefit of the proposed titration schedule and dosing appears to outweigh the potential risks (side effects) in this clinical population, we propose additional safeguards (i.e., the dose titration protocol will be modified – slower titration, lower final dose) if the participant experiences side effects requiring such a modification.

**Serious but rare side effects:** We will counsel the participants about the symptoms of priapism, a rare but serious side effect of doxazosin. We will inform them that this condition, if occurs, requires emergent evaluation and treatment. Should these symptoms occur, the study physician and/or the participant's personal clinician will be immediately contacted, and the participant will be directed to go to the emergency department right away. Our clinical experience corroborates the package insert information that this is indeed a rare condition. However, to further mitigate the risk, we have added an exclusionary criterion that those receiving medications commonly prescribed for erectile dysfunction, such as sidenafil or tadalafil, will not be eligible. Recent or current use of trazodone, another medication which can increase the risk of priapism in combination with doxazonsin, is also an exclusionary criteria.

**6. Risk of Confidentiality failure**: All data will be coded by participant number only and any personal identifiers linking participants to their reports on surveys and questionnaires will be detached and destroyed as soon as participation is completed or disqualification occurs. All data are stored electronically on a secure server in the Department of Psychology, or in two UW sponsored electronic databases Qualtrics (self-report questionnaires, study forms) and OnCore (participant-tracking), which have accepted measures to protect participant confidentiality and are compliant with all national clinical research policies. PHI will link to individuals' participation in OnCore and HealthLink only and only the minimal necessary information will be entered into the participant's medical record in order to protect their confidentiality regarding alcohol and drug use status. In addition, a Certificate of Confidentiality (CoC) has been secured from the National Institute of Alcohol Abuse and Alcoholism in order to protect identifiable research information from forced disclosure. A CoC allows an investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

**7. Risk of alcohol craving**: There is a possibility that following the NPU stressor task in study visits 1 and 2, alcohol-dependent participants will experience alcohol craving, due to the mild stressor exposure. Generally, cravings subside with the simple passage of time. However, all participants will also receive brief (30 minute), standardized Motivational Enhancement Therapy (MET) to support continued abstinence at study visits 1 and 2 following completion of the NPU task. Participants will complete a brief alcohol craving questionnaire, a 6-item subset of the 14-item version of the Desires for Alcohol Questionnaire (DAQ6) upon arrival at the laboratory and after completing all study procedures at each study visit. The items include: "I want a drink so much I can almost taste it", "My desire to drink now seems overwhelming", "I would do almost anything to have a drink now", "I am going to drink as soon as I possibly can", "I would consider having a drink now", "I would accept a drink now if it was offered to me." Participants will be required to remain at the CRU until their craving ratings return to baseline on each item of the scale. In our recent study with 58 abstinent alcoholics, only 5 participants were required to stay in the lab for a brief period of time until their cravings returned to baseline simply by the passage of time.

Thirty minutes of motivational therapy will be administered to participants two times during the regular course of the study. Additionally, if participants report strong cravings or alcohol use, an additional 30 minute session of motivational counseling will be provided to help them to recover their abstinence goals. Referrals to local treatment providers will always be available to participants, and referral to these providers or back to the participant's own treatment provider will be made in case further intervention is warranted.

**D3. Potential Benefits of the Proposed Research to Human Subjects and Others**

Considering the safeguards outlined above, any potential risks associated with participation in this project appear to have been minimized. There is strong reason to believe that participants assigned to receive doxazosin treatment may have a reduced risk of relapse to alcohol use during the 8 week treatment period. However this is unknown to date and is indeed a goal of the study to determine the efficacy of doxazosin. It is possible that simple accountability related to study participation and contact with research/medical study staff will reduce participants' relapse risk. Including brief MET at study visits 1-2 is likely to further support those goals of relapse prevention.

All participants will be paid for their time invested during study procedures. Participants will be paid $320 for time spent in visits, plus a $100 bonus for completing all eight visits, as well as up to $75 in bonuses for attending/not rescheduling/being on time to all visits, and a $25 bonus for meeting a 90% threshold for medication compliance. These modest inducements represent reasonable compensation for time spent in the study and are not considered coercive.

Aside from these factors, there is not likely to be any immediate, direct benefit to the participant other than a better understanding of the processes and purposes of psychological and biomedical research acquired through experience and debriefing. However, the knowledge that can reasonably be expected to result from the proposed study has potentially important implications for the field of addiction treatment.

**D4. Importance of the Knowledge to be Gained**

As indicated above, the risks associated with this research appear to have been minimized. In contrast, the potential importance of the knowledge to be gained and its clinical application is high. Specifically, the costs to both individuals and the society as a whole resulting from alcoholism are high. The research proposed in this application is designed to address potentially important affective and pharmacological mechanisms in the etiology and maintenance/relapse of alcohol dependence. Most importantly, this study aims to investigate the utility of doxazosin as a potential treatment of stress-induced relapse in alcoholism, which is not well treated by any currently available pharmacotherapy for drug addiction.

**D5. Data and Safety Monitoring Plan**

**Monitoring the progress of study and the safety of participants.** The Principal Investigator will be responsible for routine monitoring of the study's progress. This includes scheduled monthly meetings with

study staff and the study MD, and review of written documentation. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number treated and the stage of treatment, summary of adverse events, individual review of serious adverse events and study participation and outcome data. In addition, any unanticipated health events that raise concerns (e.g., serious mood or behavioral changes, suicidal ideation, abnormal test results) will be immediately reported to the PI and the study physicians.

To facilitate participant safety, study participants must meet study eligibility criteria. Once enrolled, study protocol will assess for the presence of adverse events at each study visit by querying participants as to whether they have experienced any adverse side effects associated with study medications. Participants who report development of severe side effects associated with doxazosin (which is unlikely) will be discontinued from further study participation as a precaution. Such events will be immediately reported to the PI and study physicians. If significant psychiatric or medical symptoms are reported, the participant will be referred, as needed, to the appropriate emergency medical or psychiatric services.

**Stopping rules.** Study will be stopped if two patients experience SAEs diagnosed to be related to the study drug and affect same organ system (e.g., cardiac, hepatic, renal or central nervous system). More specific examples are a three-fold elevation above baseline of serum liver enzyme (hepatic function) and creatinine (kidney function) levels, and QTc interval prolongation over 500 ms (or 50 ms increase over baseline) or other documented serious ECG abnormalities.

The study would resume after thorough evaluation and if it is deemed that the continuation of study activities is determined safe to participants by the study physicians, the study investigators, the IRB, and the funding agency representative.

**Plans for assuring compliance with requirements regarding the reporting of adverse events.** This Data Safety and Monitoring Plan requires that investigators notify NIH and the University of Wisconsin IRB of the occurrence of any serious adverse event (SAE), or any adverse event (AE), which is severe, unexpected, and possibly related to study medication or protocol. Such notification must occur within five days of investigators becoming aware of the event. If the serious adverse event might be related to drug use, both the Food and Drug Administration and the manufacturer will also be notified within five days of investigators becoming aware of the event. Examples of serious adverse events would be untoward medical or treatment occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital abnormality/birth defects. Unanticipated adverse events would include less serious problems that merit reporting because they are severe, unexpected, and possibly related to study participation. Any serious adverse event (SAE) will be queried and reported even if it appears that the serious adverse event is unrelated to treatment participation. The PI will be responsible for the accurate documentation, investigation and follow-up of all study-related adverse events.

Adverse event assessment, recording, reporting and investigation will be accomplished through staff training, structured or standardized assessments of untoward occurrences/events, and regular monitoring by study investigators. The Principal Investigator has ultimate responsibility for ensuring that serious adverse events are detected and reported in a timely manner. All serious or unanticipated adverse events will be reviewed by the study physicians. Additionally, the IRB will receive an annual report of all serious adverse events and adverse events meeting the criteria listed above.

**Plans for assuring that any action resulting in a temporary or permanent suspension of an NIH-funded clinical trial is reported to the NIH grant program director responsible for the grant.** The NIH grant program director will be notified within five days if the Principal Investigator deems it necessary to suspend the study. In the case of a temporary suspension, the Principal Investigator will develop a plan for continuation of the study and discuss this plan with the NIH grant program director in a reasonable time frame.

**Plans for assuring data accuracy and confidentiality and protocol compliance.** The Principal Investigator will refine existing protocols for assuring data accuracy and protocol compliance. Such protocols will include

data verification and protocol compliance checks as well as other quality assurance procedures. The Principal Investigator will also be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data.

## Data and Record Keeping:

**Data Management**

Study staff will collect and maintain all information on secure servers managed by the university, including the university Qualtrics and OnCore servers, or on a private secure server managed by the research team. Any hard copy study data will be kept in a locked cabinet which only the Project Director and Project Coordinator can access, in a locked room in the Psychology department in Dr. Curtin's laboratory.

The Principal Investigator will oversee data verification and protocol compliance checks as well as other quality assurance procedures. The Principal Investigator will also be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data.

**Confidentiality**

The UW Institute of Clinical and Translational Research (ICTR) provides UW researchers with comprehensive data management software tools (Online Collaborative Research Environment; OnCore) and support, which helps ensure confidentiality of data. The self-report and psychophysiological measures that will be used in the proposed research are generally of a benign nature. However, some self-report questionnaires could yield sensitive information. Consequently, all data will be coded by participant number only and any personal identifiers linking participants to their reports on surveys and questionnaires will be detached and destroyed as soon as participation is completed or disqualification occurs.

**Data Collection Methods**

All research materials obtained from participants will be collected directly from them. They will consist exclusively of self-reports, medical evaluations, biological samples, and records of psychophysiological responding. There will be no use of archival records or other such data.

Surveys and interviews will be administered to the participant by study staff via iPad. The iPads access the University's secure Qualtrics account and data is entered there directly. At no time is data ever saved on the iPads.

Physiological data is collected by study staff using our lab's psychophysiology equipment, and saved directly to our secure server in the Department of Psychology

Biologic samples (blood, urine) will be collected by medical staff at the Clinical Research Unit (CRU) according to standard medical practice, and handled and disposed of using standard CRU procedures.

Smart cap data will be stored in an online password protected platform. All data stored on this platform is coded only.

The SCID-RV interviews and the MET sessions will be audio recorded. The SCID or MET clinician will review these recordings alongside the licensed clinical psychologist for supervision purposes. These recordings will be deleted immediately after review.

**Study Records Retention Policy**

All de-identified data and associated study documents will be archived according to IRB and University policies and retained for seven years.

In accordance with Federal Open Access policies, de-identified datasets and analysis materials will be made available using approved Data Sharing practices identified by the University's Research Data Services.

Bibliography and References


1. Insel, T. R. Next-generation treatments for mental disorders. *Sci Transl Med* **4,** 155ps19 (2012).
2. Miller, G. Is Pharma Running Out of Brainy Ideas? *Science* **329,** 502–504 (2010).
3. Raskind, M. *et al.* A Trial of Prazosin for Combat Trauma PTSD With Nightmares in Active-Duty Soldiers Returned From Iraq and Afghanistan. *Am. J. Psychiatry* (2013). doi:10.1176/appi.ajp.2013.12081133
4. Berridge, C. Noradrenergic modulation of arousal. *Brain Res. Rev.* **58,** 1–17 (2008).
5. Baker, T., Piper, M. E., McCarthy, D. E., Majeskie, M. R. & Fiore, M. C. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol. Rev.* **111,** 33–51 (2004).
6. Kassel, J. D., Stroud, L. R. & Paronis, C. A. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. *Psychol. Bull.* **129,** 270–304 (2003).
7. Koob, G. F. Brain stress systems in the amygdala and addiction. *Brain Res.* **1293,** 61–75 (2009).
8. Shaham, Y., Erb, S. & Stewart, J. Stress induced relapse to heroin and cocaine seeking in rats: A review. *Brain Res. Rev.* **33,** 13–33 (2000).
9. Smith, R. J. & Aston-Jones, G. Noradrenergic transmission in the extended amygdala: role in increased drug-seeking and relapse during protracted drug abstinence. *Brain Struct. Funct.* **213,** 43–61 (2008).
10. Lê, A. *et al.* Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. *Psychopharmacology (Berl.)* **218,** 89–99 (2011).
11. Smith, R. & Aston-Jones, G. α2 Adrenergic and Imidazoline Receptor Agonists Prevent Cue-Induced Cocaine Seeking. *BPS* **70,** 712–719 (2011).
12. Simpson, T. *et al.* A Pilot Trial of the Alpha-1 Adrenergic Antagonist, Prazosin, for Alcohol Dependence. *Alcohol. Clin. Exp. Res.* **33,** 255–263 (2009).
13. Fox, H. C. *et al.* Prazosin Effects on Stress- and Cue-Induced Craving and Stress Response in Alcohol-Dependent Individuals: Preliminary Findings. *Alcohol. Clin. Exp. Res.* **36,** 351–360 (2012).
14. Weinshenker, D. & Schroeder, J. P. There and Back Again: A Tale of Norepinephrine and Drug Addiction. *Neuropsychopharmacology* **32,** 1433–1451 (2006).
15. Aston-Jones, G. & Kalivas, P. Brain norepinephrine rediscovered in addiction research. *Biol. Psychiatry* **63,** 1005–6 (2008).

16. Koob, G. F., Kenneth Lloyd, G. & Mason, B. J. Development of pharmacotherapies for drug addiction: a Rosetta Stone approach. *Nat Rev Drug Discov* **8,** 500–515 (2009).

17. Lerman, C. *et al.* Translational research in medication development for nicotine dependence. *Nat. Rev. Drug Discov.* **6,** 746–762 (2007).

18. See, R. E. & Waters, R. P. Pharmacologically-induced stress: a cross-species probe for translational research in drug addiction and relapse. *Am. J. Transl. Res.* **3,** 81–89 (2011).

19. Schmitz, A. & Grillon, C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nat. Protoc.* **7,** 527–532 (2012).

20. Davis, M., Walker, D. L., Miles, L. & Grillon, C. Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacol. Rev.* **35,** 105–135 (2010).

21. Grillon, C. & Baas, J. M. A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clin. Neurophysiol.* **144,** 1557–1579. (2003).

22. Moberg, C. A. & Curtin, J. J. Alcohol selectively reduces anxiety but not fear: startle response during unpredictable vs. predictable threat. *J. Abnorm. Psychol.* **118,** 335–347 (2009).

23. Hogle, J. M., Kaye, J. T. & Curtin, J. J. Nicotine withdrawal increases threat-induced anxiety but not fear: Neuroadaptation in human addiction. *Biol. Psychiatry* **68,** 687–688 (2010).

24. Hefner, K. R. & Curtin, J. J. Alcohol stress response dampening: Selective reduction of anxiety in the face of uncertain threat. *J. Psychopharmacol. Oxf. Engl.* **26,** 232–244 (2012).

25. Gloria, R., Jaber, J. N., Baker, T. B. & Curtin, J. J. The effect of temporal precision and probability on the response to threat of shock: a fear-potentiated startle study. *Psychophysiology* **46(s1),** s80 (2009).

26. Moberg, C. A. & Curtin, J. J. Stressing the importance of anxiety in alcoholism. in *Alcoholism: Clinical and Experimental Research* **36,** 60A (2012).

27. Erb, S. *et al.* Alpha-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine seeking. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **23,** 138–50 (2000).

28. Pacák, K. *et al.* Effects of various stressors on in vivo norepinephrine release in the hypothalamic paraventricular nucleus and on the pituitary-adrenocortical axis. *Ann. N. Y. Acad. Sci.* **771,** 115–130 (1995).

29. Galvez, R., Mesches, M. H. & McGaugh, J. L. Norepinephrine release in the amygdala in response to footshock stimulation. *Neurobiol. Learn. Mem.* **66,** 253–257 (1996).

30. Pacák, K., Palkovits, M., Kopin, I. J. & Goldstein, D. S. Stress-induced norepinephrine release in the hypothalamic paraventricular nucleus and pituitary-adrenocortical and sympathoadrenal activity: in vivo microdialysis studies. *Front. Neuroendocrinol.* **16,** 89–150 (1995).

31. Pacák, K., McCarty, R., Palkovits, M., Kopin, I. J. & Goldstein, D. S. Effects of immobilization on in vivo release of norepinephrine in the bed nucleus of the stria terminalis in conscious rats. *Brain Res.* **688,** 242–246 (1995).

32. Pacák, K. *et al.* Effects of single or repeated immobilization on release of norepinephrine and its metabolites in the central nucleus of the amygdala in conscious rats. *Neuroendocrinology* **57,** 626–633 (1993).

33. Aston-Jones, G., Delphs, J. M., Druhan, J. & Zhu, Y. The Bed Nucleus of the Stria Terminalis: A Target Site for Noradrenergic Actions in Opiate Withdrawal. *Ann. N. Y. Acad. Sci.* **877,** 486–498 (1999).

34. Patkar, A. A. *et al.* Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. *Alcohol Alcohol. Oxf. Oxfs.* **38,** 224–231 (2003).

35. Patkar, A. A. *et al.* Differences in peripheral noradrenergic function among actively drinking and abstinent alcohol-dependent individuals. *Am. J. Addict. Am. Acad. Psychiatr. Alcohol. Addict.* **13,** 225–235 (2004).

36. Fujimoto, A., Nagao, T., Ebara, T., Sato, M. & Otsuki, S. Cerebrospinal fluid monoamine metabolites during alcohol withdrawal syndrome and recovered state. *Biol. Psychiatry* **18,** 1141–1152 (1983).

37. Bremner, J., Krystal, J., Southwick, S. & Charney, D. Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synap. N. Y. NY* **23,** 39–51 (1996).

38. Taggart, P., Carruthers, M. & Somerville, W. Electrocardiogram, plasma catecholamines and lipids, and their modification by oxyprenolol when speaking before an audience. *Lancet* **2,** 341–346 (1973).

39. Taggart, P. & Carruthers, M. Endogenous hyperlipidaemia induced by emotional stress of racing driving. *Lancet* **1,** 363–366 (1971).

40. Marinelli, P. W. *et al.* The CRF1 receptor antagonist antalarmin attenuates yohimbine-induced increases in operant alcohol self-administration and reinstatement of alcohol seeking in rats. *Psychopharmacology (Berl.)* **195,** 345–355 (2007).

41. Feltenstein, M. W., Ghee, S. M. & See, R. E. Nicotine self-administration and reinstatement of nicotine-seeking in male and female rats. *Drug Alcohol Depend.* **121,** 240–246 (2012).

42. Brown, Z., Tribe, E., D'souza, N. & Erb, S. Interaction between noradrenaline and corticotrophin-releasing factor in the reinstatement of cocaine seeking in the rat. *Psychopharmacology (Berl.)* **203,** 121–130 (2009).

43. Lee, B., Tiefenbacher, S., Platt, D. M. & Spealman, R. D. Pharmacological blockade of alpha2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **29,** 686–693 (2004).

44. Platt, D. M., Rowlett, J. K. & Spealman, R. D. Noradrenergic mechanisms in cocaine-induced reinstatement of drug seeking in squirrel monkeys. *J. Pharmacol. Exp. Ther.* **322,** 894–902 (2007).

45. Banna, K. M., Back, S. E., Do, P. & See, R. E. Yohimbine stress potentiates conditioned cue-induced reinstatement of heroin-seeking in rats. *Behav. Brain Res.* **208,** 144 (2010).

46. Shepard, J. D., Bossert, J. M., Liu, S. Y. & Shaham, Y. The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. *Biol. Psychiatry* **55,** 1082–1089 (2004).

47. Walker, B., Rasmussen, D., Raskind, M. & Koob, G. F. alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. *Alcohol* **42,** 91–7 (2008).

48. Froehlich, J. C., Hausauer, B. J., Federoff, D. L., Fischer, S. M. & Rasmussen, D. D. Prazosin Reduces Alcohol Drinking Throughout Prolonged Treatment and Blocks the Initiation of Drinking in Rats Selectively Bred for High Alcohol Intake. *Alcohol. Clin. Exp. Res.* (2013). doi:10.1111/acer.12116

49. Rasmussen, D. D., Alexander, L. L., Raskind, M. & Froehlich, J. C. The alpha1-adrenergic receptor antagonist, prazosin, reduces alcohol drinking in alcohol-preferring (P) rats. *Alcohol. Clin. Exp. Res.* **33,** 264–272 (2009).

50. Verplaetse, T. L., Rasmussen, D. D., Froehlich, J. C. & Czachowski, C. L. Effects of prazosin, an α1-adrenergic receptor antagonist, on the seeking and intake of alcohol and sucrose in alcohol-preferring (P) rats. *Alcohol. Clin. Exp. Res.* **36,** 881–886 (2012).

51. O'Neil, M. L., Beckwith, L. E., Kincaid, C. L. & Rasmussen, D. D. The α1-adrenergic receptor antagonist, doxazosin, reduces alcohol drinking in alcohol-preferring (P) Rats. *Alcohol. Clin. Exp. Res.* **37,** 202–212 (2013).

52. Wee, S., Mandyam, C., Lekic, D. & Koob, G. F. Alpha 1-noradrenergic system role in increased motivation for cocaine intake in rats with prolonged access. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **18,** 303–11 (2008).

53. Greenwell, T., Walker, B., Cottone, P., Zorrilla, E. & Koob, G. F. The α1 adrenergic receptor antagonist prazosin reduces heroin self-administration in rats with extended access to heroin administration. *Pharmacol. Biochem. Behav.* **91,** 295–302 (2009).

54. Forget, B. *et al.* Noradrenergic α1 Receptors as a Novel Target for the Treatment of Nicotine Addiction. *Neuropsychopharmacology* **35,** 1751–1760 (2010).

55. Skelly, M. J. & Weiner, J. L. Chronic treatment with prazosin or duloxetine lessens concurrent anxiety-like behavior and alcohol intake: evidence of disrupted noradrenergic signaling in anxiety-related alcohol use. *Brain Behav.* **4,** 468–483 (2014).

56. McEwen, B. S. From molecules to mind. Stress, individual differences, and the social environment. *Ann N Acad Sci* **935,** 42–9 (2001).

57. McEwen, B. S., Eiland, L., Hunter, R. G. & Miller, M. M. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology* **62,** 3–12 (2012).

58. Sapolsky, R. M. in *Behavioral endocrinology (2nd ed.).* (eds. Becker, J. B., Breedlove, S. M., Crews, D. & McCarthy, M. M.) 409–450 (MIT Press, 2002).

59. Sapolsky, R. M. Stress and plasticity in the limbic system. *Neurochem. Res.* **28,** 1735–1742 (2003).

60. Davis, M., Antoniadis, E., Amaral, D. & Winslow, J. Acoustic startle reflex in rhesus monkeys: A review. *Rev. Neurosci.* **19,** 171–185 (2008).

61. Davis, M. Neural systems involved in fear-potentiated startle. *Ann. N. Y. Acad. Sci.* **563,** 165–183. (1989).

62. Davis, M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. *Am. Psychol.* **61,** 741–756 (2006).

63. Koch, M. The neurobilogy of startle. *Prog. Neurobiol.* **59,** 107–128 (1999).

64. Walker, D. & Davis, M. Light-enhanced startle: further pharmacological and behavioral characterization. *Psychopharmacology (Berl.)* **159,** 304–310 (2002).

65. Walker, D. *et al.* Differential effects of the CRF-R1 antagonist GSK876008 on fear-potentiated, light- and CRF-enhanced startle suggest preferential involvement in sustained vs phasic threat responses. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **34,** 1533–1542 (2009).

66. Walker, D. & Davis, M. Role of the extended amygdala in short-duration versus sustained fear: A tribute to Dr. Lennart Heimer. *Brain Struct. Funct.* **213,** 29–42 (2008).

67. Walker, D. & Davis, M. Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. *J. Neurosci. Off. J. Soc. Neurosci.* **17,** 9375–9383 (1997).

68. Koob, G. F. The role of CRF and CRF-related peptides in the dark side of addiction. *Brain Res.* **1314,** 3–14 (2010).

69. Gresack, J. & Risbrough, V. Corticotropin-releasing factor and noradrenergic signalling exert reciprocal control over startle reactivity. *Int. J. Neuropsychopharmacol.* **14,** 1179–94 (2011).

70. Berridge, C. W. & Dunn, A. J. Restraint-stress-induced changes in exploratory behavior appear to be mediated by norepinephrine-stimulated release of CRF. *J. Neurosci.* **9,** 3513–3521 (1989).

71. Kiss, A. & Aguilera, G. Participation of alpha 1-adrenergic receptors in the secretion of hypothalamic corticotropin-releasing hormone during stress. *Neuroendocrinology* **56,** 153–160 (1992).

72. Manion, S., Gamble, E. & Li, H. Prazosin administered prior to inescapable stressor blocks subsequent exaggeration of acoustic startle response in rats. *Pharmacol. Biochem. Behav.* **86,** 559–65 (2007).

73. Kehne, J. H., Commissaris, R. L. & Davis, M. Antagonism of apomorphine-enhanced startle by alpha 1-adrenergic antagonists. *Eur. J. Pharmacol.* **108,** 233–241 (1985).

74. Rasmussen, D. D. & Kincaid, C. L. Acoustic Startle in Alcohol-Naïve Male Rats Predicts Subsequent Voluntary Alcohol Intake and Alcohol Preference. *Alcohol Alcohol* agu065 (2014). doi:10.1093/alcalc/agu065

75. Morgan, C. A. *et al.* Yohimbine — facilitated acoustic startle reflex in humans. *Psychopharmacology (Berl.)* **110,** 342–346 (1993).

76. Stine, S. M. *et al.* Methadone patients exhibit increased startle and cortisol response after intravenous yohimbine. *Psychopharmacology (Berl.)* **154,** 274–81. (2001).

77. Grillon, C., Baas, J. P., Lissek, S., Smith, K. & Milstein, J. Anxious responses to predictable and unpredictable aversive events. *Behav. Neurosci.* **118,** 916–924 (2004).

78. Hefner, K. R., Moberg, C., Hachiya, L. & Curtin, J. Alcohol stress response dampening during imminent versus distal, uncertain threat. *J. Abnorm. Psychol.* (2014).

79. Bradford, D. E., Shapiro, B. L. & Curtin, J. J. How bad could it be? Alcohol dampens stress responses to threat of uncertain intensity. *Psychol. Sci.* **24,** 2541–2549 (2013).

80. Bradford, Daniel E. *et al.* Alcohol induced stress neuroadaptation: Cross sectional evidence from startle potentiation and ERPs in healthy drinkers and abstinent alcoholics during uncertain threat. (2013). at <<http://onlinelibrary.wiley.com/doi/10.1111/psyp.12111/full >>

81. Grillon, C. *et al.* The benzodiazepine alprazolam dissociates contextual fear from cued fear in humans as assessed by fear-potentiated startle. *Biol. Psychiatry* **60,** 760–766 (2006).

82. Miles, L., Davis, M. & Walker, D. Phasic and Sustained Fear are Pharmacologically Dissociable in Rats. *Neuropsychopharmacology* **36,** 1563–1574 (2011).

83. Grillon, C., Cordova, J., Morgan, C. A. I., Charney, D. S. & Davis, M. Effects of the beta-blocker propranolol on cued and contextual fear conditioning in humans. *Psychopharmacology (Berl.)* **175,** 342–352 (2004).

84. Fiore, M. C. *et al. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report*. (Rockville, MD: U.S. Department of Health and Human Services, U.S. Public Health Service, 2008).

85. Mayo-Smith, M. *et al.* Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch. Intern. Med.* **164,** 1405–12 (2004).

86. Covey, L. S. & Glassman, A. H. A meta-analysis of double-blind placebo-controlled trials of clonidine for smoking cessation. *Br. J. Addict.* **86,** 991–998 (1991).

87. Frishman, W. Smoking cessation pharmacotherapy--nicotine and non-nicotine preparations. *Prev. Cardiol.* **10,** 10–22 (2007).

88. Glassman, A. H. *et al.* Heavy smokers, smoking cessation, and clonidine. Results of a double-blind, randomized trial. *J. Am. Med. Assoc. JAMA* **259,** 2863–6. (1988).

89. Brunet, A. *et al.* Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *J. Clin. Psychopharmacol.* **31,** 547–550 (2011).

90. Pitman, R. K. *et al.* Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* **13,** 769–787 (2012).

91. Doxey, J. C., Lane, A. C., Roach, A. G. & Virdee, N. K. Comparison of the alpha-adrenoceptor antagonist profiles of idazoxan (RX 781094), yohimbine, rauwolscine and corynanthine. *Naunyn. Schmiedebergs Arch. Pharmacol.* **325,** 136–144 (1984).

92. Millan, M. J. *et al.* Agonist and antagonist actions of yohimbine as compared to fluparoxan at alpha(2)-adrenergic receptors (AR)s, serotonin (5-HT)(1A), 5-HT(1B), 5-HT(1D) and dopamine D(2) and D(3) receptors. Significance for the modulation of frontocortical monoaminergic transmission and depressive states. *Synap. N. Y. N* **35,** 79–95 (2000).

93. Green, B. Prazosin in the treatment of PTSD. *J. Psychiatr. Pract.* **20,** 253–259 (2014).

94. Ralevski, E., Olivera-Figueroa, L. A. & Petrakis, I. PTSD and comorbid AUD: a review of pharmacological and alternative treatment options. *Subst. Abuse Rehabil.* **5,** 25–36 (2014).

95. Raskind, M. *et al.* The alpha1-adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. *J. Clin. Psychiatry* **61,** 129–133 (2000).

96. Raskind, M. *et al.* Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J. Clin. Psychiatry* **63,** 565–568 (2002).

97. Raskind, M. *et al.* Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am. J. Psychiatry* **160,** 371–373 (2003).

98. Raskind, M. *et al.* A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol. Psychiatry* **61,** 928–934 (2007).

99. Leggio, L. & Kenna, G. A. Commentary: Doxasozin for alcoholism. *Alcohol. Clin. Exp. Res.* **37,** 191–193 (2013).

100. Müller, C. A., Geisel, O., Banas, R. & Heinz, A. Current pharmacological treatment approaches for alcohol dependence. *Expert Opin. Pharmacother.* **15,** 471–481 (2014).

101. Froehlich, J. C., Hausauer, B. J. & Rasmussen, D. D. Combining Naltrexone and Prazosin in a Single Oral Medication Decreases Alcohol Drinking More Effectively Than Does Either Drug Alone. *Alcohol. Clin. Exp. Res.* (2013). doi:10.1111/acer.12148

102. Taylor, S. H. Clinical pharmacotherapeutics of doxazosin. *Am. J. Med.* **87,** 2S–11S (1989).

103. Jaillon, P. Clinical pharmacokinetics of prazosin. *Clin. Pharmacokinet.* **5,** 365–376 (1980).

104. Kaplan, S. A., Meade-D'alisera, P., Quinones, S. & Soldo, K. A. Doxazos1n in physiologically and pharmacologically normotensive men with benign prostat1c hyperplasia. *Urology* **46,** 512–517 (1995).

105. Kirby, R. S. *et al.* Morning vs evening dosing with doxazosin in benign prostatic hyperplasia: efficacy and safety. *Prostate Cancer Prostatic Dis.* **1,** 163–171 (1998).

106. De Jong, J., Wauben, P., Huijbrechts, I., Oolders, H. & Haffmans, J. Doxazosin Treatment for Posttraumatic Stress Disorder: *J. Clin. Psychopharmacol.* **30,** 84–85 (2010).

107. Newton, T. *et al.* Noradrenergic α1 Receptor Antagonist Treatment Attenuates Positive Subjective Effects of Cocaine in Humans: A Randomized Trial. *PLoS ONE* **7,** e30854 (2012).

108. Shorter, D., Lindsay, J. A. & Kosten, T. R. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: A pilot study. *Drug Alcohol Depend.* **131,** 66–70 (2013).

109. Reardon, S. NIH rethinks psychiatry trials. *Nature* **507,** 288–288 (2014).

110. Insel, T. R. & Gogtay, N. National Institute of Mental Health clinical trials: new opportunities, new expectations. *JAMA Psychiatry* **71,** 745–746 (2014).

111. Insel, T. R. A New Approach to Clinical Trials. *Director's Blog* (2014). at <http://www.nimh.nih.gov/about/director/2014/a-new-approach-to-clinical-trials.shtml>

112. Baker, T. B. *et al.* New methods for tobacco dependence treatment research. *Ann. Behav. Med. Publ. Soc. Behav. Med.* **41,** 192–207 (2011).

113. Thornton, M. The next front on the war on cancer. *Wall Street Journal* (2009).

114. NIMH. FAST: Fast-Fail Trials: Accelerating the Pace of Psychiatric Drug Discovery. at <http://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml>

115. Collins, F. S. Mining for therapeutic gold. *Nat. Rev. Drug Discov.* **10,** 397 (2011).

116. Allison, M. NCATS launches drug repurposing program. *Nat. Biotechnol.* **30,** 571–572 (2012).

117. Cuthbert, B. & Insel, T. The data of diagnosis: new approaches to psychiatric classification. *Psychiatry* **73,** 311–314 (2010).

118. Cuthbert, B. & Insel, T. R. Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. *Schizophr. Bull.* **36,** 1061–1062 (2010).

119. Insel, T. R. & Cuthbert, B. Endophenotypes: Bridging Genomic Complexity and Disorder Heterogeneity. *Biol. Psychiatry* **66,** 988–989 (2009).

120. Sanislow, C. A. *et al.* Developing constructs for psychopathology research: Research domain criteria. *J. Abnorm. Psychol.* **119,** 631–639 (2010).

121. NIMH · Negative Valence Systems: Workshop Proceedings. (2011). at <http://www.nimh.nih.gov/research-priorities/rdoc/negative-valence-systems-workshop-proceedings.shtml>

122. First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. B. W. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)*. (Biometrics Research, New York State Psychiatric Institute, 2002).

123. Skinner, H. A. & Allen, B. A. Alcohol dependence syndrome: Measurement and validation. *J. Abnorm. Psychol.* **91,** 199–209 (1982).

124. Flannery, B. A., Volpicelli, J. R. & Pettinati, H. M. Psychometric properties of the Penn Alcohol Craving Scale. *Alcohol. Clin. Exp. Res.* **23,** 1289–1295 (1999).

125. Watson, D., Clark, L. A. & Tellegen, A. Development and validation of brief measures of positive and negative affect: The PANAS scales. *J. Pers. Soc. Psychol.* **54,** 1063–1070 (1988).

126. Simons, J. S. & Gaher, R. M. The distress tolerance scale: development and validation of a self-report measure. *Motiv. Emot.* **29,** 83–102 (2005).

127. Patrick, C. J., Curtin, J. J. & Tellegen, A. Development and validation of a brief form of the Multidimensional Personality Questionnaire. *Psychol. Assess.* **14,** 150–163 (2002).

128. Hogle, J. M. & Curtin, J. J. Sex differences in negative affective response during nicotine withdrawal. *Psychophysiology* **43,** 344–356 (2006).

129. Stout, R. L., Wirtz, P. W., Carbonari, J. P. & Del Boca, F. K. Ensuring balanced distribution of prognostic factors in treatment outcome research. *J. Stud. Alcohol. Suppl.* **12,** 70–75 (1994).

130. Wei, L. J. & Lachin, J. M. Properties of the urn randomization in clinical trials. *Control. Clin. Trials* **9,** 345–364 (1988).

131. Takata, Y., Yoshizumi, T., Ito, Y., Hirota, Y. & Fujishima, M. Doxazosin withdrawal and ambulatory blood pressure monitoring in normotensive subjects. *Angiology* **45,** 17–23 (1994).

132. Simpson, T. L., Kivlahan, D. R., Bush, K. R. & McFall, M. E. Telephone self-monitoring among alcohol use disorder patients in early recovery: a randomized study of feasibility and measurement reactivity. *Drug Alcohol Depend.* **79,** 241–250 (2005).

133. Kranzler, H. R., Abu-Hasaballah, K., Tennen, H., Feinn, R. & Young, K. Using daily interactive voice response technology to measure drinking and related behaviors in a pharmacotherapy study. *Alcohol. Clin. Exp. Res.* **28,** 1060–1064 (2004).

134. Blumenthal, T. D. *et al.* Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology* **42,** 1–15 (2005).

135. Miller, W. R., Zweben, A., DiClemente, C. C. & Rychtarik, R. G. *Motivational Enhancement Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals With Alcohol Abuse and Dependence*. **2,** (Diane Pub Co, 1999).

136. DiClemente, C. C., Bellino, L. E. & Neavins, T. M. Motivation for change and alcoholism treatment. *Alcohol Res. Health J. Natl. Inst. Alcohol Abuse Alcohol.* **23,** 86–92 (1999).

137. Miller, W. R. *Motivational interviewing: helping people change*. (Guilford Press, 2013).

138. McCaul, M. E. & Petry, N. M. The role of psychosocial treatments in pharmacotherapy for alcoholism. *Am. J. Addict. Am. Acad. Psychiatr. Alcohol. Addict.* **12 Suppl 1,** S41–52 (2003).

139. Britt, E., Hudson, S. M. & Blampied, N. M. Motivational interviewing in health settings: a review. *Patient Educ. Couns.* **53,** 147–155 (2004).

140. R Development Core Team. *R: A language and environment for statistical computing*. (R Foundation for Statistical Computing, 2015). at <http://www.R-project.org>

141. Sobel, M. E. Asymptotic Confidence Intervals for Indirect Effects in Structural Equation Models. *Sociol. Methodol.* **13,** 290–312 (1982).

142. MacKinnon, D. P., Fairchild, A. J. & Fritz, M. S. Mediation Analysis. *Annu. Rev. Psychol.* **58,** 17.1–17.22 (2007).

143. MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G. & Sheets, V. A comparison of methods to test mediation and other intervening variable effects. *Psychol. Methods* **7,** 83–104 (2002).

144. Fritz, M. S. & MacKinnon, D. P. Required sample size to detect the mediated effect. *Psychol. Sci.* **18,** 233–239 (2007).

145. Cohen, J. A power primer. *Psychol. Bull.* **112,** 155–159 (1992).

146. First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. B. W. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. (American Psychiatric Press, Inc., 1996).

147. First, M. B. & Gibbon, M. in *Comprehensive Handbook of Psychological Assessment* (eds. Hilsenroth, M. J. & Segal, D. L.) **2: Personality Assessment,** 134–142 (John Wiley & Sons Inc., 2004).

148. Kenna, G. A. *et al.* Role of the α1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial. *Addict. Biol.* (2015). doi:10.1111/adb.12275

# Appendix A: Surveys, Questionnaires and Interviews

All self-report surveys, questionnaires, and interviews are completed by the participant in the privacy of the Addiction Research Center or an outpatient room in the Clinical Research Unit in the University of Wisconsin Hospitals and Clinics. Questionnaires are administered on paper, lab computers, or iPads via the UW-Madison Qualtrics Survey Hosting Service.

**Surveys and Questionnaires**

- Alcohol Dependence Scale (ADS): Standard questionnaire providing a quantitative measures of the severity of alcohol dependence.
- Alcohol Use Disorders Identification Test (AUDIT): Standard questionnaire about quantitative alcohol use.
- Alcohol Use History Questionnaire – questions about alcohol use history
- Anxiety Sensitivity Index (ASI-3): Standard questionnaire about anxiety.
- Demographics: Standard questionnaire about age, gender, race, and ethnicity.
- Depression Anxiety Stress Scales (DASS): Standard questionnaire about depression and anxiety symptoms.
- Desires for Alcohol Scale (DAQ): Subset of items from standard questionnaire about the participants' desire/craving of alcohol.
- Distress Tolerance Questionnaire (DTQ): Standard questionnaire about reactions to stressful situations.
- Feedback: Standard questionnaire about the participant's experience in the study.
- Intolerance of Uncertainty Scale (IUS): Standard questionnaire about anxiety and reactions to uncertainty.
- Mindful Attention Awareness Scale (MAAS): Questions about positive/negative affect and mindfulness
- Multidimensional Personality Questionnaire- Short form (MPS): Standard questionnaire about personality and temperament.
- Obsessive Compulsive Drinking Scale (OCDS): Standard questionnaire about obsessionality and compulsivity related to craving and drinking behavior.
- Penn Alcohol Craving Scale (PACS): Standard questionnaire for assessing alcohol craving.
- Perceived Stress Scale (PSS): Standard questionnaire about the perception of stress.
- Post-Experiment Questionnaire (PEQ): Standard questionnaire about the participants' emotions during the experiment.

**Interviews**

- Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar): Standard assessment of Alcohol Withdrawal Symptoms.
- Screening Survey (previously referred to as MSQ): Standard questionnaire from our laboratory about health-related behaviors for screening purposes.
- Structured Clinical Interview for DSM Disorders (SCID): Standard structured clinical interview for diagnoses of DSM Disorders. Module E: Substance Use Disorders.
- Timeline Follow Back (TLFB): Standard questionnaire about estimates of daily drinking in past month.

## Appendix B: Participant Handouts

1. Research Participation Information and Consent Form
2. Information Sheet for Research Subjects
3. Authorization to Use and/or Disclose Identifiable Health Information for Research
4. Doxazosin Package Insert
5. Directions to CRU & Map
6. Health Facts For You

# Appendix C: Eligibility Criteria Checklist

**Inclusion Criteria: General**

| Criteria | Eligible Response | Assessment | Measure | Assessor |
|---|---|---|---|---|
| Can the participant read and write in English? | Yes | Self-report | Screening Survey | ARC Staff |
| Age (Date of birth) | Age 18-65 | Self-report | Screening Survey | ARC Staff |
| Last alcohol consumption | ≤8 weeks ago | Self-report | SCID | ARC Staff |
| Last alcohol consumption | >1 week ago | Self-report | SCID | ARC Staff |
| Meets criteria for DSM5 past Alcohol Use Disorder, Mild (≥2 criteria) | Yes | Clinical Interview | SCID | ARC Staff |
| Meets criteria for DSM5 Alcohol Use Disorder, Moderate (>4 criteria) | Yes | Clinical Interview | SCID | ARC Staff |
| Currently pursuing abstinence from alcohol | Yes | Self-Report | Screening Survey | ARC Staff |

**Exclusion Criteria: Medical**

| Criteria | Eligible Response | Assessment | Measure | Assessor |
|---|---|---|---|---|
| Is blood alcohol concentration above 0.00? | No | BAC breath test | n/a | ARC Staff |
| Heart rate >100 beats/ minute after five minutes seated? [Tachycardia] | No | Clinical Assessment | n/a | Medical Staff |
| Heart rate <56 beats/ minute after five minutes seated? | No | Clinical Assessment | n/a | Medical Staff |
| Heart rate 56-59 beats/minute after five minutes seated AND clinical judgment from study physician that heart rate precludes safe participation | No | Clinical Assessment | n/a | Medical Staff |
| Systolic BP <100 after five minutes seated? [Pre-existing hypotension] | No | Clinical Assessment | n/a | Medical Staff |
| Systolic blood pressure > 160 mmHg after five minutes seated? [Pre-existing hypertension] | No | Clinical Assessment | n/a | Medical Staff |
| After five minutes seated, stand up: Systolic BP drop >20mm Hg or diastolic BP drop >10mm Hg and report of dizziness, lightheadedness, unsteadiness or other problems (nausea, blurry vision) after two minutes standing? [Orthostatic hypotension] | No | Clinical Assessment | n/a | Medical Staff |
| Frequent dizziness, unsteadiness, lightheadedness or other symptoms upon standing (> once/week)? | No | Self-Report | Screening Survey | ARC Staff |

| | | | | |
|---|---|---|---|---|
| Colorblind<br>[For NPU stress task] | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Hearing/Seeing problems<br>[For NPU stress task] | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Current treatment for chronic pain condition<br>[For NPU stress task] | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Past or current coronary artery disease, cerebrovascular accident, congestive heart failure? | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Current renal insufficiency, liver insufficiency or moderate hepatic impairment, diabetes, immunosuppressive therapy, or cancer with systemic effects or therapy? | No | Medical History and Clinical Exam | n/a; Labs | Medical Staff |
| Polyneuropathy? | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Past or current pancreatitis? | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Benign positional vertigo, Meniere's disease or narcolepsy? | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Previous allergic or adverse reaction to doxazosin or other alpha1 norepinephrine antagonist? | No | Medical History | n/a | Medical Staff |
| Scheduled or reported plans for cataract surgery prior to study completion?<br>[Floppy Iris Syndrome] | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Currently symptomatic of alcohol withdrawal?<br>[CIWA-Ar Score $\geq$ 10, or positive for any 'visual, auditory or tactile disturbances,' or for 'orientation and clouding of sensorium'] | No | Medical History and Clinical Exam | CIWA-Ar | Medical Staff |
| Discharged from inpatient treatment for alcohol use disorder or alcohol detoxification within past 7 days? | No | Medical History and Clinical Exam | n/a | Medical Staff |
| Currently stable? | Yes | Medical History and Clinical Exam | n/a | Medical Staff |
| ECG clinical over-read indicates concerns of cardiac function? | No | ECG | n/a | Medical Staff |
| Other self-reported acute or unstable illness that, in the opinion of the study team, would preclude a safe and reliable study participation? | No | Medical History, Clinical Exam, Clinical Interview | Screening Survey | Medical Staff and ARC Staff |

**Exclusion Criteria: Medical (Female Participants)**

| Criteria | Eligible Response | Assessment | Measure | Assessor |
|---|---|---|---|---|
| Are pregnancy test results positive or undetermined? | No | Urine pregnancy test | n/a | UW Lab |
| Women of childbearing potential (see definition below) must agree to use one of the following forms of birth control until after study completion (see definition below). | Yes | Consent Process | Screening Survey | ARC Staff |
| Breastfeeding? | No | Consent Process | Screening Survey | ARC Staff |

*Definition: Women of childbearing potential are females who have experienced menarche and do not meet the criteria for women **not** of childbearing potential. Women **not** of childbearing potential are females who are permanently sterile (e.g., hysterectomy, bilateral oophorectomy) or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.*
*Definition: Acceptable birth control is defined as the following methods of contraception: abstinence; hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy of partner and tubal ligation; "single" barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) with use of spermicide; or "double barrier" method of contraception (e.g. male condom with diaphragm, male condom with cervical cap).*

**Exclusion Criteria: Psychological/Behavioral**

| Criteria | Eligible Response | Assessment | Measure | Assessor |
|---|---|---|---|---|
| Self-reported lifetime diagnosis of schizophrenia schizoaffective disorder, psychotic disorder NOS, bipolar disorder (with manic episode), borderline personality disorder, or any neurocognitive disorder that may impair a reliable, safe participation? | No | Clinical Interview, Self-report | Screening Survey; SCID | Medical Staff; ARC Staff |
| Current suicidal ideation? | No | Clinical Interview | SCID | ARC Staff |
| Meets criteria for DSM5 Substance Use Disorder AND not currently pursuing abstinence, other than alcohol or tobacco? | No | Clinical Interview | SCID | ARC Staff |

**Exclusion Criteria: Medications/Therapies**

| Criteria | Eligible Response | Instrument | Measure | Assessor |
|---|---|---|---|---|
| Currently prescribed or used within past week: doxazosin or other alpha1-NE antagonist (e.g., prazosin, terazosin)? | No | Medication Inventory | n/a | Medical Staff |
| Currently prescribed or used within past week: substances with stimulant properties (e.g., d-amphetamine, methylphenidate, ephedra, pseudoephedrine)? | No | Medication Inventory | n/a | Medical Staff |

| | | | | |
|---|---|---|---|---|
| [Medications directly alter CNS noradrenergic neurotransmission.] | | | | |
| Currently prescribed or used within past week: Sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)? [Increased risk of hypotension in combination with alpha1-NE antagonists.] | No | Medication Inventory | n/a | Medical Staff |
| Currently prescribed or used within past week: beta-blockers (e.g., propanolol), alpha2 agonists (e.g., clonidine, guanfacine, dexmedetomidine), and SNRI (e.g., venlafaxine, duloxetine, atomoxetine, viloxazine), antivirals (boceprevir), chemotherapy (pazopanib)? [Medications directly alter CNS noradrenergic neurotransmission.] | No | Medication Inventory | n/a | Medical Staff |
| Currently used daily or used within past week: alpha1 agonists (e.g., midodrine, metaraminol, oxymetazoline, phenylephrine)? [Medications that alter alpha1 noradrenergic neurotransmission.] | No (within 72 hours of Study Visit 1 or 2) | Medication Inventory | n/a | Medical Staff |
| Currently used daily or used within past week: Benzodiazepines (e.g., diazepam, chlordiazepoxide, lorazepam, clonazepam, alprazolam), zolpidem (Ambien), zaleplon (Sonata), zopiclone (Imovane), eszipclone (Lunesta), dozapin (Silenor)? | No | Medication Inventory | n/a | Medical Staff |
| Currently prescribed and used daily or used within past 2 weeks: Trazodone? | No | Medication Inventory | n/a | Medical Staff |
| Currently prescribed or used within 2 weeks: Disulfiram (Antabuse)? [Medication alters noradrenergic metabolism.] | No | Medication Inventory | n/a | Medical Staff |

**Discharge criteria**

| **Criteria** | **Discharge Response** | **Assessment** | **Measure** | **Assessor** |
|---|---|---|---|---|
| Alcohol craving self-report returned to baseline? | Yes | Self-report | 6 item Desires for Alcohol Questionnaire | ARC Staff |

# Appendix D: Glossary & Abbreviations

**Abbreviations**

**AE:** Adverse Event
**ARL**: Addiction Research Lab
**ARL Staff**: Addiction Research Lab Staff. Supervised by John Curtin (PI)
**BAC:** Blood alcohol concentration
**BP:** Blood pressure
**CNS:** Central nervous system
**CRU:** Clinical Research Unit
**DSM-5:** Diagnostic and Statistics Manual of Mental Disorders – Fifth Edition
**ICTR:** Institute for Clinical and Translational Research
**IRB:** Institutional Review Board
**MET:** Motivational Enhancement Therapy
**NE:** Norepinephrine
**NIAAA:** National Institute of Alcohol Abuse and Alcoholism
**NIH:** National Institutes of Health
**NPU Task:** No Shock, Predictable Shock, Unpredictable Shock Task
**OnCore**: Online Collaborative Research Environment
**PI:** Principal Investigator
**QD:** One dose per day
**PRC:** Pharmaceutical Research Center
**RCT:** Randomized Clinical Trial
**SAE:** Serious Adverse Event
**UW:** University of Wisconsin

**Glossary**

**Women of childbearing potential:** Females who have experienced menarche and do not meet the criteria for women not of childbearing potential.
**Women not of childbearing potential:** Females who are permanently sterile (e.g., hysterectomy, bilateral oophorectomy) or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.
**Acceptable birth control:** The following methods of contraception: abstinence; hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy of partner and tubal ligation; “single” barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge) with use of spermicide; or “double barrier” method of contraception (e.g. male condom with diaphragm, male condom with cervical cap).