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TITLE: A Pilot Study on the safety and efficacy of Mifepristone for the prevention of relapses of alcohol drinking

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CLINICAL PROTOCOL

A Pilot Study on the safety and efficacy of Mifepristone for the prevention of relapses of alcohol drinking

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PROTOCOL SYNOPSIS

Objective: The primary objectives of the study include: A) Establish the safety and tolerability of using 600mg of mifepristone and 32.4mg yohimbine while consuming alcohol; and B) Demonstrate the feasibility of the study design and obtain an effect size to estimate a sample size for an appropriately powered larger R01 application using mifepristone and yohimbine together when administering alcohol.

Rationale: Glucocorticoids (GC) mediate adaptation to stress and regulate termination of the stress response through the hypothalamic–pituitary–adrenal (HPA) axis feedback action. The link between stress and chronic relapsing alcohol-use disorders (AUD) and substance-use disorders (SUD) has long been established in the addiction research field. Preclinical studies show the GC-receptor antagonist, mifepristone, reduces behavioral hyperexcitability during the acute phase of alcohol withdrawal, suggesting that mifepristone is a promising pharmacotherapy for alcoholic individuals to reduce the cognitive deficits caused by chronic alcohol use and withdrawal symptoms. In our preclinical studies, we showed that in conditions where stress is limited, mifepristone has no effect on alcohol intake, corroborating the hypothesis that GC blockade represents a key element in the preoccupation/anticipation (craving) stage of the addiction cycle. However, what remains unknown is the role of mifepristone in stress-induced craving and relapses of alcohol drinking in humans.

Overview of Study Design: The design will be a randomized within, crossover, double-blind, placebo-controlled human study with mifepristone in non-treatment-seeking-alcohol-dependent individuals. The study will be conducted in in consecutive phases (Figure 1):

Visit#1: Screening;

Visit#2: Randomization and drug/placebo dispensed (for seven days);

Visit#3: First lab-session: single dose of yohimbine;

Visit#4: Washout period, follow-up (one month) and drug/placebo dispensed (for seven days);

Visit#5: Second lab-session, single dose of yohimbine; Motivational session (MET);

Visit#6: Follow-up (one month); END of STUDY.

Study Population: Sixty-five non-treatment-seeking, alcohol-dependent participants will be recruited. Fifty-eight participants will be enrolled for screening with **50 participants (*n* = 50)** expected to complete the study. Participants will primarily be recruited via advertisements placed in local newspapers and posted on buses.

Safety Measurement/Parameters: Risks of medication side effects will be minimized through careful and detailed screening of participant. Signs of anxiety and stress, adverse events and vital signs will be assessed at each visit by psychometric assessments. Safety laboratory tests and will be evaluated at baseline, and at the end of the study participants will receive a behavioral motivational session at the end of Visit 5.

Financial considerations: There will be no cost(s) to participate in this study. The study medications and all procedures that are not part of routine care, but are required for the study, will be provided to the participant. If eligible for the study, participants will receive $25 for the randomization visit (Visit# 2) and for the follow-up visits (Visits #4 and #6). During the laboratory phase, at each visit (Visits #3 and #5) participants are compensated $100 + another possible $3/drink as incentive for not drinking (max $24). Therefore, each participant may be compensated up to $323 during the entire study period. Participants will be also compensated for their travel costs.

Specific Aims:

Aim 1: to assess the safety and tolerability of mifepristone and yohimbine while consuming alcohol.

Aim 2: to test the hypothesis that an increase in alcohol craving induced by yohimbine is antagonized by pre-administration with mifepristone.

Aim 3: to test the hypothesis that an initial priming drink and alcohol consumption induced by yohimbine is antagonized by pre-administration with mifepristone.

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STUDY AIMS

Although stress has long been linked to alcohol intake and relapse during abstinence, there are no available medications that target stress-induced alcohol relapse. Furthermore, the effects of anxiolytics on craving and relapse in alcohol-dependent individuals have been inconsistent. The benefits of reducing stress conditions using pharmacological interventions that blunt the activation of stress systems in ethanol-dependent preclinical models have been well described; however, the integral mechanisms by which stress influences alcohol consumption in humans are not well understood. The leading goal of this study is to evaluate preventive pharmacological interventions that can dampen the influence of stress on alcohol consumption and relapse in AUD populations. This protocol will test a preclinical model that investigated whether mifepristone, a glucocorticoid receptor antagonist, plays a role on yohimbine-induced reinstatement of ethanol seeking. This model builds on the hypothesis and evidence that glucocorticoid receptors play a role in the reinstatement behaviors elicited by yohimbine, an *α*-2 adrenoceptor antagonist, known to induce reinstatement of ethanol-seeking behaviors.

Translating preclinical paradigms into effective models for assessing pharmacological approaches for stress-induced alcohol relapse in humans requires a comprehensive model capable of integrating: alcohol-proximal variables that influence drinking (withdrawal symptoms, craving), neuroendocrine variations (cortisol), and stress-risk factors (different temporal traumatic events). A comprehensive stress model is needed because emotional distress, neuroendocrine activation, stress-related genetic variations, craving, and alcohol consumption do not necessarily overlap in alcohol-dependent individuals. Mifepristone may be a valuable pharmacotherapeutic strategy for preventing relapse to AUD, and yohimbine is a pharmacological stressor capable of increasing craving, creating recall of traumatic memories, and altering neuroendocrine levels in alcohol-dependent individuals. As FDA-approved medications, both mifepristone and yohimbine have the advantage of being directly applicable to an alcohol clinical setting and being utilized in the translational efforts described in this application.

The *overall objective* of this study is to conduct a randomized pilot laboratory study consisting of a placebo-controlled assessment of the effects of 600 mg of mifepristone for a week, in a stress-induced condition triggered by a single dose of 32.4 mg of yohimbine in non-treatment-seeking-alcohol-dependent individuals. In the following specific aims, I propose:

Aim 1: to assess the safety and tolerability of mifepristone and yohimbine while consuming alcohol. Randomized participants will complete two alcohol laboratory sessions along with a battery of physiological and psychological assessments that measure adverse events and pharmacokinetic (PK)/pharmacodynamic (PD) interactions.

Aim 2: to test the hypothesis that an increase in alcohol craving induced by yohimbine is antagonized by pre-administration with mifepristone. To test this hypothesis, we will establish the effect of mifepristone on alcohol cue-elicited craving during a cue-reactivity (CR) experiment along with a series of physiological and psychological tests assessing alcohol craving.

Aim 3: to test the hypothesis that an initial priming drink and alcohol consumption induced by yohimbine is antagonized by pre-administration with mifepristone. To test this hypothesis, we will **e**stablish the effect of mifepristone in an alcohol self-administration (ASA) experiment. We will also establish if mifepristone has an effect on alcohol PK/PD levels. The data obtained from this pilot trial will demonstrate the feasibility of the study design and obtain the PK/PD safety data to support a future study and an effective sample size for an appropriately-powered larger R01 application.

RATIONALE AND SIGNIFICANCE TO THE ALCOHOL FIELD

Stress and alcohol dependence. Stressful events may lead to a wide range of health and psychiatric illnesses including alcohol use disorders (AUD)[1-4]. Furthermore, exposure to stress at multiple time points across an individual life course is associated with risk for AUD[4,5]. Though stress has been difficult to define[6,7], it has been widely studied in the AUD field because it has been identified as one of the key factors contributing to escalation from social drinking to alcohol dependence[8]. In addition, AUD prognosis appears to be affected by stress and anxiety, both of which appear to promote alcohol craving[9,10] and affect relapse[11,12].

Clinical relevance. Stress could influence alcohol intake in different ways. Acute stress has been found to contribute to relapse drinking in an alcohol cue reactivity paradigm[13]. Alcohol consumption, utilized to dampen the negative effect of stress[14,15], can be used as a coping strategy[16]. Stress can also influence alcohol consumption by altering the rewarding efficacy of alcohol[17]. Furthermore, the impact of stress does not halt when individuals stop drinking. Alcohol abstinence is well known to increase anxiety during the withdrawal phase, which is an important factor in relapse[18]. One of the most difficult aspects in treating AUD is relapse to uncontrolled drinking that can be triggered by stressful events after a period of abstinence[19].

Although it is a priority of NIAAA to develop new AUD therapeutic interventions, currently there are only four FDA-approved medications to treat AUD. All of these interventions exhibit limited efficacy[20], may require life-long ongoing therapy, and none target the stress component. Furthermore, the effects of anxiolytics used off-label for alcoholism have been inconsistent[21-23]. The stress system is thus ideally suited as a target for short-term therapeutic interventions with a long-enduring effect, as this strategy may both lessen acute distress and promote stress resilience during alcohol abstinence. Thus, blunting and resetting the stress system could represent an effective and exciting novel pharmaceutical target for treating AUD.

Pharmacological stress targets. Stress responses involve the (**a**) neural corticotropin releasing factor (CRF) system, and (**b**) activation of the hypothalamic-pituitary-adrenal (HPA) axis leading to increases in glucocorticoids (GCs)[24]. The use of alcohol dysregulates the stress system both at the neural CRF[25-27] and HPA levels[28-31], as repeated alcohol use leads to stimulation of the HPA axis, and the interruption of chronic alcohol use increases activation of CRF[32]. There are no medications that target stress-induced craving at the neural CRF level in order to reduce compulsive alcohol seeking, although CRF-receptor-1 antagonists have shown efficacy in preclinical ethanol models[33,34] and are currently in clinical trials (NCT01187511 and NCT01227980). Preliminary results from those studies, in line with preclinical findings[35,26], report that medications targeting the CRF system may be more effective in treating alcohol-dependent individuals to prevent stress-induced craving and relapse than preventing alcohol relapse that is not related to stressor triggers[36].

Alternative pharmacological targets within the stress system are the GCs, which interact with many neuroendocrine systems[37-39] and mediate adaptation to stress response through the HPA axis feedback action[40,41]. During chronic stress conditions, this feedback becomes dysregulated, leading to a variety of maladaptive syndromes including anxiety, depressive disorders[42] and alcohol dependence[43]. An effective treatment for AUD would ideally reverse the neurohormonal adaptations caused by excessive GC stress hormonal response. Furthermore, identifying targets that can modulate the stress system has the potential to benefit other mental disorders, such as posttraumatic stress disorder and psychotic major depression that have high comorbidity with AUD.

Mifepristone. In preclinical models, the GC-receptor antagonist, mifepristone, specifically affects ethanol-dependence behaviors[44], limiting ethanol self-administration[45] and preventing ethanol seeking during abstinence[46]. Those results, in addition to our findings[47], suggest that GC blockade may represent a promising pharmacotherapeutic approach for preventing future alcohol exposures[48]. Mifepristone is a FDA-approved oral medication for the termination of early pregnancy, and has a safe and tolerable profile. Due to its specific antagonism effect of GC function, mifepristone is used to treat disorders that occur when the body is exposed to high levels of cortisol (Cushing syndrome[49] and psychological disorders[50]). Mifepristone may have the potential to “reset” a dysregulated HPA axis, as it upregulates GC receptor function, restores normal HPA feedback, decreases depression-like behavior, and attenuates relapse[51].

Preclinical studies showed that in conditions without stress-induction, mifepristone has no effect on alcohol intake[47,52-54], corroborating the hypothesis that GC receptors represent a key element in the preoccupation/anticipation (craving) stage of the addiction cycle. What remains unknown is the effect of mifepristone in acute stress precipitating alcohol craving and relapse in humans.

Stress-induced models. One of the most challenging aspects in designing a human laboratory study is the inclusion of an acute stress condition intended to represent a comprehensive naturalistic environment in chronic alcohol-dependent individuals. Hence, testing pharmacotherapies in stress-induced relapse models in alcohol laboratory paradigms is critical for the identification and development of therapeutic interventions to prevent alcohol relapse. Because the level of stress experienced by individuals suffering from AUD in real life situations is far greater than one can apply to participants in the traditional alcohol laboratory setting, for this pharmacotherapy proposal, I will use a model that integrates a pharmacological stress-induction paradigm with cue-reactivity (CR session) and alcohol self-administration (ASA session) laboratory measures in non-treatment-seeking alcohol-dependent individuals.

Pharmacological challenges such as yohimbine, an *α*-2 adrenoceptor antagonist, have been shown to activate the primary events of stress response (CRF/ACTH/cortisol) in addition to increasing sympathetic nervous system activity[55], facilitating recall of traumatic memories[56], and increasing alcohol craving correlated with alcoholism severity[57]. Although acute psychological stressors presented in the laboratory have the advantage of modeling stress-induced emotions (anxiety, frustration, and embarrassment) encountered by individuals in the real world, they do not create the cascade of neuroendocrine events that likely trigger the urge to drink and lead to relapse under naturalistic conditions. Physical stressors (cold presser test or isometric handgrip) induce cardiovascular activation and discomfort, but produce limited cortisol activation and no increase in craving in alcoholics[58,59]. Yohimbine provides a safe[57,60] pharmacological opportunity to overcome methodological weaknesses in studying the impact of realistic mobilization of neuroendocrine processes during an acute, transient stress on human cognition. Yohimbine, being a FDA-approved oral medication, has the advantage of being directly applicable to an alcohol clinical setting and utilized in the translational efforts described in this application.

Integration: psychoneuroendocrinology and trauma factors. In addition to acute life stressors, direct contributors to stress neuroendocrine dysregulation include early-[61-63] and late-life[64] trauma. Individuals who experienced life trauma may use alcohol to help cope with trauma-related symptoms. Recent investigations highlight the importance of assessing trauma among patients with alcohol use disorders[65-67]. This stress study will incorporate the life traumatic experiences to evaluate their association with neuroendocrine changes[68,69] and the later development of AUD[65].

Significance to the field and for NIAAA. This proposed study is consistent with the mission of *National Institute on Alcohol Abuse and Alcoholism (*NIAAA) to "promote the identification and prevention of alcohol and other drug use problems in our society through research." This proposed study meets two of the needs of research on the field of alcoholism: 1) to develop new pharmacotherapies for alcoholism; and 2) to elucidate mechanisms by which the medications are likely to have beneficial effects. This research will add to the current knowledge about the potential benefits of mifepristone by examining its effects on cue-elicited urge, the effects of drinking, and its effects on alcohol-free choice during stressful events. Although it is a priority of NIAAA to develop new AUD therapeutic interventions, currently there are only four FDA-approved medications to treat AUD. All of these interventions exhibit limited efficacy [20], and none target the stress component. The stress system is ideally suited to develop a short-term therapeutic interventions with a long-enduring effect, as it can lessen acute distress, and promote stress resilience during long alcohol abstinence. Thus, blunting and resetting the stress system, in order to improve both physical and psychological factors in alcohol-dependent individuals, represents an effective and exciting novel pharmaceutical target for treating AUD. Finally, our approach builds from a network of sciences that may have the potential to target other mental disorders (posttraumatic stress disorder and psychotic major depression) that have high comorbidity with AUD.

Innovation. This research is innovative in three ways. First, it focuses on a novel target for the prevention of alcohol relapse, the stress system. The second major innovation of this proposal is the development of a translational research clinical model that integrates administration of pharmacological stressors with alcohol

laboratory study methods developed from personal neuroscience and neuropharmacology knowledge. As the design of this project has built logically on our prior work, it is our intent to translate our neuroscience safety results to clinical research, which includes examining the effects of pharmacokinetic (PK) interactions (alcohol, yohimbine, mifepristone) on Pharmacodynamics (PD) additive responses (CNS depressant properties of alcohol or increased sedation/depression of respiratory and/or cardiac functions). Although not observed in our preclinical models, possible negative outcomes may be observed in stress-induced conditions in alcohol-dependent individuals, such as potentiation of the stimulant phase of alcohol, increase in behavioral effects of alcohol intoxication, or worsening alcohol withdrawal syndrome. Our strong team includes well-established clinicians in the fields of experimental pharmacotherapeutics in alcohol laboratory studies, psychiatry and neuropsychopharmacology, to ensure safety and answer additional clinical questions that may arise during or between alcohol laboratory sessions. This interdisciplinary-validated human laboratory protocol is critical to determine safety and tolerability of stress-induced pharmacological procedures before moving forward into a larger randomized clinical trial and to pave new hypotheses to be explored in alcohol and stress neuroscience research. Finally, by providing safety measures and PK/PD data, this proposed application will pave the way for new therapeutic targets that could be utilized in other stress/anxiety mental disorders that have high comorbidity with AUD.

The Investigator Team. The PI, Dr. Haass-Koffler, is a T32-funded postdoctoral fellow at CAAS. This REA proposal represents a logical extension of her previous experimental pharmacology and preclinical work with mifepristone on alcoholism done at the Gallo Center at University of California San Francisco (UCSF) before moving to the Center for Alcohol Addiction Studies (CAAS) at Brown. As such, under the supervision of her mentor, Dr. Kenna, this application will allow Dr. Haass-Koffler to 1) conduct a translational clinical study, the rationale of which is directly driven from her preclinical work; 2) gain experience and receive mentorship on human behavioral pharmacology research; and 3) collect pilot data that will support the feasibility and background of her NIH R01 proposal.

The qualified medical personnel during the laboratory sessions.

Responsibilities for each visit for each member of the Research Staff are described in Appendix Z.

The PI, Dr. Haass-Koffler has extensive experience in the PK/PD drug-drug interactions. She obtained her PK/PD training during her doctorate at UCSF, and she applied her PK/PD knowledge at a clinical level in her postdoctoral training in the department of Pharmacology and Experimental Therapeutics in the School of Medicine at UCSF; she also taught drug-drug interaction lectures in the core PK course to UCSF Pharmacy students (for two years). Dr. Haass-Koffler is also familiar with possible physiological adverse events that may arise during the administration of mifepristone, yohimbine and alcohol, since she ran the same mifepristone-yohimbine-alcohol study at a preclinical level. She also authored a drug-drug interaction book chapter in a medical Substance Abuse Textbook (please see CV, publications) and she was part of the Medication Use and Safety Subcommittee (MUSS), San Francisco General Hospital (SFGH) (please see CV, Hospital Committees). Dr. Haass-Koffler is a trained military officer nurse who served in Italian Army/Air Force Hospitals and International Relief Missions (Somalia, Rwanda and Ex-Yugoslavia) for four years. She was the Lieutenant in change of medical training for the nurses' qualification in Air Mobile Search and Rescue, School of Medicine, Italian Air Force. The medical experience in military hospitals and in war zones professionally prepared Dr. Haass-Koffler to assess both physical and psychological human distress and determine situations that may trigger a call to the study physician (please see CV, military service). Furthermore, regarding specific training in addictive behaviors in the alcohol-dependent population, Dr. Haass-Koffler worked at the Department of Public Health, Community Behavioral Health Services, San Francisco General Hospital (SFGH) as a Drug Information intern for two years during her doctoral training (please see CV, Hospital appointment). She was responsible for researching and presenting scientific and clinical information that would provide recommendations intended to represent the best-practice guidelines for the use of medications for the treatment of alcohol dependence and other psychiatric disorders (please see CV, list of CBHS publications). To augment her formal training on addictive behaviors, Dr. Haass-Koffler also attended the University of Utah, School on Alcoholism and Other Drug Dependencies training. This program focuses on keeping pace with increased awareness of the health and social problems of alcoholism and other drug dependencies. Academically, Dr. Haass-Koffler received her

PharmD with the double track in Pharmaceutical Science at UCSF, School of Pharmacy (#1 Pharmacy School in the US). She performed research at the prestigious Ernest Gallo Clinical and Research Center in California under the mentorship of Dr. Antonello Bonci, now one of the top directors at NIH. This high selective doctoral program allowed her to receive a double concurrent appointment at UCSF in the Neuroscience Department (Gallo Center) and in the Department of Clinical Pharmacology and Experimental Therapeutics (School of Medicine).

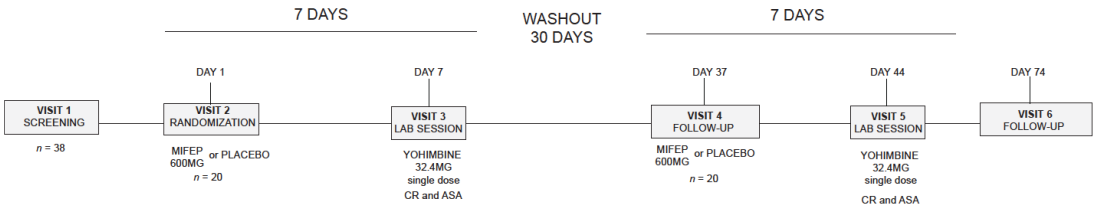
The study physician, either Dr. Swift, will be present during the screening visit. They will perform the physical exam and psychological assessments. Dr. Swift, is a practicing physician and is Board Certified in Addiction Psychiatry. Dr. Swift is Staff Psychiatrist at the VA Medical Center at Roger Williams Medical Center and at CAAS; he has extensive alcohol laboratory experience and contributed to the advancement of knowledge in the AUD research field through several selected publications[23,70-86]. Dr. Haass-Koffler and the RA will immediately call the study physician if any safety issues arise during or between sessions (i.e. CIWA score ≥7).

Dr. Haass-Koffler has the support of Research Associates (RA) who have been trained in administering psychological assessments (i.e. CIWA, SCID, HAM-D/A), conducted similar alcohol and pharmacological studies for many years at Brown and included in our peer-review. They also will collect blood, saliva and urine samples and monitor blood pressure and heart rate using a Dinamap Adult Vital Signs Monitor.

METHODS

Overview of Proposed Research. The design will be a randomized within, crossover, double-blind, placebo-controlled human study with mifepristone in non-treatment-seeking alcohol-dependent individuals. The study will be conducted in two consecutive phases with one month washout period (**Figure 1**): Visit #1, Screening; Visit #2: randomization and drug/placebo dispensed; Visit #3: first lab-session: single dose of yohimbine; Visit #4: After one-month washout period **(30 days, plus or minus two days to accommodate the schedule of the next visit)**, follow-up and drug/placebo dispensed; Visit #5: second lab-session, single dose of yohimbine, motivational session (MET); Visit #6: follow-up (one month). END of STUDY.

Figure 1 – Study Design



Medications and doses: Participants receive an oral dose of 600 mg of mifepristone or matching placebo for approximately seven days (plus three extra pills). Participants will receive detailed information on the study medications, including their current use and possible side effects. Mifepristone treatment in clinical setting has shown to be safe, tolerable, and acceptable[87-89], including in participants suffering from depression, anxiety, and PTSD[90-92]. On Days 7 and 44, all participants will receive a single oral dose of 32.4 mg yohimbine approximately one hour (t_{max}=1 hour) prior to the lab session. The oral dose of yohimbine for this study is based on prior studies in which yohimbine was administered to examine neuroendocrine probe in human studies[57,93,94]. Ample data support the safe use of yohimbine to induce craving in alcohol-dependent individuals[57], and the safe induction of stress in PTSD veterans[95] and gamblers[60]. *We already obtained the Investigational New Drug (IND#121984) from FDA that determined that the clinical investigation of mifepristone and yohimbine while consuming alcohol is safe to proceed (see attaché letter form FDA). Our IND was also cross-referenced by the IND of Corcept Therapeutics (IND#059737) for chemistry, manufactory, pharmacological, and toxicology data of mifepristone (see attached letter form Corcept). Participants will receive detailed information on the study medications, including their current use and possible side effects.*

STUDY PROCEDURES:

Visit 1 (Screening). All procedures and responsibilities of each member of the research team are described in Appendix Z (page 1). Following a breath analyzer (BrAC) that must be 0.00, participants will then be assessed on demographics, medical history, physical examination, vital signs and ECG. Blood, urine, cortisol and clinical assessments are performed to screen individuals for inclusion/exclusion criteria and monitor adverse effects; we will collect a baseline salivary cortisol sample (three samples by spitting in a tube) and administer psychometric assessments. The salivary cortisol samples will be stored in Dr. Haass-Koffler's lab. A study physician will administer the Brief Trauma Questionnaire (BTQ, Appendix J). After a study physician reviews and approves the medical history and lab results, the participants will be called with the results and scheduled for Visit 2. When the RA or Dr. Haass-Koffler administers the SCID, Drs. Swift will review the SCID the screening day. They will review the rest of the other blood, saliva and urine laboratory analysis before enrolling any participant in the study. Session will last approximately 3-4 hours. *Randomization will be performed on Visit 2*.

Visit 2 (Randomization): All procedures and responsibilities of each member of the research team are described in Appendix Z (page 2). BrAC = 0.00 before initiating any procedure; participants in addition to the psychometric assessments (see complete list in Appendix Z) they will then be assessed for life trauma exposure. We will assess lifetime history of trauma exposure using Life Events (LEC) and Post Traumatic Stress Disorder (PTSD) (PCL) Checklists. The participants will then be randomized and we dispense the study medication (see Appendix Z). The overall descriptions of the measures and the specific questions and responses that may trigger a call to the licensed clinician are provided in the Protection of Human Subject section. *Compensation*: sessions will last approximately 3 hours, and subjects will receive $25 for participation**.**

Visits 3 and 5 (Stress-induction and Alcohol Laboratory Session): All procedures and responsibilities of each member of the research team are described in Appendix Z (page 3 and 5). Participants will be instructed not to consume alcohol for 24 hours and must have a BrAC of 0.00 prior to any assessment. A sample of salivary cortisol will be collected and a single oral dose of 32.4 mg yohimbine will be administered to participants. The lab-session will begin one hour later in order to allow yohimbine to take effect[96], at which time a second sample of cortisol will be collected. The CR will be run first, followed by the ASA (Assessments Schedule, Appendix Z). The PI will schedule Visit #3 and Visit #5 (alcohol laboratory sessions) only if Dr. Swift will be in proximity of CAAS laboratory. The PI will not schedule Visit #3 and Visit #5 if both study physicians are traveling or not in Providence**.**

Cue-reactivity (CR). The CR will be similar to previously published studies[73,97-101]. The entire procedure takes about 45 minutes. The water trial provides a controlled baseline that controls for all aspects of stimuli and movement, except for the nature of the beverage. Next, participants will undergo two 3-minute alcohol cue exposure trials that will be identical to the water trial except that the glass of water will be replaced with their preferred alcoholic beverage and the bottle of water will be replaced with the appropriate commercially-labeled alcohol bottle. After every 3-minute beverage exposure, participants will rate their urge to drink alcohol by completing the alcohol urge and craving questionnaire (ACQ) to assess attention to the sight and smell of water and alcohol cues. Saliva (weight in cotton rolls, mg), heart rate (HR; beats/min) and blood pressure (systolic, diastolic, and mean arterial pressure-MAP) will be monitored continuously using a Dinamap Adult Vital Signs Monitor. After the conclusion of the CR, participants will undergo the ASA. Consistent with recommendations[102], participants will be informed they will receive alcohol following the CR. The last of salivary cortisol (by spitting in a tube) will be collected at the end of the CR.

Alcohol Self-Administration (ASA). Participants are presented with a priming dose of alcohol designed to raise blood alcohol levels to 0.03 g/dl. Consistent with previous studies[78,103,104], we will wait 40 minutes before presenting more alcohol. We will assess craving and whether stress-induced craving will modify responses to the priming drink using the ACQ. Stimulant and sedative effects of alcohol will be assessed using the Biphasic Alcohol Effects Scale (BAES)[105]. The "free-choice" phase of the ASA lasts 120 min and the ACQ will be

administered every 30 min[78,103,104,106]. Each participant will get $3.00 per drink (max possible is $24), provided as an alternative reinforcer for not drinking. Each beverage is calculated to raise the blood alcohol levels by 0.015g/dl. If the participant's BrAC has reached 0.1, then the alcohol consumption period will stop. We will also collect multiple BrAC values in order to monitor the mifepristone effects on alcohol pharmacokinetic and pharmacodynamic levels. Participants wait until BrAC = 0.00 (repeated twice) before being discharged. At the end of Visit 5, a Motivational Enhancement Therapy (MET) will be performed to provide education about alcoholism and to explore participants' desire to get treatment if they wish to receive it, and then we will assess at last follow-up to ascertain that drinking has not increased.

Participants are strongly encouraged to remain in the lab until no longer intoxicated. After the laboratory session, we will provide food and water and they can watch television. If they want to leave, we will provide a taxi ride.

Compensation: sessions will last approximately 6 hours, and subjects will receive $100 for participation plus another possible $3/drink as incentive for not drinking (max $24).

Washout period: During the washout and follow up period (30 days, plus or minus two days to accommodate the schedule of the next visit) we will contact participants weekly by telephone to ensure that there are not unexpected side effects. We will alert the study physicians in the event of anxiety, depression and suicidality. We will also send a text reminder for the next visit (Visit #4 and Visit #6).

Visits 4 and 6 (Follow-up): All procedures and responsibilities of each member of the research team are described in Appendix Z (page 4 and 6). After a one-month Washout period (30 days, plus or minus two days to accommodate the schedule of the next visit), participants will be asked to return for a follow-up and for dispensing of medication: mifepristone 600 mg/day or placebo for a week. The purpose of setting a month-long follow-up is because mifepristone may have the potential to "reset" a dysregulated HPA axis. In this manner, we will assess if there is an enduring effect of mifepristone beyond when the drug is stopped. The follow-up after one month will exclude pharmacokinetic mechanisms and will assess if the mifepristone antagonism at GC-receptors is responsible for resetting the HPA axis feedback loop. Due to the distinct circadian rhythm of cortisol, we will schedule Visits 3 and 5 at the same time of day as Visit 1 in order to collect salivary samples to be measured both under natural (Visit 1) and induced-stress response (Visits 3 and 5) conditions. At the follow-up visits, the participants will complete assessments, including a urine drug screening, as outlined in Appendix Z. As there is no medication or alcohol administration during the randomization (Visit #2), medication dispensing (Visit #2 and Visit #4), and follow-ups (Visit #4 and Visit #6), these visits may be conducted without the physical presence the of the study physicians in the CAAS laboratory, but preferably within the Providence area.

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Compensation: sessions will last approximately 2 hours, and subjects will receive $25 for participation.

Data analysis

This study will represent the first intervention of mifepristone on yohimbine-induced alcohol craving and consumption in this population. As this is a safety and tolerability study, adverse events evaluation (AEE) will be reported as the number and their intensity. We will compare the number and intensity of AEE in the mifepristone vs. placebo groups weekly and during the alcohol laboratory sessions. These events will be rated as none, mild, moderate, and severe. Paired *t*-tests will be used to test for medication effects. Generalized Estimating Equations (GEE) will be used for dichotomous data if events are rare. To guard against Type II errors, we will also report additional descriptive data on adverse events (the distribution of the maximum level of an adverse event collapsed across time points per condition). This study integrates self-reported and clinician-administered assessments with clinical laboratory analysis. A series of analyses of covariance (ANCOVA) will be conduct to test the effect of mifepristone on alcohol craving while controlling for variance

attributed to stress and anxiety level. The dependent variables will be baseline and post-laboratory session scores of Alcohol Urge and Craving Questionnaires (ACQ), Alcohol Visual Attention Scale (A-VAS) and Alcohol Attention Scale (AAS). The covariates will be trauma experienced as measured by Life Event Checklists (LEC), stress level measured by Perceived Stress Scale (PSS) and PTSD (PCL) Checklist scores, and anxiety level measured by Hamilton Anxiety Rating Scale (HAM-A), Self-Evaluation Questionnaire for state (STAI-y1) and Self-Evaluation Questionnaire for trait (STAI-y2). To examine the relationship between mifepristone compared to placebo on neuroendocrine fluctuations, we will use repeated measures ANCOVA with the cortisol baseline curve (three time-points: neutral, yohimbine challenge and after cue-reactivity) change during the laboratory sessions. Finally, to examine the effect of mifepristone compared to placebo in increasing the alcohol consumption during the alcohol self-administration, we will utilize an analysis of variance (ANOVA) with repeated measures. We will also attempt to establish an effect size for applying this paradigm on craving and drinking. These dependent measures will be operationalized by the ACQ and the ml of alcohol consumed during the drinking session, respectively. An effect size also will be obtained so that a target sample size to ensure adequate statistical power may be calculated for future proposed studies. Naturalistic drinking will be tracked via Alcohol Timeline Followback (TLFB) outside of the lab at each visit (by keeping track of the drinking behavior in the participants' calendar).

Alternative Design Considerations. We considered **(1)** testing the stress-induced model by yohimbine in AUD populations before initiation of the mifepristone trial; however, yohimbine challenge demonstrated to (a) be safe[57,60,93], (b) induce a robust cortisol response, (c) elevate alcohol craving correlated with alcoholism severity but (d) not anxiety[57], demonstrating that yohimbine as a pharmacological challenge produces robust and reproducible responses that are well suited for medication development. Similarly, we considered **(2)** testing only mifepristone in AUD population; however, (a) this approach is already ongoing (NCT01548417) and our previous results[47], aligned with other preclinical data[52-54], showed that in conditions where stress is limited, mifepristone has modest effect on alcohol intake. In addition, we considered **(3)** inclusion criteria for women that were less stringent than our proposal by including women with childbearing potential willing to use double barrier methods of birth control; however, due to the FDA abortifacient indication of mifepristone, we opted for a more prudent approach that has been used by others (NCT01548417). We understand that the exclusion of pre-menopausal women in this study could be a source of variability in medication response since the age range for male and female participants could end up being different; therefore we considered **(4)** changing the age to 45-65. However, this approach would limit the field of participants, and furthermore, it will provide a source of variability in medication response in different age populations, which is a critical feature in AUDs

PROTECTION OF HUMAN SUBJECTS

The PI, Dr. Carolina Haass-Koffler, is a T32-funded postdoctoral fellow at CAAS. This study is an extension of her previous experimental pharmacology and preclinical work with mifepristone, yohimbine on alcoholism done at the Gallo Center at University California San Francisco (UCSF) before moving to the Center for Alcohol Addiction Studies (CAAS) at Brown. She has previously tested these drugs with alcohol in preclinical models. To ensure participant safety, the investigator team includes well-established clinicians in the fields of experimental pharmacotherapeutic in alcohol laboratory studies, psychiatry and neuropsychopharmacology , to ensure safety and answer additional clinical questions that may arise during or between alcohol laboratory sessions. Research Assistant (RA) trained to administer psychological assessments (including SCID) or the PI (when completed her training at Butler Hospital) will assess the withdrawal syndrome by administering the CIWA (Appendix F). Self-report scales will provide the anxiety level by (STAY-y1/2, appendix R and S) and the stress level PSS (Appendix P) if there is need to call the study physician (Dr. Swift). Specific questions and responses during the psychological assessment that may trigger a call to the licensed clinician are included (page 13-15). When the RA or Dr. Haass-Koffler will administer the SCID, Dr. Swift will review the SCID the same day of screening.

Protections Against Risks: This human subject research meets the definition of Phase I Clinical Trial Research that has received an IND121984 from FDA to Dr. Haass-Koffler. This is a randomized within, crossover, double-blind, placebo-controlled human laboratory study with mifepristone (600 mg/ day for seven days) in a stress-induced condition triggered by yohimbine (32.4 mg, single dose) in non-treatment-seeking alcohol-dependent individuals. Participants will be recruited primarily through advertisements in the media. The participants will be 21 to 65 years (inclusive) in good physical health and competent to provide consent. Inclusion and Exclusion Criteria are outlined in **Table 1**.

This study involves non-treatment-seeking alcohol-dependent individuals who are heavy drinkers but do not meet the threshold criteria for alcohol withdrawal (CIWA-Ar ≤7). This is first to ensure participants' safety, and also because our study evaluates the neuroendocrine response to alcohol craving triggered by stress and anxiety-related negative emotions rather than withdrawal syndrome. If we identify individuals who meet the threshold criteria for clinically significant withdrawal syndrome during recruitment/eligibility process, we will follow a standard referral protocol (**Potential Risks** session, below), which includes calling the study physician (Dr. Swift). Regardless of eligibility, all screened participants will receive a local resource sheet of mental health and substance abuse services. Any unexpected ethical issues that arise with our study population will be discussed during weekly team meetings. Referrals and emergency protocols will be reviewed by mentors and Brown Research Protections Office (RPO)/Institutional Review Board (IRB).

Recruitment and Informed Consent: Participants will be recruited through newspaper, TV and radio advertisements and screening efforts conducted at CAAS, Brown University, centrally located in Providence, Rhode Island. After routine screening involving telephone interviews and completion of a research initiated screening instrument, each participant will receive an explanation of the study protocol, its risks and potential benefits. In specific, each participant must acknowledge they understand that *this is not a treatment study*. Should participants want treatment, treatment program information will be provided. At baseline following a breath alcohol level (BrAC) = 0.00, participants will provide written informed consent that is approved by the Brown IRB/RPO. Following resolution of questions from interested participants, volunteers will be asked to read and initial each page of the informed consent, acknowledging their understanding of each page. An entire copy of the informed consent will be given to each participant.

Participants will be enrolled based on inclusion and exclusion criteria (**Table 1**). Careful participant evaluation by trained staff will minimize the risk of including individuals with excluded medical and/or psychiatric conditions. The PI, Dr. Haass-Koffler will be responsible for administering the procedures described in the protocol. A RA, is also a phlebotomist, will be responsible for drawing blood, and collecting urine and salivary cortisol samples during the study. The risk of hematomas will be minimized by using single-use butterfly needles or BD vacuntaiers. Eligible volunteers will receive the Emergency card (Appendix T) for the study to keep in the wallet; they will be closely monitored during the entire study period. During the trial individuals' substance use and psychiatric status will be monitored. Participants with positive BrAC levels or evidence of intoxication will be monitored until no longer intoxicated, or referred for appropriate treatment. Intoxicated individuals who drove to a visit and who refuse to stay for whatever reason will be sent home via taxi. Participants will be given a card (Appendix X) identifying themselves as participants in a research study, and containing emergency numbers of the PI and study physicians on call 24 hours a day. The blind will be broken if necessary for emergency assessment or treatment. Adverse events will be systematically evaluated and recorded. If adverse events are serious or intolerable, participants will be immediately withdrawn from the study and given treatment and or referral as the situation dictates. Participants will be referred for treatment according to their needs and wishes if they show severe deterioration such as withdrawal syndrome (tremor, anxiety, and agitation) monitored by administering the CIWA (score ≥7 will call the study physician) (Appendix F), and continued evaluation of them will provide ongoing information concerning their clinical status. Given the nature of alcohol-dependent participants, we are aware that special consideration and safety precautions must be provided for our subjects. Our first precaution is the comprehensive assessment that we conduct on the subjects prior to initiating the study. Subjects are screened by interview, questionnaire, medical history, physical examination and laboratory testing to eliminate subjects with a personal history of current substance abuse or dependence or other psychiatric comorbidity whose symptomatology precludes participation in a

research study. A second precaution is the orientation to the procedures, conducted prior to the experimental sessions. Subjects will sit in the lab room and be acclimated to the blood pressure cuff. This will serve to diminish any anxiety and will identify subjects who are too anxious or paranoid to undergo subsequent testing, assessed by PSS (Appendix P) and STAY-y1/2 (Appendix R and S). A third precaution is the monitoring and medical backup present throughout the study. Finally, a follow-up visit will be performed at the end of the study. Finally, individuals should always carry their ID (appendix X) and Emergency card (Appendix T). Individuals will be referred for further evaluation and treatment should any medical or psychiatric conditions occur.

Insuring Informed Consent and Comprehension: The Informed Consent Form will be written at 8th grade reading level. At the initial visit, participants will be provided with information about the study, its rationale, risks, and potential benefits. Participants will be informed that they are participating of their own free will and can withdraw their consent at any time during the study. Participants who elect to withdraw or are discontinued for any reason will be provided with information about places to receive treatment should they desire. All questions pertinent to the study raised by the potential subject will be answered before consent is requested. All participants will consent in writing. The consent form will be dated and countersigned by a staff member. A copy of the consent form will be given to the subject, as is mandated by the Brown Institutional Review Board. The consent form will contain details of whom to contact in case of an adverse event, details of the principal investigator, and information on how to contact the Institutional Review Board to register a complaint. Another copy of the form will be kept on file. Participants who complete screening but who are not eligible for study inclusion will be provided with the self-help pamphlet on how to achieve alcohol cessation, as well as the address and telephone number of a local treatment center.

Psychosocial assessments: This is a stress study; therefore, to minimize risks of assessments, participants who are distressed or who show clinical deterioration will be referred for further assessment or intervention as required. The baseline assessments can be conducted over more than one day if necessary to minimize participant fatigue. **These measures are utilized to establish clinical eligibility at screening and for safety during the course of the trial**.

- **Structured Clinical Instrument for the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID-I/P)** is used for exclusion criteria such as current substance dependence (other than alcohol and nicotine), diagnosis of Major Depressive Disorder or anxiety disorder, schizophrenia, bipolar disorder, or other psychoses and life time of attempted suicide.

- **Clinical Institute Withdrawal Assessment Alcohol (CIWA) (please see Appendix F)** is used to assess symptoms of alcohol withdrawal syndrome (Research studies require a score of <10 to participate, in this protocol we adopt a more conservative score, ≤7) and exclude potential participants who might experience withdrawal symptoms during the course of the study. This assessment is implemented at every session before initiating any procedure to ensure participants' safety.
  Overall: For monitoring withdrawal syndrome.
  Specific questions and scores that will trigger a call to the study physician:
  #4 Anxiety: observation, moderately anxious (so anxiety is inferred), score >4
  #5 Agitation: observation, restless, Score >4
  #6 Tactile Disturbance: moderately, severe hallucinations, score >4
  #7 Auditory Disturbance: moderately, severe hallucinations, score >4
  #8 Visual Disturbance: moderately, severe hallucinations, score >4

- **Post traumatic Stress Disorder Check List (PCL) (please see Appendix H)**
  Overall: To monitor stress.
  Specific questions:
  #9 *Loss of interest in activities that you used to enjoy* (so depression is inferred), score >4

- **Perceived Stress Scale (PSS) (please see Appendix P)**
  Overall: To monitor stress over ti13)me, we will adopt the Perceived Stress Scale (PSS) PSS-10 scores are obtained by reversing the scores on the four positive items, e.g., 0=4, 1=3, 2=2, etc. and then summing across all 10 items. We will call the study physician with participants scoring >30.

- **Side Effects Report Form (please see Appendix Q)**
  Specific questions and scores that will trigger a call to the study physician:
  #19 and 20 Restlessness and Nervousness (so anxiety is inferred), score >3

- **Drinking Inventory consequences, (DrInC) (please see Appendix L)**
  Specific questions and scores that will trigger a call to the study physician:
  #34 I have lost interest in activities because of my drinking (so depression is inferred), score >3

- **Hamilton Anxiety and Depression Rating Scale (HAM-A; HAM-D) (please see Appendices O and O2)**
  in addition to being utilized as research outcomes, in our proposed study, these measures are used to monitor participants' anxiety and depression during the course of the trial. These assessments are critical to assess anxiety (HAM-A) — especially during yohimbine administration — and monitor for possible symptoms of depression that can lead to suicidality (HAM-D). It is important to know the clinical state of each participant before initiating any procedure.
  Overall: To monitor for anxiety we will use the Hamilton Anxiety rating scale (HAM-A) and for depression we will use the Hamilton Depression Rating scale (HAM-D). Each item of the HAM-D is rated from 0 (not present) to 4 (severe) with a total score range from 0 to 56, where <17 (mild severity), 18-24 (mild to moderate) and 25-30 (moderate to severe). We will alert the study physician with a score of >24.
  Specific question in the HAM-D and score that will trigger a call to the study physician:
  #3 Suicide: *Feel life is not worth living* (so suicide may be considered), score >0

- **Self-Evaluation Questionnaire (STAI y1/2) (please see Appendix R and S)**
  Overall: State-Trait Anxiety Inventory (STAI) -y1 and -y2, which are a commonly used measure of trait and state anxiety. The STAI has 40 items allocated to each of the State-anxiety and Trait-anxiety subscales. Responses for the S-Anxiety scale assess intensity of current feelings "at this moment," and the T-Anxiety scale assesses frequency of feelings "in general" from 1 (never) to 4 (always). We will alert the study physician to a score of > 60 on each subscale.
  Specific question:
  #22 *I feel nervous and restless* (so anxiety is inferred), score >3

NOTE - Suicidality: *To assess the risk of suicidality we included the Suicide Assessment Five-Step Evaluation and Triage (Appendix K). It is a 5-step screening tool developed in collaboration with the Suicide Prevention Resource Center and Screening for Mental Health. This assessment will be done by the study physician during screening (see Appendix Z for assessments schedule).. Also, the HAM-D question # 3 is about suicide; if participants score >0 during the course of the trial, we will alert Dr. Swift iimmediately.*

Screening and Randomization: Potential participants will be screened by telephone using a standardized questionnaire, which includes alcohol use, personal medical/mental health history and the major inclusion/exclusion criteria for the study. Eligible participants will receive information of the logistics (duration, commitment, compensation, measures) and on the medications that will be administered in the study. Interested volunteers are asked to come for a comprehensive visit at CAAS. At screening, **subjects must have their BrAC mesured (must be = 0.00), and must be = 0.00 every time before initiating any procedure at every visit.** During this visit, participants will be assessed using Inclusion/Exclusion criteria (**Table 1**), psychometric scales (**Appendix Z**), vital signs, ECG, blood **(two tubes)** and urine analysis; three samples of salivary cortisol will also be collected **(by spitting tube) to measure cortisol level.** All participants

will undergo careful medical and psychiatric assessment and must meet all inclusion and no exclusion criteria to qualify for this study.

Table 1 – Inclusion and Exclusion Criteria
Inclusion
• Male or female, 21 to 65 years of age • Females must be postmenopausal for at least one year or surgically sterile (proven by medical record) • **Meet criteria for Alcohol Use Disorders (AUD) DSM-5 diagnosis** • Meet criteria for heavy drinking (≥35 drinks/week for men; ≥28 drinks/week for women) • Must be in good health as confirmed by medical history, physical examination, ECG, lab tests • Participants must be willing to take oral medication and adhere to the study procedures • Breath alcohol (BrAC) = 0.00 at each visit • Be able to understand informed consent and questionnaire in English at an 8th grade level
Exclusion
• Individuals expressing interest in treatment for alcoholism • Premenopausal women • Participants who have significant alcohol withdrawal symptoms, defined as a CIWA-Ar score ≥7 • A repeated positive urine drug screen at baseline for any illegal substance except marijuana. • Individuals diagnosed with a current "severe" Substance Use Disorder (SUD) diagnosis, other than alcohol or nicotine • Meet DSM-5 criteria for a diagnosis of schizophrenia, bipolar disorder, or other psychoses • An active illness within the past six months of the screening visit that meets the DSM-5 criteria for a diagnosis of Major Depressive Disorder (MDD) or Anxiety Disorder, or history of attempted suicide • Clinically significant medical abnormalities: unstable hypertension, clinically significant abnormal ECG, bilirubin >150% of the upper normal limit, ALT/AST >300% the UNL, creatinine clearance ≤60 dl/min • Current use of psychotropic medications that may have an effect on alcohol consumption • Current use of any medication involved in the metabolism of alcohol such as aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH) and CYP2E1: Cefamandole, Cefotetan, Sulfamethoxazole, Nitroglycerin, Chlorpropamide, Glyburide. • Current use of any medication (CYP3A4 inhibitor and substrate) that may interact with mifepristone: cyclosporine, fentanyl, heparin, escitalopram, lovastatin, simvastatin, warfarin • Current use of any medication (CYP2D6 inhibitor and substrate) that may interact with yohimbine: amitriptyline, doxepin, nortriptyline, venlafaxine • Medical contraindications for use of mifepristone or yohimbine • A history of adverse reaction or hypersensitivity to mifepristone or yohimbine • History of suicide • History of seizure disorders • Hypokalemia (low potassium level)<3.5mEq/L • Participated in any behavioral and/or pharmacological study within the past **30 days** • Neuroendocrine disorders • Taking corticosteroids • Bleeding disorders • Pre-existing QT prolongation on ECG • History of porphyria (Mifepristone progesterone receptor antagonist is an inducer of CYP-450 and therefore may have the ability to precipitate or exacerbate attacks of acute porphyria) • Not willing to engage in protected sex (condom). **This risk includes both women and men.** Mifepristone long half-life ($t_{1/2}$ = 18 hrs) and its three main metabolites retain considerable affinity toward human progesterone and glucocorticoid receptors, with serum level similar to the parent mifepristone and there

are no studies on the presence of mifepristone or metabolites in semen

Sources of materials: Research data include: interviews, self-reported and clinician-administered questionnaires, breath, saliva, blood, and urine samples. All data will be gathered and obtained exclusively for research purposes. Cortisol and other data will be obtained by physical examination, clinical laboratory evaluation, and data from observation of participants by study staff during the visits. Standardized diagnostic and psychological assessments **and the time of research staff responsibilities are described in Appendix Z**. To evaluate safety and tolerability data, we will assess adverse events and they will be reported as the number and their intensity. To assess pharmacological intervention efficacy, we will gather quantitative data at baseline, between alcohol sessions, and one month post-intervention. Subject numbers will be entered to code all data. To ensure participants' privacy, only authorized persons will have access to the data.

Description of Potential Risks. Participants will be carefully screened at the beginning and closely monitored during the study procedures. Eligible individuals will be informed of each study procedure and the associated potential risks. Risks include distress during assessments, breach of confidentiality, issues related to coercion, and effects of alcohol withdrawal syndrome (including tremor, agitation, anxiety).

Assessments and Breach of Confidentiality: There is always some risk that participants will be identified as participants in a study or that clinical assessments will involve questions on illegal behaviors, or will adversely affect participants' well-being; while this does present a confidentiality risk, studies have been performed in the open public without evidence of participant harm. Inadvertent breach of confidentiality concerning drinking behavior is also a risk. All data will be used for research purposes only, and will not be revealed without the participant's written consent. Data will be kept in a secure locked file in the locked study office. Data will be entered into a computer database at the study site, which is password protected involving only numerical identifications that can only be linked with subjects' identification locked in a cabinet known only to the research staff. Access to data will be available only to investigators involved in the study. The research staff is trained in confidentiality procedures. As an additional layer of security, we will use a "Subject Number" from a Log and keep contact information in a separate locked location.

We will apply for a **Certificate of Confidentiality** issued by the National Institutes of Health to protect identifiable research information from forced disclosure. The certificate will allow those of us 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. By protecting us and Brown University from being compelled to disclose information that would identify research subjects. A Certificate of Confidentiality helps achieve the research objectives and promote participation in studies by helping to assure confidentiality and privacy to our participants.

Coercion: Risks of coercion are minimized by having participation payments be reasonable for the amount of time and effort required and comparable to other studies in this area. The likelihood of financial coercion is low because the compensation is commensurate with the amount of time and effort required for this study. There will be no cost(s) to participate in this study. The study medications and all procedures that are not part of routine care, but are required for the study, will be provided to the participant. If eligible for the study, participants will receive $25 for the randomization visit (Visit# 2) and for the follow-up visits (Visits #4 and #6). During the laboratory phase, at each visit (Visits #3 and #5) participants are compensated $100 + another possible $3/drink as incentive for not drinking (max $24). Therefore, each participant may be compensated up to $323 during the entire study period. Participant will be also compensated for their travel costs. Participation fees and tasportation expenses will have been approved by the Brown University IRB. There will be no other inducements.

Alcohol withdrawal: Since participants must have BrAC = 0.00 before initiating any procedure, there is risk of withdrawal syndrome. Our experience across numerous alcohol studies suggests that the risks for withdrawal from alcohol are minimal in this study as any potential participant with a CIWA ≥7 or having

significant hepatic dysfunction (by blood laboratory analysis) will be excluded during screening. As a result of our screening we can recruit people who drink enough to qualify for this study yet don't drink at a level that would potentially put them at risk for withdrawal. Alcohol craving following yohimbine administrations are reported to be modest, but significantly higher than placebo, however with not increased anxiety ratings. Alcohol craving will be monitored by psychometric scales. However, it is still possible that some participants may experience some withdrawal symptoms if they stop or reduce their drinking on their own. These symptoms may become severe enough to require hospitalization in order to be managed safely. Again, any participant with a CIWA score ≥7(agitation, tremor, sweats) at any time will be excluded from the study and immediately referred for medical attention at a Hospital Emergency Room or mental health clinic. Compliance: We will use a modified Medical Management (MM) used by the COMBINE study that has been revised and tailored for this study[107].The use of these components of MM in this study is aimed to facilitate participant adherence to pharmacotherapy. Sessions are conducted by trained research staff.. We will be dispensing the medication or placebo in blister packs to facilitate compliance. The initial session will be 30-45 minutes in order to establish rapport and will include a discussion of how the medications work, discussion of potential side effects and what to do about them, and a motivational interviewing-oriented discussion related to medication adherence, including the participant's experience with medications compliance, when and why they might miss doses, and what mechanisms could be useful to enhance medication adherence. Another important part of the MM is the focus on alcohol-related medical problems (such as liver panel exam).

Medications and Drug-Drug Interactions: Corcept Therapeutics will provide mifepristone (600 mg, for seven days plus three extra day doses) or matching placebo. Participants will receive a blister pack containing 10 capsules of mifepristone or placebo (7 days + three extra doses). Participants will return for the first follow-up visit and they will receive the additional blister pack. Bayview pharmacy will provide yohimbine (32.4 mg) formulated in a single capsule that will be administered at CAAS under team supervision prior to the alcohol laboratory session. Risks of medication side effects will be minimized through careful and detailed screening of participants *by the PI (Dr. Haass-Koffler)* to minimize recruitment of those who might be at higher risk for adverse events, as well as careful and detailed monitoring of adverse events and participant well-being during the study.

Mifepristone: Since mifepristone is a FDA-approved oral medication for the termination of early pregnancy, we will exclude women with childbearing potential regarding the birth control methods used. The following complications or risks have been reported, are known, or may occur with mifepristone: the most commonly reported side effects associated with the use of mifepristone include: abdominal or stomach pain, back pain, diarrhea, dizziness, headache, nausea or vomiting. Other less common side effects associated with the use of mifepristone include: cough, fainting, fever, heartburn, indigestion, lack of strength, or stomach discomfort. Rare side effects associated with the use of mifepristone include: sleepiness, pain during sexual intercourse, pale skin, shaking chills, shortness of breath, stuffy or runny nose, and unusual bleeding or bruising. Mifepristone may cause low blood potassium (hypokalemia); symptoms may include muscle weakness, aches, or cramps, or abnormal palpitations. Subjects with low potassium levels at screening will be excluded. In eligible participants, hypokalemic symptoms will be monitored during the entire study. Mifepristone progesterone receptor antagonist is an inducer of CYP-450 and therefore may have the ability to precipitate or exacerbate attacks of acute porphyria (exclusion criteria).

Because mifepristone has been used safely for termination of early pregnancy by the FDA since September 2000 at doses of 600 mg (single dose), we considered mifepristone titration in our study (one week therapy); however, mifepristone has been used at 600 mg dose in other clinical research studies and is currently being evaluated by Corcept Therapeutics in conducting studies using a similar dose including: control of hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Additionally, Corcept Therapeutics is engaged in the discovery, development and commercialization of drugs for severe metabolic, psychiatric and oncologic disorders. Current trials include: Metastatic Triple Negative Breast Cancer (phase I), A Study of Mifepristone vs. Placebo for individuals With Major

Depression With Psychotic Features (phase III) and Mifepristone in Children With Refractory Cushing's Disease in collaboration with National Institute of Child Health and Human Development.

It will be stated clearly in the consent form and to the participants verbally, that participants must engage in protected sex (i.e. wear a condom). This risk includes men and women. Mifepristone has a long half-life ($t_{1/2}$ = 18 hrs); its three main metabolites retain considerable affinity toward human progesterone and glucocorticoid receptors, with serum levels similar to the parent mifepristone and there are no studies on the presence of mifepristone or metabolites in semen. This will be clearly spelled out in the consent form document

Yohimbine: The oral dose of yohimbine for this study is based on prior studies in which yohimbine was administered to examine neuroendocrine probe in human studies. Ample data support the safe use of yohimbine to induce craving in alcohol-dependent individuals, and the safe induction of stress in PTSD veterans and gamblers. In this study, yohimbine (32.4mg) is administered below the therapeutic index to a dose considered dangerous (>100mg). Furthermore, yohimbine will be administered only once, during the laboratory session and under direct supervision of the study personnel. It will be given at a safety-tested dose to increase noradrenergic activity already being evaluated in psychiatric individuals with clinically relevant stress conditions such as PTSD, anxiety, and depression. Finally, yohimbine's short half-life ($t_{1/2}$ = 1-2 hour) provides a transient effect. The protocol includes close monitoring of blood pressure, heart rate, and cortisol levels by Dr. Haass-Koffler or research laboratory staff, and we have Dr. Swift on call. In addition, the Hamilton Anxiety Rating Scale (HAM-A) (Appendix O), Self-Evaluation Questionnaire for state (STAI-y1) and Self-Evaluation Questionnaire for trait (STAI-y2) (Appendix R and S) to assess and compare anxiety at baseline and prior to releasing the participants after laboratory session are included in the assessments (**Appendix Z**). If anxiety is higher at the end of the study we will call Dr. Swift to have him meet with the participant before release. The most common side effects reported by the use of yohimbine are: an allergic reaction, irregular or fast heartbeat, confusion, dizziness, anxiety, irritability, or nervousness, tremor, headache, skin flushing.

Drug-drug interactions: To reduce risk of drug-drug interactions, participants will be instructed to call our study team before taking any new prescription or over-the-counter medication. Participants will be asked to avoid taking medications that could interact with mifepristone and yohimbine. A wallet card identifying themselves as participants in a study receiving mifepristone and yohimbine (single dose) will be provided. This card will also contain the contact numbers of our study team, including emergency numbers of the PI and study physicians on call 24 hours a day (**Appendix X**). Participants will be asked to carry this card that will, in case of emergency, alert the medical personnel treating the participants that they may be taking mifepristone. This card, which should be kept at all times, will also include appropriate drug information and precautions.

As this project is guided by Dr. Haass-Koffler's neuroscience pre-clinical work, she did not observe any **two-way drug interactions** in preclinical models when administering the combination of mifepristone (systematically and by brain microinfusion into the central nucleus of the amygdala) and yohimbine[47].

Moreover, pharmacokinetically, yohimbine and mifepristone do not share liver microsome metabolic pathways; yohimbine is metabolized by CYP2D6, and mifepristone via CYP3A4. In Dr. Haass-Koffler's preclinical models, she did not observe any **three-way drug interactions** when administering the combination of mifepristone, yohimbine, and alcohol. The primary enzymes involved in the metabolism of alcohol are aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH) and CYP2E1. Pharmacodynamically, both mifepristone and yohimbine do not show the CNS depressant properties of alcohol and we should not expect increased sedation or depression of respiratory and/or cardiac functions. Dr Haass-Koffler has pharmacy background and they will include: 1) a search using Lexicomp, and 2) systematic symptom monitoring of drug-drug interactions between yohimbine, mifepristone and alcohol. While we recognize that both drugs, as well as alcohol, have indirect adverse effects, we note that Dr. Swift have experience in administering multiple drugs (aripiprazole with topiramate at clinical doses) and alcohol. Their experience suggests that without direct interactions, the side effects from both drugs may be broader but not additive with each other. *Finally, we have already obtained the Investigational New Drug*

(IND#121984) from FDA that determined that the clinical investigation of mifepristone and yohimbine while consuming alcohol is safe to proceed. In addition, our IND was cross-referenced by the IND of Corcept Therapeutics (IND#059737) for chemistry, manufactory, pharmacological, and toxicology data of mifepristone. Participants will receive detailed information on the study medication, including its current use and possible side effects**.**

The following medications are contraindicated with mifepristone: antithrombin alfa, antithrombin iii, argatroban, aspirin, bemiparin, bivalirudin, budesonide, cisapride, clobetasone, cortisone, cyclosporine, dabigatran, dalteparin, deflazacort, dexamethasone, dihydroergotamine, dronedarone, enoxaparin, ergotamine, fentanyl, fludrocortisone, fondaparinux, heparin, hydrocortisone, lepirudin, lovastatin, methylprednisolone, phenindionem, pimozide, prednisolone, prednisone, protamine, quinidine, simvastatin, sirolimus, tacrolimus, thioridazine, tinzaparin, triamcinolone, warfarin**.**

The following medications are contraindicated with yohimbine: amitriptyline, doxepin, nortriptyline, venlafaxine

The following medications are contraindicated with alcohol: cefamandole, cefotetan, sulfamethoxazole, nitroglycerin, chlorpropamide, glyburide.

The most common medications are listed in the emergency card and in the consent form.

Drug Storage and Accountability. The investigator will ensure that all study drugs are stored in a secured area under recommended storage conditions and in accordance with applicable state regulatory requirements in a locked closet in a room accessible only by a card-activated lock.

Mifepristone and yohimbine administration: The use of mifepristone and yohimbine in these studies will be under FDA-approval via IND#121984 (Dr. Haass-Koffler is the IND holder). Only healthy individuals will be eligible for enrollment. Medications will be prepared by Bayview Pharmacy. Females with childbearing potential are excluded regardless of the birth control method adopted, unless the woman has had a surgical sterilization. Participants will be monitored by Dr. Haass-Koffler or research laboratory staff for symptoms of adrenal insufficiency (weakness, nausea, fatigue, and hypotension) that may result by mifepristone administration and increasing BP and HR that may result from the adrenergic effect of yohimbine. Dr. Swift will be alerted immediately if any adverse effect arises during the entire study duration. Dr. Swift will determine if a participant is in need of hospitalization or other mental health intervention.

Alcohol Cue-reactivity (CR) and Alcohol Self-Administration (ASA) Sessions: The PI will schedule Visit #3 and Visit #5 (alcohol laboratory sessions) only if Dr. Swift will be in proximity of CAAS laboratory. The PI will not schedule Visit #3 and Visit #5 if both study physicians are traveling or not in Providence. To assess for medical/psychiatric conditions requiring an intervention, all participants will be evaluated at the end of each laboratory session and at follow-up visits. Individuals will be referred for further evaluation and treatment should any medical/psychiatric conditions occur. Participants are selected for the study and monitored carefully throughout the alcohol laboratory session; should a participant display an adverse effect, Dr. Swift will be called immediately. Dr. Swift will determine if a participant is in need of hospitalization or other mental health intervention.

Adverse Events

We included the list of side effects and occurrence associated with the two study drugs administered separately.

Side effects and occurrence with study medications	
Mifepristone	*Yohimbine*
Abdominal pain, cramping (96%) *Uterine cramping (83%)* *Nausea (43-61%)* *Headache (2-31%)* *Vomiting (1-26%)*	*Anxiety* *Irritability* *Headache* *Sweating* *Nausea*

Diarrhea (12-20%) *Dizziness (1-12%)* *Fatigue (48%)* *Nausea (48%)* *Headache (44%)* *Endometrial hypertrophy (38%)* *Hypokalemia (34%)* *Arthralgia (30%)* *Vomiting (26%)* *Peripheral edema (26%)* *Hypertension (24%)* *Dizziness (22%)* *Decreased appetite (20%)* *Abnormal thyroid test (18%)* *Xerostomia (18%)* *Back Pain (16%)* *Dyspnea (16%)* *Myalgia (14%)* *Pain (14%)* *Sinusitis (14%)* *Nasopharyngitis (12%)* *Extremity pain (12%)* *Diarrhea (12%)*	*Tachycardia* *Priapism* *Worsening of panic attack* *The frequency not defined*

Adverse Effects: Adverse events (AEs) will be recorded and tracked for this protocol and will be reported to Brown University IRB and FDA. At the follow-up visit, AEs will be recorded and followed to resolution only if they are serious or unexpected, or if the study physician assesses them to be clinically significant. In accordance with FDA reporting requirements, all AEs occurring during the course of the study will be collected, documented, and reported by the investigators. The occurrence of AEs will be assessed starting on the day of randomization.

Unexpected Adverse Events: An unexpected AE is one that is not described with respect to nature, severity, or frequency in the current protocol.

Serious Adverse Events (SAEs): Each adverse event or reaction will be classified by a study physician as being serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The Code of Federal Regulations Title 21 part 312.32 and International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration, defines a SAE or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death
- is life-threatening; (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical

judgment that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of an SAE (assessed by the Side Effect Reporting Form (Appendix Q), the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization. The research laboratory staff will continue to monitor by contacting the participant (phone) until the problem prompting hospitalization has been resolved or stabilized with no further change expected or is discovered to be clearly unrelated to study medication or progresses to death.

Unexpected and Serious Adverse Events Reporting: Any Unexpected or SAE, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the investigational product, will be reported within 24 hours of knowledge of the event to our local IRB and to the Project Officer of this project via fax or phone call.

Detailed written documentation for all SAEs/unexpected AEs will be submitted **within seven (7) days** to our Brown IRB. Required documents that must be submitted include the following information:

- title of protocol
- description of the unanticipated adverse event
- a determination of whether the event was related to the research study
- name of the drug
- where and when the event occurred
- to whom else the event has been reported

Upon receipt of a notification of an unanticipated adverse event or death, the IRB will determine whether further investigation of the event is required. Depending on the circumstances, the investigator may be required to suspend the study pending the outcome of an IRB review. Also, the IRB may require modification of the risks section of the consent form. These documents may be submitted by facsimile, as e-mail attachments, or via overnight courier.

Reporting to FDA: In agreement with the IND regulations, the investigators will report SAEs/Unexpected AEs to the FDA as well as the Program Officer at NIAAA:

- in 7 days if the SAE is unexpected, life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report 8 days later
- in 15 days if the SAE is unexpected, but not immediately life-threatening
- in an annual report in all other cases

Follow-Up of All AEs/SAEs: All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. All outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. Any SAEs and/or unexpected AEs among study participants during the follow-up period will be reported within 24 hours of knowledge of the event to the FDA, to our local IRB and to the Project Officer of this project via fax or phone call. All follow-up AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

Periodic Review of the Safety Data: Drs. Haass-Koffler and Swift will meet prior to the enrollment of the first subject to review the research protocol, informed consent documents and plans for safety and data monitoring of the study. This review will determine the risks and benefits to research subjects, protection and safety of the subjects and offer suggestions for improving the study design. Moreover, Drs. Haass-Koffler and Swift will meet in a regular basis during the duration of the study. These meetings will take place every 10 weeks for the entire duration of the study. 'Ad hoc' and/or emergency meetings will take place if needed for specific and/or safety reasons. Minutes of these meetings will be taken and filed in the regulatory binder of this project. The goals of these meetings will be to:

(1) determine adherence to research plan

(2) review interim analysis, if applicable, and determine specific data to be analyzed

(3) evaluate end point/stop point rules
(4) review protocol violations and deviations to assess adequacy of study
(5) ensure documentation of informed consent
(6) enrollment (followed eligibility criteria, enrollment numbers, visit compliance, screening failure information)
(7) discuss investigator or key personnel changes
(8) review completeness and quality of data collection forms, vital signs, clinical tests, and confidentiality
(9) evaluate the aggregate analysis of adverse events/serious adverse events

The major outcomes following data review include:

(1) continuing the trial unchanged
(2) modifying the protocol and/or consent form
(3) terminating the study

If the protocol and/or consent form should be changed, or the study should be terminated, Dr. Haass-Koffler will be responsible for all the necessary communications with the Project Officer, the FDA and the Brown University IRB.

Potential Benefits of Proposed Research: There are no benefits of participating in this study. The level of risks and potential side effects are outweighed by the potential for benefits to be gained. However, we believe that the risk-benefit ratio justifies the conduct of this study, given the magnitude of alcohol dependence and the need to identify novel targets for alcoholism.

Importance of the Knowledge to be Gained: Alcohol abuse and dependence is a major public health problem for which treatment options are limited. This study provides an opportunity to explore a novel pathway that could represent a target for possible pharmacological approaches able to help problem drinkers to reduce or stop their alcohol consumption. On this point, this study provides much needed data necessary for potential future clinical trials testing other new possible compounds (glucocorticoid-receptor antagonists).

Inclusion of Women and Minorities

Women will be encouraged to participate in this research. Our experience is that between 29% and 33% of alcoholics in our research centers are women and that about 36% of subjects who enrol in similar studies are women. However, due to the FDA abortifacient indication of mifepristone, women with childbearing potential will be excluded regardless of the birth control methods adopted. Based on Dr Swift's alcohol studies, between 15% and 33% of the women enrolled are postmenopausal or surgically sterile; therefore, we expect about 24% of those enrolled in our study to be women. We will attempt to target women for recruitment by advertising in the women's health section of the major state newspaper as well as sections that focus on women's health in local newspapers and magazines. In our radio ads we will target women and women of color who are typically underrepresented in studies of alcoholism.

All ethnic and minority groups will be welcome to participate. Our experience suggests that involvement in studies reflects the most recent (2009) Rhode Island demographics with about 2.7% of participants Asian, 5.5% African-American and about 11.4% Hispanic. That said, the Hispanic population makes up 36% of the Providence area; therefore, we will aim to enroll a greater amount than 11.4% Hispanic individuals. We will attempt to target minorities for recruitment by advertising in local newspapers in cities with significant minority populations.

Inclusion of Children

As this is an alcohol study, children are ineligible for enrollment.

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