STUDY PROTOCOL - 960249

TITLE: Guanfacine to reduce relapse risk in women with alcohol use disorder (AUD)

INVESTIGATORS: Helen C Fox (PI), PhD; James Swain, MD; Ricardo Caceda, MD, PhD (back up MD); Asif Karim, MD (back up MD)
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APPROVAL OF SUBMISSION

November 13, 2020

Helen Fox
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Dear Helen Fox:

On 11/12/2020, the Stony Brook University IRB (FWA# 00000125) reviewed the following submission:

Type of Review:	Modification and Continuing Review
Title of Study:	Guanfacine to reduce relapse risk in women with alcohol use disorder (AUD)
Investigator:	Helen Fox
IRB ID:	960249_MODCR004
Sponsor:	Name: National Institutes of Health, Oracle Project/Award/Task Number: 1137556-1-77228, Sponsor's Funding ID: R21 AA024880
Documents Reviewed:	• Protocol version uploaded on 9/2/2020 • Guanfacine dosing schedule document uploaded on 10/1/2019 • Intuniv (Guanfacine) Prescribing Information document dated 8/2013 (upload date: 10/1/2019) • FDA IND Waiver explanation document uploaded on 10/1/2019

The IRB approved the study from 11/13/2020 to 11/11/2021 inclusive. If continuing review approval is not granted before the expiration date of 11/11/2021, approval of this study expires on that date.

All research must be conducted in accordance with this approved submission and you are required to follow the requirements listed in the Stony Brook University's SOPs, which can be found by navigating to our website located at:
http://research.stonybrook.edu/orc/humans/CORIHS/index.shtml#human-subjects-

Protocol – IRB960249

A. SPECIFIC AIMS

Approximately 5.7 million women in the US meet criteria alcohol use disorder (AUD). While this figure remains significantly lower than men, the traditional gender gap is rapidly converging as a result of sharp elevations in women's drinking patterns due, in part, to socioeconomic gains within the labor force. As gender specific risk factors for AUD place women at a considerable disadvantage in terms of clinical health outcomes, this sharp increase in alcohol consumption urgently necessitates the development of interventions that have been specifically tailored to women. In view of this, preliminary data from our laboratory has shown that the alpha2 adrenergic agonist, Guanfacine, attenuates the negative reinforcing effects of alcohol and enhances cognitive regulation in the face of stress, preferentially in early abstinent women compared with men. We suggest that this may be due to gender-specific variation in sympathetic sensitivity. Thus, we propose a double blind, placebo-controlled, 10-week randomized clinical trial to examine the preliminary effects of Guanfacine extended release (GXR, 3mgs/daily) in 60 women with AUD. A parallel experimental study using a stress versus neutral imagery exposure paradigm will also be conducted following 7 weeks of treatment (when at full dose), to examine the stress- to take part in the 10-week outpatient trial for GXR (3mgs/daily) versus placebo (PLA). This will include twice weekly appointments comprising medical management and contingency management protocols, collection of urine, breathalyzer screens, and vitals. Measures of craving and mood will also be assessed. In week 10 participants, will take part in a laboratory challenge sessions, where they will be exposed to a personal stress versus relaxing imagery condition in a randomized order. Craving, anxiety, mood, cognitive control, HRBP, and biological stress system markers will be assessed at baseline, following imagery and at various recovery timepoints. A follow-up interview will be conducted 30 days following outpatient completion. As our prior research has also shown to Guanfacine to be highly efficacious in reducing nicotine craving following exposure to stress in both cocaine dependent and alcohol dependent populations, we additionally include a sub-sample of treatment-seeking nicotine dependent women who do not meet criteria for AUD. In view of prior research, we anticipate that GXR will be safe and well tolerated in women with AUD (H1); lead to greater abstinence and treatment adherence compared with the PLA group (primary outcome measures) (H2a) as well as greater attenuation of withdrawal symptoms and improved regulatory function (secondary outcome measures) both during outpatient treatment (H2b) and following stress exposure in the laboratory (H3a). We also anticipate that GXR-related changes to stress response in the laboratory will predict improved primary alcohol use outcomes (H3b). Exploratory aims will examine the effects of GXR versus placebo on a sub-sample of nicotine dependent women who do not meet criteria for AUD. Findings will help to elucidate unique stress-system mechanisms which support attenuation of drinking and smoking in women with AUD prior to further assessment in larger randomized clinical trials. This is of paramount importance to developing medications that are integral to the health and well-being of an increasingly vulnerable sub-population of drinkers

B. BACKGROUND AND SIGNIFICANCE

1.1 Overview: Over the last decade, the traditional gender gap in alcohol use and abuse rates has been converging across ethnicities 41 due to socioeconomic factors 42, 43. For example, between 1999 and 2008, the number of young women admitted to emergency rooms for being dangerously intoxicated rose by 52%, while the rate for young men, rose just 9% 44. Moreover, although the number of women who fit research criteria for alcohol abuse is increasing 45, they continue to be under-represented in clinical trials 46 and as such sex-specific treatment information for alcohol is sporadic 6. Factors such as "telescoping", or propensity for the comparatively quick progression from use to dependence typically observed in women 47, as well as a dearth in FDA-approved medications tested and validated in populations of alcoholic women 6, together highlight the urgent need for gender-sensitive medications. In view of this, we

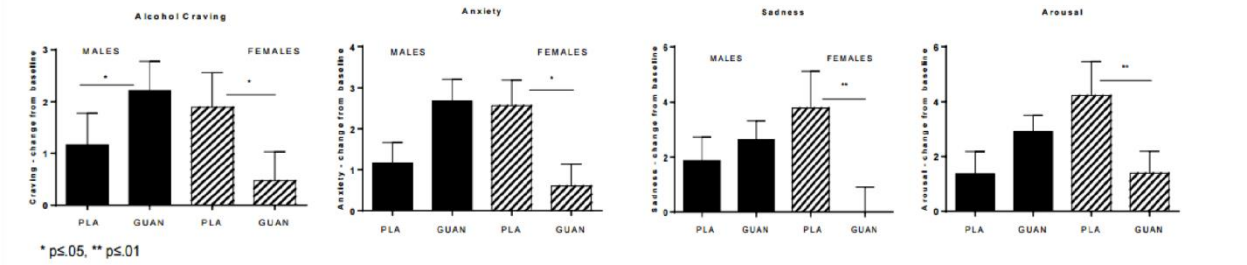
propose a preliminary double blind, placebo controlled, 10-week randomized clinical trial (RCT) to examine the initial safety and efficacy of the alpha2 adrenergic agonist, Guanfacine extended release (GXR; 3mgs/day) in 60 women with AUD, and a sub-sample of nicotine dependent women without AUD. The design also incorporates an experimental challenge study using a stress versus neutral imagery exposure paradigm to further elucidate some of the stress mechanisms potentially underlying GXR's efficacy in improving primary drinking outcomes in women with AUD. We anticipate that findings will help to form the basis of a larger Phase II clinical trial.

1.2 Stress system changes underlying alcohol withdrawal, craving & relapse: Extensive evidence shows that overactive hypothalamic CRH 21, 48, 49, as well as hyperactivity in sympathetic neurotransmission, 10, 13, 38, 50, and signaling 7, 9 all play a critical role in withdrawal symptom development 51, alcohol craving 13 nicotine craving 160,161, and relapse 52, 53. As such, chronic core stress system up-regulation may contribute to increased risk of alcohol relapse in several ways: First, the pathophysiology of both AUD, anxiety disorders, negative affect and physiological hyperarousal all share common elevated extra-hypothalamic CRF and NE circuitry 53-57. This suggests that these mechanisms play a key role in the negative reinforcing and aversive motivational states underlying alcohol craving and compulsive alcohol seeking 6, 38, 39, 58. Second, sympathetic overdrive impinges upon medial prefrontal circuits 59 inducing α1 receptor stimulation and desensitizing alpha2 receptors, impairing attentional processes by attenuating salient "signals" and increasing irrelevant "noise" 60-62. Taken together, elevated HPA-SAM activity during early withdrawal from alcohol underlies negative reinforcement and weakens prefrontal adrenergic systems allowing for less control over rewarding and aversive motivational states, hence, promoting compulsive alcohol seeking.

1.3 Sympathetic dominance in women with AUD: Prior research from our own laboratory and those of others, has shown that enhanced anxiety and emotional sensitivity to stress as well as dysregulated autonomic output may represent unique risk factors for drinking in women, compared with men 26, 27, 34. We have used a well-validated human paradigm to model stress-related craving within the laboratory and demonstrate that enhanced anxiety, arousal and negative affect following personalized stress are selective aspects of the motivational craving or wanting "state" in socially drinking, substance abusing and alcohol dependent women relative to men 26, 27, 34, 63. High basal heart rate and NE levels are also specific to alcoholic women 6, 64, as well as female smokers 159 and linked to a dampened sympathetic and cardiovascular arousal response to stress 38, 64, providing a gender-sensitive pathway to elevated alcohol craving, and one which is qualitatively different to that observed in men 6, 27. These findings also corroborate clinical surveys and longitudinal studies which have shown that internalizing emotions such as negative mood and anxiety are predictive of drinking to a much greater extent in women than men 65-67. In addition, sexual dimorphism of LC-NE activation, dendritic morphology and feedforward regulation of the HPA axis 67-70 suggests that these core sympathetic systems may play a key role in the vulnerability of women to stress exposure and the negative reinforcing aspects of alcohol craving during early abstinence. We therefore propose that Guanfacine, which inhibits NE levels via stimulation of presynaptic alpha2-adrenergic receptors 71, 72, will be particularly effective in attenuating the gender-sensitive anxiolytic and autonomic arousal aspects of craving and relapse vulnerability in AUD women.

1.4.1 Preliminary Data 1: We conducted a randomized, double blind, placebo-controlled laboratory study examining the gender effects of 3-weeks Guanfacine immediate release (GUA 2 to 3mgs; b.i.d) using a 12 day titration schedule in a sample of early abstinent treatment-seeking alcohol dependent men and women (N=24; 8F/16M). Method: Following 3-weeks of abstinence, all participants were exposed to three, 10-min personalized guided imagery scenarios (i) stress, ii) cue, iii) combined stress/cue), one per day, across 3 consecutive days in a random, counterbalanced order. Alcohol craving, nicotine craving, anxiety, negative mood, cardiovascular, HPA and sympathetic measures were acquired at baseline, immediately following imagery, and at various recovery time-points until 1 hour post imagery. Results: GUA was found to be safe and well tolerated in both men and women, with fatigue being the most commonly reported side-effect. All symptoms were reported as being mild to moderate and dissipated within the initial two weeks of inpatient stay. At baseline, GUA reduced cardiovascular output in women compared with both PLA groups ($p<.0001$, in all cases). Following imagery exposure, a series of Medication Group X Gender X Time-point interactions showed that immediately following all 3 imageries the GUA females reported significantly attenuated anxiety [$F5, 644 = 2.8$, $p<.02$], sadness [$F5, 644 = 2.4$, $p<.04$], arousal [$F5, 644 = 3.7$, $p=.003$] behavioral arousal (sweaty palms, crying) [$F1, 30 = 3.6$, $p=0.06$] as well as increased positive mood [relaxed state: $F5, 644 = 2.7$, $p<.02$; Joy: $F5, 644 = 2.8$ $p<.02$] compared with the PLA females (Fig 1). Importantly these attenuations in stress reactivity occurred alongside decreased alcohol craving across all conditions in the GUA females compared with the PLA females [$F5, 644 = 2.7$, $p=.02$]. No such discrepancy was observed between GUA and PLA males, with the exception of nicotine craving and SBP which was attenuated in both the male and female GUA groups. Findings support preclinical studies showing attenuation of alcohol-seeking, relapse and other negative reinforcing aspects of alcohol craving following alpha2 agonism.

Fig. 1 Response to stress-, cue- & combined stress & cue-related imagery: GUA vs PLA in alcoholic men & women

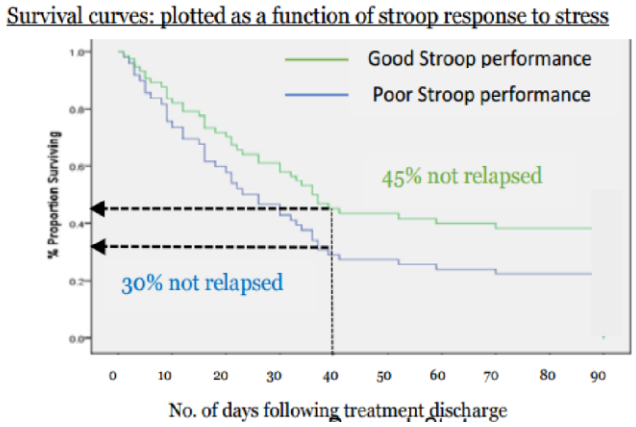


Importantly, the robust effects of GUA in women may again be related to a sensitized sympathetic profile in the PLA women relative to PLA males, suggesting the need for a particular threshold of emotional and sympathetic arousal to optimize Guanfacine's efficacy in women. This also corroborates studies that have shown GUA and GXR to be effective in treating conditions characterized by elevated catecholaminergic psychopathology, including attention-deficit hyperactivity disorder (ADHD) 73-77 and drinking in high, but not low alcohol consuming rats 23. On the basis of these findings we propose that 10-weeks of GXR will be well-tolerated and safe in AUD women (H1a). GXR will also promote abstinence and adherence to treatment (H2a) by attenuating withdrawal, craving, anxiety, and negative mood, during treatment (H2b), and during stress in the laboratory (H3a).

1.4 Regulatory processes as a target for treatment: Stress-related sympathetic sensitivity may highlight an important gender-sensitive aspect of compulsive alcohol seeking in AUD women. In addition, aberrations in sympathetic stress arousal also impinge upon prefrontal networks integral to cognitive reappraisal 78. For example, greater activity in regulatory regions such as the VMPC and sub-genular ACC following stress is associated with lower autonomic arousal 79-82. These

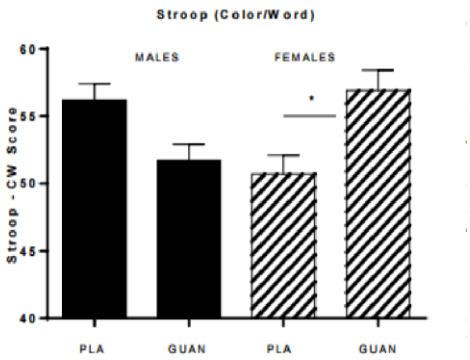
control circuits are therefore intrinsically enmeshed with the stress response, and reflect an overall ability to cognitively regulate or reappraise during provocation 83. As such, they play an integral role in marshalling attention and supporting goal-oriented behaviors including planning, decision-making and impulse control, which contribute to treatment outcome 84-86. Targeting regulatory mechanisms which profoundly impact everyday life 87 may therefore allow for the development of medications that are gender-sensitive and also demonstrate high ecological validity outside of the laboratory. In support, data from two prior studies show that a) inability to cognitively inhibit during stress in the laboratory can predict fewer number of days to relapse following treatment discharge (Fig. 2a), and b) that GXR strengthen these relapse-related cognitive processes preferentially in substance abusing women (Fig. 2b).

1.6.1 Preliminary Data 2 (Fig. 2a):



Sixty-two early abstinent alcoholics were compared with 107 cocaine dependent individuals and 74, socially drinking controls on Stroop color/word performance, prior to and following exposure to 3 personalized imagery conditions (stress, cue, neutral). Following exposure to stress, both cocaine (p=.002) and alcohol dependent (p=.05) individuals were less able to inhibit or regulate pre-potent responses compared with controls. The alcohol group was subsequently categorized into either “good” or “bad” performers of Stroop (using a median split) and survival curves were plotted for both groups as a function of Stroop performance following stress. Proportional hazards modeling indicated that good ability to regulate in the face of stress challenge, was significantly associated with a reduced chance of relapse following discharge (x^2 = 8.78; p=.01; HR = 1.46; 95% CI, 0.96-2.2). Similar findings were also observed following an identical analysis in the cocaine dependent individuals (not shown).

1.5.2 Preliminary Data 3 (Fig. 2b):



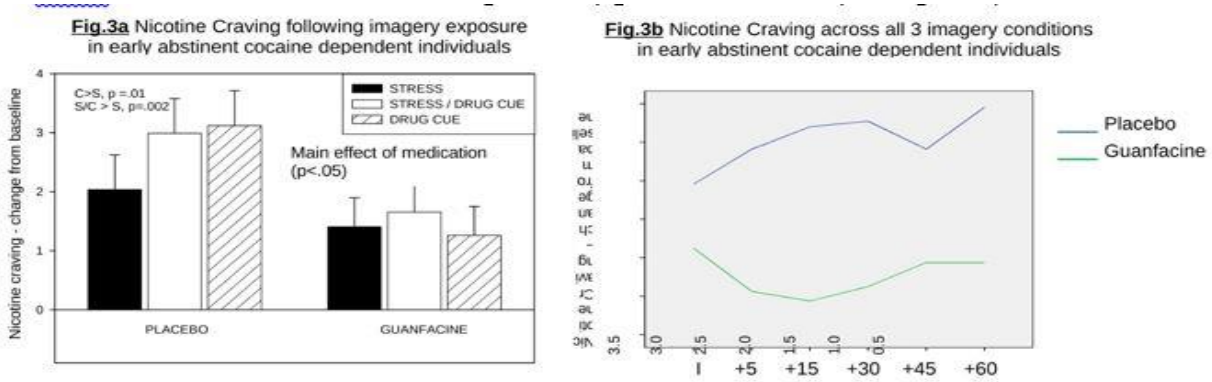
We subsequently examined whether GUA (immediate release) could enhance these mechanisms during early abstinence. Using a sample of men and women co-dependent on alcohol and cocaine (N=40; 13F/27M) we administered the Stroop test prior to and following exposure to 3 imagery conditions (stress, cue, combined stress/cue). After adjusting for baseline variation, a Medication X Gender effect [F1, 19 = 5.6, p<.03] showed Stroop performance to be significantly enhanced following all imagery conditions in the GUA women, but not the GUA men (Fig 2b). These findings corroborate GUA-related improvements in sustained attention, motor and response inhibition across a variety of species 88-92, via stimulation of post-synaptic alpha2 receptors93, 94. It also corroborates our own research demonstrating increased BOLD activation in ventral and lateral regions of the prefrontal cortex during stress in cocaine and alcohol co-dependent men and women 18. The current gender-effects of GUA may also emphasize the role of stress and its effect on regulatory processes, as providing a key target mechanism for drinking in women. We therefore propose that during a 10-week period, GXR will promote abstinence and adherence to treatment (H2a) by improving

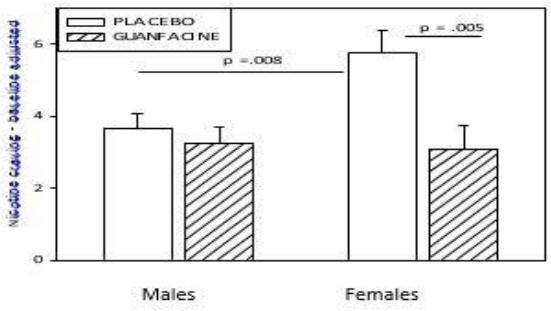
emotion regulation, cognitive regulation and impulse control during treatment (H2b), and during stress in the laboratory (H3a).

In order to more fully elucidate the mechanisms underpinning GXR's effects in AUD women, we additionally examine whether GXR-related changes to tonic and phasic stress system activity in the laboratory can predict drinking outcome measures during treatment. Our preliminary and published findings indicate that sensitized autonomic stress activity and ability to regulate during challenge are known to a) have a substantial impact on achieving and maintaining alcohol abstinence 85, and b) also characterize drinking in women. As such, we propose that attenuated craving, anxiety, negative mood, autonomic function and enhanced cognitive control following stress in the lab will predict improved outcome during a 10-week treatment trial (H3b).

As an exploratory aim, we propose examining the efficacy of GXR versus placebo in a small subsample of women who are dependent on nicotine, but do not meet criterial for AUD. Prior preclinical research has indicated greater anxiety-like behaviors following stress-related nicotine exposure in female compared with male rats 157,158. Moreover, studies from our own laboratory have indicated that Guanfacine significantly reduces stress- and cue-induced nicotine craving in both cocaine dependent and alcohol dependent individuals co-morbid for nicotine 18,29,30. Moreover, attenuation was significantly greater in females (See Fig 3a-c.).

Fig.3c Nicotine Craving across all 3 imagery conditions & time-points in early abstinent cocaine dependent individuals





D. RESEARCH DESIGN AND METHODS

Rationale / overview

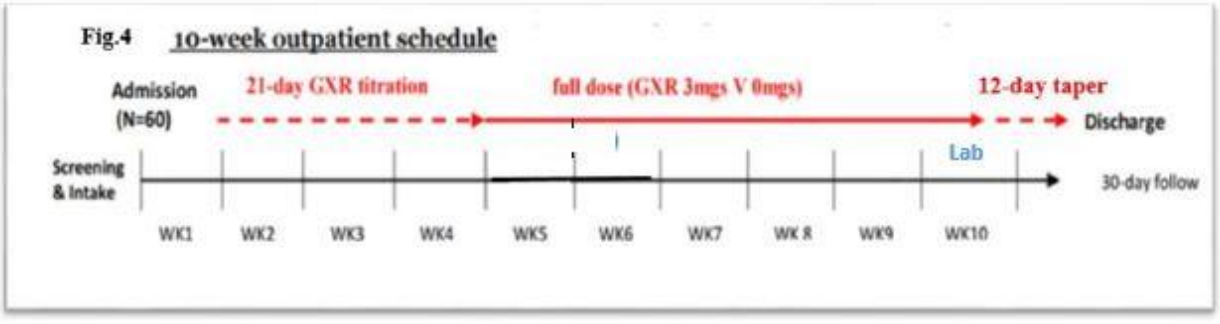
Sixty women meeting criteria for moderate to severe alcohol use disorder (AUD) will be recruited to take part in a 10-week outpatient treatment trial for GXR (3mgs/daily) versus PLA. On the basis

that up to 30% of women may drop-out following the initial few sessions109, 110 we anticipate that at least 42 women will also run through a parallel laboratory paradigm during week 10 Outpatient treatment will include twice weekly appointments comprising medical management (MM) and contingency management (CM) protocols, collection of urine drug screens, breathalyzers, and vitals. Alcohol craving, use, and withdrawal as well as perceived stress, anxiety, mood, impulsivity and emotion and cognitive regulation will also be assessed. All participants who have been on Guanfacine for 9 weeks will take part in a laboratory challenge session, where they will be exposed to 2, personalized guided imagery conditions (stress and neutral in a counterbalanced order). Craving, anxiety, mood, cognitive control, HRBP, plasma cortisol, ACTH, and catecholamines will be assessed at baseline, following imagery exposure and at various recovery time-points. A follow-up interview will be conducted 30 days following outpatient treatment completion.

Research Site

The proposed R21 will be conducted at the Health Sciences Center (HSC) located at University Hospital Stony Brook, which additionally offers a wide range of treatment modalities for dementia, depression, anxiety, psychotic and bipolar spectrum disorders, as well as all psychiatric disorders associated with acute and chronic medical illness. The facility is excellently equip for running phase I clinical trials in alcohol and substance abusers, offering treatments in psychopharmacology, individual and group counseling as well as comprehensive evaluation and medical management. The department is also fully staffed with highly experienced, multi-disciplinary board-certified psychiatrists and clinicians, including Dr. Ricardo Caceda who specializes in addiction psychiatry. Physical examinations and other medical evaluations necessary to determine eligibility for the current research will be conducted at the Clinical Research Center (CRC), located at 33 Research Way in Setauket, by a study nurse coordinator. The laboratory challenge studies will also be conducted at the CRC. The department of Psychiatry is fully staffed with substance abuse clinicians and a range of mental health professionals well versed in outpatient procedures and NIH protocols. Excellent laboratory and office space is available to conduct stress induction procedures, cognitive testing and day to day research.

Study sample



Human Subjects: This study aims to recruit 60 women seeking out-patient treatment and who meet current DSM-V criteria for moderate-to-severe alcohol use disorder (AUD). In addition we will recruit a separate small sub-sample of 10 women who are nicotine dependent and treatment-seeking, but do not meet criteria for AUD. On the basis that up to 30% of participants may drop-out of treatment after the initial few sessions109, 110, we anticipate that at least 49 AUD women will run through the laboratory stress challenge. AUD women enrolled in this study will predominantly come from low socio-economic backgrounds in Suffolk County, Long Island. In addition the Health Science Center at Stony Brook Hospital comprises a dedicated Comprehensive Psychiatric Emergency Program (CPEP) which sees 6200 patient visits per

year, with referrals commonly being made for persons with alcohol abuse and mental illness. Each patient is evaluated by a psychiatrist with regard to present episode, past psychiatric history, substance abuse, family and psychosocial context, medical history, and current status. Mental status and physical examinations are also made and potential referrals filtered into the appropriate research programs. CPEP additionally has close links to 67 alcohol and substance use disorder facilities across Long Island, including 8 detoxification centers, 6 inpatient clinics, and 7 residential programs all in close proximity. In relation to the racial and ethnic background of the women typically referred to CPEP: 70% are Caucasian (and of those 10% are Hispanic) and 30% are African American. As a result, we expect that the projected demographics of our sample will follow the above race breakdown. Subjects will be recruited by the research team based in the Department of Psychiatry at Stony Brook, through general practitioners at Stony Brook hospital and advertisements in local area newspapers, radio and other print media as well as study flyers posted in community buildings in the Suffolk County area. We propose the following strategies to encourage women into the study:

Recruitment & retention strategies tailored to women: a) Research indicates that community involvement plays an integral role in recruiting both women and ethnic minorities into clinical trials 142. In view of the proposed study, both Dr Fox and the recruitment teams based at Stony Brook Psychiatry, will maintain regular contact with Suffolk County Communities of Solution and the Long Island Counsel of Alcohol and Drug Dependence. Regular meetings will be organized with objectives to work closely with prominent community leaders within the local area in order to devise culturally appropriate community-based participatory recruitment strategies encouraging women from ethnic minorities into our research projects. **b)** As women are more likely to seek care for alcohol use disorders within primary care settings143, we intend to focus recruitment efforts within medical health centers and approach a local network of general practitioners within Stony brook hospital willing to inform women of our treatment program; **c)** Treatment will predominantly be focused on psychoeducational techniques directed at the needs of women, incorporating issues associated with stress, self-esteem, domestic violence, parenting, caregiving status, trauma, anxiety, negative mood and eating; **d)** As research has shown that programs which allow women to bring their children have higher rates of retention and are a predictor of better treatment outcomes, we will encourage women to bring their children with them to all visits. The outpatient department at Stony Brook, employs several research assistants and associates with additional expertise in running developmental research protocols, and the Child and Adolescent Psychiatry Department is well-equipped to offer onsite child-care assistance while mothers complete the treatment visits with clinical staff; **e)** we have budgeted for local transportation if required146; The following inclusion / exclusion criteria will be required for eligibility:

Addendum as per COVID -19 CDC guidelines:

All potential / ongoing participants will be screened for exposure to the COVID-19 virus using the CDC guidelines below:

1. *Have you traveled to the following places in the last 14 days?*
   -China, Iran, Japan, any country in Europe or South Korea? (Note that all level 3 and level 2 countries/regions listed on the CDC website are included; CDC is checked regularly for updates.

2. *Have you had any of the following symptoms in the last 14 days without confirmation it was NOT COVID -19*

A flu positive test result or chronic medical condition? Fever greater than 100.4 deg F? Cough, difficulty breathing, sore throat?

3. *In the past 14 days have you lived with, visited, cared for, or been in a room for a prolonged period of time with someone who is under investigation or has been confirmed for COVID-19/ Corona virus infection?*
    - *Any **YES** response the subject will be asked to make an appointment for a later date and will be directed* to the Coronavirus Hotline/phone triage center set up at Stony Brook Hospital 631-638-1320.

Any and all subjects need to be asymptomatic for all scheduled visits ongoing through the study. Safe distancing practices will be implemented at all in office meetings, should they occur. Virtual visits will be utilized for any visits as the need sees fit.

Inclusion/Exclusion Criteria: Inclusion Criteria: i) Females, aged 18-60 years, ii) must meet DSM-V criteria for AUD, iii) must produce positive urine toxicology screens on admission to study, or have recently been through a detox protocol, iv) must demonstrate good health as verified by screening examination. Liver Function Tests (LFT) should not exceed 3 units above; Bilirubin Total 0-1 MG/DL Conjugated, (D. Bilirubin) 0-0.35 MG/DL, Unconjugated (I.D. Bilirubin) 0.2-0.65 MG/DL, SGOT 10-40 IU/L, SGPT 10-40 IU/L, Alkaline Phosphatase 40-112 U/L, Total Protein 6-8.5 GM/DL Albumin 3.5-5 GM/DL, and Globulin 2-3.5 GM/DL.v) must be able to read English and complete study evaluations vi) must be able to provide informed written and verbal consent. Women currently stable on SSRI medication will be included in the study. Exclusion Criteria: i) Meeting current use disorder for any other psychoactive substance, excluding nicotine. ii) Having any other current Axis I psychiatric disorders requiring treatment/medication, with the exception of SSRIs, iii) EKG evidence at baseline screening of any clinically significant conduction abnormalities, including a Bazlett's QTc of >470 msec. iv) must not be on monophasic contraceptives, nursing or pregnant, v) active significant medical illness within the past six months (i.e. cancer), vi) documented autoimmune disease (i.e. Lupus, Crohn's/UC, Hashimoto's) vii) documented neurological illness (i.e. seizure disorder, h/o stroke, excluding a single childhood febrile seizure) or a history of migraine headaches as determined by a physician, viii) documented diagnosis of diabetes mellitus or use of diabetic agents, ix) documented history of head trauma with prolonged loss of consciousness.

A small sub-sample of women will be recruited that meet all Inclusion and Exclusion criteria with the exception of not meeting criteria for AUD, and instead meeting criteria for tobacco use disorder. The inclusion & exclusion criteria for this group will be as follows:
Inclusion Criteria: i) Females, aged 18-60 years, ii) they must meet criteria for tobacco use disorder (TUD) as determined by the DSM 5, iii) they must demonstrate good health as verified by screening examination, iv) they must be able to read English and complete study evaluations v) They must be able to provide written and verbal consent . Exclusion Criteria: i) meeting current use disorder for any psychoactive substance, excluding nicotine. ii) having any other current Axis I psychiatric disorders or medical conditions requiring treatment/medication, with the exception of SSRIs. iii) EKG evidence at baseline screening of any clinically significant conduction abnormalities, including a Bazett's QTc of >470 msec. iv) must not be on monophasic contraceptives, nursing or pregnant.

SAFETY GUIDELINES FOR THE COVID-19 VIRUS DURING ALL SCREENING VISITS:

Addendum as per COVID -19 CDC guidelines:

All potential / ongoing participants will be screened for exposure to the COVID-19 virus using the CDC guidelines below:

4. *Have you traveled to the following places in the last 14 days?*
   -China, Iran, Japan, any country in Europe or South Korea? (Note that all level 3 and level 2 countries/regions listed on the CDC website are included; CDC is checked regularly for updates.

5. *Have you had any of the following symptoms in the last 14 days without confirmation it was NOT COVID -19*

A flu positive test result or chronic medical condition? Fever greater than 100.4 deg F? Cough, difficulty breathing, sore throat?

6. *In the past 14 days have you lived with, visited, cared for, or been in a room for a prolonged period of time with someone who is under investigation or has been confirmed for COVID-19/ Corona virus infection?*
   - *Any **YES** response the subject will be asked to make an appointment for a later date and will be directed* to the Coronavirus Hotline/phone triage center set up at Stony Brook Hospital 631-638-1320.

Any and all subjects need to be asymptomatic for all scheduled visits ongoing through the study. Safe distancing practices will be implemented at all in office meetings, should they occur. Virtual visits will be utilized for any visits as the need sees fit.

Screening

Screening & intake: After consented telephone screening, eligible participants will meet with a research assistant for an initial intake session where informed consent, physical examinations, blood work (liver function tests, glucose and complete blood count) and alcohol screening will be conducted. We will also take a blood sample in order to collect exosomal microRNA in order to assess whether any differences in transcription factors that are known to affect stress and drinking, exist between several candidate microRNA genes [miR-21; miR-26; miR-146a; miR-10a]. Demographic data will be assessed using standard self-report forms. The SCID-I 119 will be used to determine AUD and/or Tobacco Use Disorder, and the possible presence of any Axis 1 psychiatric and/or substance use disorder. The State/Trait Anxiety Inventory (STAI); 120 will be used to ascertain the presence of state and trait anxiety symptoms. The Alcohol Urges Questionnaire (AUQ) 121: is a reliable and valid 8item scale that can be used for repeated assessments of alcohol craving 122. The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening instrument designed to distinguish between low risk drinkers and individuals with hazardous and harmful patterns of alcohol consumption (WHO, 1992). We will also include The Drinking Motives Questionnaire (DMQ; Cooper, 1994) which is a 20-item well-established scale that assesses social, coping, enhancement and social conformity motives for drinking. The Perceived Stress Scale (PSS; 123): is a 14 item self-report assessing the degree to which situations are appraised as threatening or demanding. The Early Trauma Inventory (ETI; 162) is a 56-item interview to measure childhood trauma. The Beck Depression Inventory (BDI 124) is regarded as a well-established, sensitive self-report measure of depressive symptoms. The

Menstrual Cycle Questionnaire (MCQ) is a 30-item standardized instrument documenting symptoms, typical cycle and period length. Female subjects will complete the questionnaire at baseline. The Barratt Impulsiveness Scale (BIS-11125) is a globally well-established questionnaire designed to assess the personality/behavioral construct of impulsiveness126. The Difficulties in Emotion Regulation Scale (DERS; 127): is a well-validated measure of emotion dysregulation. Items reflect impulse control; emotional awareness, regulation and clarity. We will also administer the UPPS Impulsive Behavior Scale (UPPS or UPPS-P; Whiteside and Lynam, 2001) to more thoroughly examine a personality model of impulsivity. The scale comprises 45-items which measure impulsivity across dimensions of the Five Factor Model of personality, including urgency, sensation seeking, lack of premeditation and lack of perseverance. The Fagerström Test for Nicotine Dependence (FTND;128) will be used to determine smoking dependence. The Shipley Institute of Living Scale 129 provides a global measure of cognitive functioning and IQ. The Time-Line Follow Back (TLFB) Interview 130 will be used to assess all alcohol and drug use in the last 3 months. The assessment uses a calendar prompt to facilitate recall of alcohol use during a targeted period. Urine samples & Breathalyzers: will ensure current alcohol use. Urine samples will also ensure the potential participants are not pregnant. The Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al., 1988) has good internal and test–retest reliability, and is a measure of subjectively assessed social support within the three domains of “family” “friends” and “Significant Other”. The Hurt Feelings Scale (Leary, 2013) and Adult Rejection Sensitivity Scale (Downey & Feldman, 1996) are both well-validated measures of interpersonal social pain and rejection.

The following updates and safety guidelines to the current are proposed due to the Covid-19 pandemic:

INITIAL INTAKES:

INTAKE 1: Subject will be read the entire consent via virtual media (ZOOM) using the share screen option. The subject will have the opportunity to ask questions during the virtual consenting. A copy will be mailed (via email or regular mail if no email available) to the subject for signature prior to the first intake **Subject Signature** will be obtained by web application Docu-sign

https://www.docusign.com

Subjects will initially be screened over the phone. They will then be emailed the consent form to read and scheduled for a consent appointment over zoom, where they will be taken through the consent procedure with a research coordinator and given time to ask questions. Consent will be proved using Docu-sign. Participants will then be scheduled for an appointment at the CRC where they will provide a baseline blood draw, HCG urine test and urine toxicology. An EKG test will also be performed. If a stay at home order is in place, subjects will be required to provide a current EKG (within the last three months) as well as the last blood pressure reading from their most recent primary care physician visit. If they are unable to provide this, they will be waitlisted until they are able attend the CRC. All questionnaires and clinical interviews (including the SCID) will be performed over ZOOM by virtual visit. All clinical testing will be reviewed by the study physician (Dr Ricardo Caceda).

If the subject proves to be in good health (as confirmed with the study physician) and meets study inclusion / exclusion criteria, a package will be sent out in the mail by UPS. The package will contain a blood pressure monitor kit, urine toxicology cups, disposable breathalyzers for alcohol and 1 week of medication (dose determined by week in study)

timeline calendar, blood pressure heart rate daily log, and written instructions on how to perform these tests.

INTAKE 2: Intake 2 will be conducted early in the morning in order to ensure that the initial medication dose is as close to 8am as possible.
Once the package is received by the participant, the second intake will be performed over virtual media (ZOOM). The subject will first meet briefly with the study physician in order to establish good health. The subject will then meet with the study RA to complete questionnaires, the timeline follow back and take a tutorial on how to use the blood pressure monitor. All subjects will also provide a urine sample to assess drug use by taking a photo of the test strip on the urine cup using their cell phone, and sending it to the study site cell phone to be printed and stored in the participant binder.
Disposable breathalyzer tests will additionally be completed and logged in the participant binder and results displayed via zoom.

Participant will then administer the first dose of study medication or virtual media visit. Questionnaires and surveys will be conducted and timeline follow back will be obtained. Sit stand blood pressure recordings will be taken at the end of this intake. Appointment for the weekly virtual visits will be scheduled.

Medication

At a second intake appointment participants will meet with the study MD, and once cleared begin the first dose of Guanfacine or placebo. They will be randomly assigned to either GXR (3mgs) or PLA, and will receive the exact amount of medication until their next visit, provided in unit/dose containers and labeled with the time and date to facilitate appropriate dosing. Riboflavin will be added to the medications and blood plasma assessed for medication levels every four weeks to ensure compliance131. The use of extended release GXR will also necessitate the use of only 1 tablet per day, increasing likelihood of adherence

ALL SESSIONS:

SAFETY GUIDELINES FOR THE COVID-19 VIRUS DURING:

WEEKLY STUDY VISITS 2 x per week – all virtual:
All assessments will be performed by virtual visit over a secured media site. Using ZOOM with end to end encryption. Subjects will be mailed via UPS with signature required: 1 BP monitoring kit, Urine toxicology cups, 1-week medication until titrations to the optimal dose of 3 mg of Guanfacine or Placebo; based on the blind randomization assigned by the pharmacist. Subjects will receive virtual tutorials form the research staff on the use of the BP monitor and utilization of the urine toxicology cups through zoom. Subjects will be monitored via virtual media during the use of these tools each visit. All adverse events to be reported and documented during these visits. Reported to study MD as needed and virtual visit with MD as needed. All SAFTEE documents will be administered and documented. One virtual visit each week will include medication management, with continued assessment of the subject during the COVID_19 crisis to insure that additional counseling is not needed.

Weekly Assessments include the following:

1. SAFTEE sheet – documenting any adverse effects

2. A series of short rating scales measuring: craving (AUQ), stress (PSS), emotion regulation (DERS), mood (POMS), anxiety (STAXI), depressive symptoms (BDI) and withdrawal symptoms (CIWA)
3. Timeline follow back (TLFB) – subject report of daily alcohol/drug use
3. Vitals – sitting to standing
4. Urine toxicology screens and breathalyzer. At week 4 and week 8 participants will also take a pregnancy test
5. All participants will additionally be required to obtain a blood draw at the CRC on week 4 and week 8 in order to assess LFTs, glucose and CBC and to quantify medication levels.

Procedures

Outpatient procedures: All AUD women will be required to attend two outpatient visits per week for 10-weeks. All women will take part in Medical Management (MM) and Contingency Management (CM) protocols. All clinicians will be fully trained in these procedures, and educated specifically in the treatment needs of women, including relationship issues, caregiving status, anxiety, mood and eating132. In week 10 of treatment a 12-day taper schedule will be implemented 133, prior to discharge

Dosing: Dosing will begin at Intake 2 appointment. Women receiving GXR will begin dosing at 1 mg/d (days 1-7). Dosages will escalate to 2mg/d (days 7-21) and 3mg/g (day 21- onwards). Please see Appendix 5 for titration and updated taper schedule. Identical placebo tablets will be used. All guanfacine and placebo tablets will contain riboflavin in order to ensure compliance

Medical management (MM) & contingency management (CM) for treatment adherence: The primary focus of the MM protocol134 is to assist clinicians in providing educational support strategies for maintaining medication adherence. It was designed for delivery in a primary care setting and as such is a suitable platform for use in outpatient clinical trials assessing new medications for alcohol 135137. Primary goals include promoting compliance via psycho-educational methods as well as encouraging participation into self-help programs aimed at women134. The initial session will be 3045 minutes followed by 10 minute follow-up sessions once per week. In addition, all subjects will receive CM providing participants with the opportunity to increase chances of winning variable dollar prizes at study completion for kept appointments See Human Studies Section for full details of gender-specific recruitment goals (1.2) & CM protocol (4.1.3). 3.5.3 Outpatient Assessments: Primary Outcomes: All participants will be required to provide a urine and breathalyzer screen at each appointment. In addition, the Time-Line Follow-Back Interview 130 will be used to assess all alcohol and nicotine use in the previous 90 days at baseline and weekly during the 10 week treatment trial. Primary alcohol use outcomes will be: (1) time to initial drink and heavy drinking (men: ≥5 drinks; women: ≥4); (2) frequency: the total number of days of alcohol use; and (3) quantity: the average amount of alcohol use (no. of drinks) per occasion. Subjects will be considered drop-outs if they receive two phone calls and two letters inviting them to return. We will attempt to assess these early terminators at the time of discontinuation, at the 10 week termination point, and at the follow-up period. These women will be withdrawn from the study but considered in the intent-to-treat efficacy analyses. Secondary Outcomes: The following measures will be administered upon admission and twice weekly to assess the effects of GXR on craving, anxiety, mood, stress and regulation: AUQ; STAI; BDI; POMS-Bi; PSS; DERS; BIS-11 and Stroop. Data Safety: The following measures will be assessed: (i) Sitting and standing vital signs: every 15 minutes for one hour (ii) Liver function tests, glucose and Complete Blood Count (CBC): weeks 4 and 8 for abnormal values (iii) Systematic Assessment of Treatment Emergent Events (SAFTEE): every week to assesses the severity and duration of potential physical or health problems. Adverse events will be documented according to the criteria outlined in the Human Subjects section 6.0. (iv) Blood draw to assess

medication levels: weeks 4 and 8 (v) urine test to ensure the participant is not pregnant: weeks 4 and 8.

SAFETY GUIDELINES FOR THE COVID-19 VIRUS DURING:

LAB SESSIONS:

Safe distancing practices to be implemented during the pandemic crisis. ***NO*** *stress challenge labs will be initiated until the STATE OF NEW YORK is cleared by the CDC, or NIH from this current DISASTER CRISIS.*

Laboratory Session: The laboratory challenge session will be conducted in the 10th week of outpatient treatment, when all participants have reached full dose. During the lab, subjects will be brought into the testing room at 1 PM following a smoke break to control for nicotine withdrawal if needed. A cotton ball will be placed inside the mouth to collect saliva, a blood pressure cuff and pulse oximeter used to periodically monitor vitals. After 10 minutes relaxation, baseline measures of alcohol craving, nicotine craving, anxiety, mood, HRBP and saliva will be collected -5 minutes prior to imagery exposure. Subjects will then be given headphones and asked to imagine the situation being described, 'as if' they were actively participating in it at that moment. The script (either stress or neutral) will be presented for exactly 5 minutes. All measures will be collected immediately following imagery (0) and again at +15 minutes and +30 minutes following imagery exposure. The Stroop task138 will be administered at baseline and following imagery only. All saliva will be placed on ice immediately, prior to storing at -20. Participants will then be given a 1-hour break to relax, before repeating the procedure. All procedures will be identical, with the exception of the imagery presented (stress or neutral). The imagery order will be counterbalanced and neither the subject not the investigator will know the order of imagery presentation prior to the study. Relaxation instructions will be provided to ameliorate any residual effects of imagery. Imagery script development, imagery training and relaxation techniques will be conducted in the week prior to the laboratory sessions (see Human Subjects Section 2.4). 3.7 Follow-up interviews: Face-to-face interviews will be conducted 30 days after outpatient treatment completion. Urine and breathalyzer screens and a daily assessment of alcohol use will be collected using the TLFB method130

All 30 day follow-up interviews will be conducted over zoom.

STATISTICS

Data Analyses Plan: Aim1: To evaluate the safety and tolerability of GXR (3mgs/day) in women with AUD. All potential adverse effects from both treatment groups will be recorded twice weekly and classified, per body system and reaction, in a frequency table. Comparisons between treatment groups will be conducted using t-tests, chi-square tests and ANOVAs as appropriate (H1a). Aim2: To determine the preliminary efficacy of 10-week GXR (3mgs/day) versus PLA treatment on outcome measures in women with AUD: All analyses will be conducted using the intent-to-treat sample, and survival analyses will be used to examine medication effects on time to relapse measures. In order to model time intervals between events, reoccurring event-time analysis will be performed 139. Hierarchical Linear Models (HLM) will be used to determine the effects of medication on continuous dependent variables, including % days abstinent and number of days in treatment (H2a), as well as secondary outcome variables, including craving, stress, anxiety, mood (H2b). Failures in treatment attendance will be accounted for by treating time as a random effect. Aim 3: To better determine the mechanisms underlying efficacy, by conducting a parallel laboratory study: Linear Mixed Effects (LME) models will examine the effects of medication on all Dependent Variables following stress versus neutral imagery within the laboratory (H3a). In order to elucidate the contribution of GXRrelated stress system changes in

the laboratory on primary drinking outcomes, correlational, regression and survival analyses will be performed as appropriate (H3b).

FUNDING STATUS, DETAILS

NIAAA have stated that they are in the process of issuing a restricted NOA, pending IRB approval.

***HUMAN SUBJECTS RESEARCH PROTECTION FROM RISK SAFETY GUIDELINES FOR THE COVID-19 VIRUS DURING:**

LAB SESSIONS:

*Safe distancing practices to be implemented during the pandemic crisis. **NO** visits will be initiated until the STATE OF NEW YORK is cleared by the CDC from this current DISASTER CRISIS.*

Risk to Subjects

Guanfacine extended release (GXR) treatment: GRX (Intuniv; manufactured by Shire) is an alpha2-adrenergic agonist that is known to preferentially bind to alpha-2A-adrenergic receptors which are highly concentrated in the prefrontal cortical regions 148. While initial reactions to Guanfacine are common, most symptoms are mild and include fatigue, sedation, light-headedness, dizziness and vertigo, and tend to disappear either on continued dosing or following dose adjustment 18, 149. In fact, one major advantage of Guanfacine over other alpha2 adrenergic agonists such as clonidine, is that it is less sedating with less hypotensive potential in both children and adults 73, 75, 111-113. No serious side effects have been noted in adult populations, between the ages 18-65 and there are no reported differences in responses between elderly and younger populations. The most serious side effect in pediatric patients are reports of mania and aggressive behavior in pediatric subjects with ADHD 150. This side effect has not been documented within adult populations and there is no evidence that Guanfacine will pose a greater risk to the proposed study sample than those seen in children and adults with ADHD. One potential risk of study participation, however, is that GXR may result in series adverse effects. As such, we have ensured that important precautions are in place to minimize this risk: **(a)** the dosing levels of GXR (3mgs) is within the range safely used in outpatient studies comprising children and adults with ADHD and tic disorders, commonly ranging from 1.5 to 4 mg/day 73, 75, 149.Moreover, our prior published and pilot data using immediate release Guanfacine indicates that doses of 3mgs are well tolerated in substance and alcohol abusing men and women18, 92. **(b)** Participants` heart rate, blood pressure and self-reports of any potential adverse effects are monitored twice weekly while taking part in outpatient treatment **(c)** As this study represents a preliminary outpatient trial in women with AUD, we propose a longer than standard “lead in” phase of 21 days. Other outpatient studies recruiting young adults and administering higher doses, have employed 16-day titration phases 118.

***Drawing of Blood:**

During each laboratory session, about four and a half ounces of blood will be drawn to measure stress system adaptations during the laboratory sessions. The amount of blood drawn for the tests is equal to about one fourth the blood obtained during a regular blood donation. People who are in good health are not usually affected by this kind of blood loss. However, to be safe, subjects will be warned against donating blood for at least six weeks after completing this study.

The Imagery Procedures:

Prior to admission, during intake procedures, a script development session will be conducted where information for script development is obtained. Our standard imagery script development procedures will be used to develop the 5-minute long personalized stress and neutral imagery scenarios. The stress imagery script will be based on participants’ description of a recent event

that has happened to them in the past year, and which has been experienced as "*most stressful*". This will be determined using a 10-point visual analog scale, where a score of 10 = "*most stressful*". Only scenarios scored as 8 or above will be used to develop into audio scripts. These may include breakup with a significant other, marital conflict or job-related stress. The neutral script will be developed from a personal nonalcohol-related relaxing situation. A 5-minute 'script' of each scenario will be written using the Scene Construction Questionnaires technique 151, 152 where verbal and non-verbal responses and physiological and bodily sensations regarding the events will be incorporated into the personalized story. The script is then written following standard format and content procedures and subsequently recorded onto audiotape for presentation in the laboratory sessions 36. In addition to script development, all women taking part in the study will also receive imagery training in the same week in order to improve and standardize ability to visualize and imagine across participants. This will involve participants visualizing some commonplace non-emotional neutral and physically arousing scenes (e.g. reading a magazine; doing sit-ups). They will then be questioned about their ability to visualize and notice changes in physiological response. The method is adapted from Lang`s imagery training procedures 36, 152, and will serve to provide clear instructions on imagery procedure to reduce imagery variability. Both the script development procedures as well as exposure to imagery in the laboratory sessions involve reliving a personal stressful event. Moreover, the objectives of our paradigm are to induce enhanced and persistent (1 hour post imagery) anxiety, negative mood and alcohol craving within a controlled experimental setting. Although this can be particularly emotionally arousing during the sessions themselves, our previous experience has shown that by approximately 1 1/2 hours post imagery, there is very little anxiety that carries over thus posing minimal risk. It is, however, possible that some craving for alcohol and low affect may linger for a prolonged period following the laboratory sessions and in order to reduce these symptoms the following safeguards will be taken: (a) Subjects will participate in lab sessions in the Department of Psychiatry, in quiet, relaxation rooms. Subjects who have difficulty reducing their craving levels will participate in relaxation procedures to return craving levels to baseline both after the imagery sessions and prior to being discharged from the unit. We have found that relaxation procedures are particularly effective in reducing craving levels after stress exposure 153, 154. (b) To enhance response to relaxation procedures, subjects will also be trained on relaxation procedures prior to the laboratory sessions. (c) Any subject reporting residual craving or emotional discomfort after completion of laboratory sessions will receive an individual counseling session by a licensed psychologist experienced in therapy. The focus of this session will be coping with emotions and cravings.

All subjects will be screened for the COVID -19 virus: subjects that have been exposed will be excluded until they are cleared by pcp

***Physical examination and other laboratory data collection:**

All subjects recruited will receive a comprehensive physical examination and laboratory blood work to ensure good physical health status. The physical examinations will be conducted by the research nurse or the study physician located either at the Department of Psychiatry or the Outpatient Department at Stony Brook. Both will be well aware of study entry criteria and will manage physical and medical assessment accordingly. Routine laboratory blood work will include CBC, ESR, glucose, BUN/creatinine, electrolytes, lipid profile, liver function tests. Abnormal findings will be further evaluated by the study physician (Dr. Caceda) and appropriate medical advice will be provided. These are routine medical procedures and should add no risks other than those normally associated with these procedures. However, the research nurse coordinator, with advice from the study physician, will ensure that potential women who may be excluded from research due to medical reasons or pregnancy, or those who are in immediate need for medical or psychiatric attention, will be referred to the primary care/psychiatric care facilities in the network so they can receive the appropriate clinical care needed to address their condition. Breath screening and urine collections are performed primarily as safeguards to

contamination of data and should add no risks other than those normally associated with these procedures.

Nonspecific risks:
Other risks from the outpatient counseling and rating scales are not beyond usual clinical procedures in a substance abuse treatment program. All research, medical and clinical staff are thoroughly and systematically trained in the confidentiality and ethical procedures associated with patient health information. Confidentiality of such data are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Principal Investigator and Project Manager. Medical Treatment for Injury: The consent form will specify that medical therapy will be provided for injuries sustained as a consequence of participation in this research. Should referral to specialists be needed, however, there are no outside funds available to cover the costs.

Adequacy of Protection against Risks

All subjects will be screened for the COVID -19 virus: subjects that have been exposed will be excluded until they are cleared by pcp

Recruitment and consent procedures:
Most assessments will be performed by virtual visits over the secured media site ZOOM with end to end encryption. However, the clinical portion of the recruitment intake process will be performed with the safety precautions using appropriate PPE set forth by the CDC .
AUD treatment-seeking women will all be screened and interviewed by fully trained research staff who will ascertain interest in participating in the current project. If an individual expresses interest, she will receive an explanation of the study, risks, benefits and description of procedures. Subjects will be informed that participation in all components of the research is entirely voluntary and that all information collected will be kept confidential. All women will be asked to sign the research consent form if they wish to participate following resolution of any questions and clear indication that they understand the nature of the study and the consent. After obtaining written informed consent for participation in the study, the study physician will interview all women and review medical and psychiatric data prior to admission.

Confidentiality:
All women who take part in this study will be free to drop out of the study at any time without penalty. All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality in regard to collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the PI in locked filing cabinets. Only the project manager and PI will have access to any forms specifying both participant name and subject number. All number coded subjective and biological data will be kept in locked offices with access only to investigators and research staff. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed. Subjects will be withdrawn from the study if they show severe psychological or symptomatic deterioration. They will subsequently be offered treatment as usual at the CNRU. Alternate treatment recommendations will be made and offered according to the subject's needs and wishes.

Federal Certificate of Confidentiality:
As the study involves the collection of sensitive data associated with alcohol use and the potential use of other illicit substances, a **federal Certificate of Confidentiality** will be obtained from NIH to further protect the information provided by subjects for research purposes. A component of this project will also involve assessing each potential participant's alcohol and illicit substance use (including cannabis, cocaine, nicotine and heroin), at several intake appointments and during a follow-up interview, both by self-report as well as using urine toxicology and breath alcohol screens. If participants are intoxicated on arrival to any of these face-to-face appointments, appropriate preventative action may be taken. For example, in the case of alcohol intoxication, this may include removal of car keys and providing participants with adequate time in which to remain at the HSC in the attendance of a research assistant until their BAC is consistently below .02, as deemed appropriate by the National Advisory Council on Alcohol Abuse and Alcoholism (1989). Other forms of transport may also be offered including taxi or bus.

Clinical deterioration, severe anxiety, depressive symptoms and suicidality:
During the intake, outpatient and follow-up sessions, all women will be required to provide psychiatric information regarding anxiety and depression symptoms as well as suicidality by use of semistructured clinical interviews, such as The Structured Clinical Interview for DSM-IV; SCID-I; 119. If participants do report severe anxiety and /or depressive symptoms or suicidal ideation during any part of the study, either verbally to the clinical and /or research staff or via self-reported questionnaires, staff will conduct a further assessment of suicidality and will discuss the risk of imminent harm with the PI and the study physician. Referral for further evaluation and/or emergency treatment will be made.

Relapse, and drop out*:* Every effort will be made to re-engage patients who miss appointments. If subjects have missed three consecutive appointments, all attempts will be made to bring the subject back to the outpatient clinic and after a comprehensive assessment of the subject's treatment need, a formal referral will be made to appropriate inpatient, detoxification or intensive outpatient care.

Potential Benefits of Proposed Research to the Subjects and Others
Financial: Although the current study provides MM counseling and CM protocols known to decrease alcohol consumption155, the procedures do not have direct short-term benefits to the subjects. Thus, all participants will be paid $50 for the screening and baseline interviews at intake, $100 for each laboratory session, $50 for the follow-up interview, in addition to $25 for each week of outpatient treatment ($25 X 10 = $250) and the potential for money obtained via 10-weeks of CM.

Medical Management (MM): Each participant will be seen by a coordinator in our research staff individual with alcohol research and health experience, psychologist, or counselor. The general purpose of the counseling sessions are to: (1) acquire information about important concepts and aspects of recovery from addiction; (2) increase self-awareness of specific problems and issues in relation to addiction and recovery. This will be particularly geared towards issues pertaining to women, such as stress, self-esteem, domestic violence, parenting, caregiving status, trauma, anxiety, negative mood and eating (3) learn new coping skills to deal with problems contributing to or resulting from the addiction and to improve functioning. The focus of this psycho-educational approach is on providing patients with frequent supportive contact, introduce them to key concepts about the recovery approach, and develop a sense of personal responsibility for recovery.

Contingency Management (CM): CM has been shown to have the largest effect size of all psychosocial therapies for alcohol and substance abuse disorders 155, 156. As such, all women will also receive CM providing them with the opportunity to earn chances of winning dollar prizes of varying magnitudes. The chance of winning prizes will be contingent upon kept appointments, not clean urine toxicology screens. This will decrease the chances of CM masking the effects of the medication. For every two biweekly appointments attended, the chance to draw for a dollar prize will increase by one, making a total of 10 chances if all appointments are met. If appointments are missed the number of prize draw "chances" are reset to one. The participants draw from a prize bowl containing slips of paper stating either a dollar amount or "good job" (50% of the slips). The prizes will be in increments of $1 (44% of slips), $20 (6% of slips), and $100 (1 slip). All slips will be returned to the bowl at the beginning of each draw to maintain probabilities. The total prize amount will be added to the participants check on study completion. If subjects are unable to achieve abstinence within four weeks, they will be offered inpatient treatment or referred to a higher level of care at another facility. If a subject achieves abstinence but has occasional relapses, outpatient treatment will continue until either abstinence is sustained or a higher level of care is clinically indicated.

Importance of the Knowledge to be Gained

First, this study will contribute in providing important information regarding the role of the adrenergic system in stress-induced alcohol craving and relapse. Using a validated human laboratory model of stress-induced alcohol craving and relapse risk is a unique way of assessing bio-behavioral mechanisms underlying these processes which may hold wider implications for the assessment and treatment of a range of addictive disorders. Second, there is a critical need to develop new pharmacotherapies in alcoholism, especially for women. This is particularly significant as, to date there exists no FDA approved treatment that has been developed in women, or which targets stress pathophysiology in alcoholism (see Section 2.0). Moreover, understanding the mechanisms underlying such dysregulation and compulsive alcohol seeking, will provide information for the development of new tailored therapeutic agents for clinical testing. This study will also specifically provide important preliminary information on treatment efficacy of GXR in alcohol women with AUD with regard to safety, tolerability and ability to attenuate alcohol craving and drinking.

H. DATA SAFETY MONITORING PLAN (for more than minimal risk studies). THESE INDIVIDUALS ARE INDEPENDENT OF THE STUDY.

Data Safety Monitoring Board: The Data Safety Monitoring Board for this study will include Kenneth Gadow, PhD, Director of Clinical Research, Cody Center for Developmental Disabilities at Stony brook (phone: 631-638-1549; email: kenneth.gadow@sbumed.org); and Evelyn Bromet, PhD, Distinguished Professor of Psychiatry and Preventative Medicine at Stony Brook (phone: 631-638-1920; email: evelyn.bromet@stonybrook.edu) ; and Jodi Weinstein, MD, Assistant Professor of Psychiatry at Stony Brook Medicine (phone: 631- 444 – 4000; email: Jodi.Weinstein@stonybrookmedicine.edu.)

Dr Kenneth Gadow, PhD is a Professor appointed in the Department of Psychiatry at Stony Brook University. He is internationally known for his research in children with autism spectrum disorder, models of pathogenesis, ADHD, aggression, Tourette's syndrome and psychopharmacology. He is a Principal investigator on several NIH-funded psychopharmacology studies and is highly experienced in the requirements of data safety monitoring. He is also independent of the current study.

Dr. Evelyn Bromet, PhD is an internationally acclaimed Professor of Psychiatric Epidemiology in the Department of Psychiatry at Stony Brook. Her research has focused predominantly on environmental risk factors associated with the onset and progress of PTSD, depression and psychosis. She is also a past and current member of several NIH advisory committees and highly experienced in the conduct of NIH protocols. She is not an investigator on this study and will function as an independent monitor.

Dr. Jodi Weinstein, MD is an assistant professor in the Department of Psychiatry at Stony Brook University. She was a medical student at Vanderbilt University and did her fellowship at Columbia University. She is not an investigator on this study and will function as an independent monitor.

The DSMB members will evaluate all Adverse and Serious Adverse Events, and will assist the PI in preparing and sending the pertinent expedited reports to the Stony Brook IRB and the NIAAA program officer as outlined below. Dr. Jodi Weinstein will be the Physician on record and will be invited to all DSMB meetings. If the physician is unable to attend, he will be sent a copy of all Adverse Events and will be required to respond "I have reviewed all of the Adverse Events, and the Clinical Trial poses NO RISK AND MAY CONTINUE OR POSES RISK AND SHOULD NOT CONTINUE." These notes will then be sent to IRB along with the Minutes. They will monitor the studies *quarterly* and review all adverse event sheets completed during that period. Although the proposed clinical trial and laboratory study includes generally safe procedures and we do not foresee termination of the study as a direct consequence of study procedures, if there is a need, the DSMB will assist the PI in making critical decisions regarding a particular patient continuing in a study for safety reasons. The DSMB will also review the summary of all Adverse and Serious Adverse Events, which will be reported annually to the Stony Brook IRB committee and the appropriate NIH Project Officer.

Monitoring and reporting Adverse Events (AEs) and Serious Adverse Events (SAEs):
Data on Adverse Events occurring during the course of conducting this study will be collected, documented and reported to the Stony Brook IRB board and to NIAAA. A summary of all AE's will be prepared annually, by the project PI and the Data Safety Monitoring Board and submitted to the Stony Brook IRB committee and to NIAAA. The Stony Brook IRB requires the re-approval of study protocols at least annually and will not re-approve the protocol without such reports.

Adverse Events (AE) will be defined on the basis of the NIH Guidelines on Data and Safety Monitoring for Intervention Trials. These guidelines define an AE as any reaction, side effect or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the study manipulations. A new illness, symptom, unfavorable or unintended sign, or worsening of a pre-existing condition or abnormality will be considered an AE. Stable chronic conditions such as diabetes that are present prior to study entry and do not worsen will not be considered AEs. AEs will include events and symptoms reported by the subjects that are of clinical importance as noted by the study staff. The AE Form will be used for recording the event and any follow-up information. The following Stony Brook IRB/FDA classification of AE "severity" and "attribution" will be used.

Coding of Severity:

0 = No adverse event or within normal limits

1 = Mild adverse event

2 = Moderate adverse event

3 = Severe, resulting in psychiatric or medical hospitalization

4 = Life-threatening adverse event5 = Fatal adverse event

Coding of Attribution:
1 = Unrelated to study interventions
2 = Unlikely relationship to study interventions
3 = Possible relationship to study interventions
4 = Probable relationship to study interventions
5 = Definite relationship to study interventions

Reporting of Serious Adverse Events (SAEs): Each AE will be classified by the project PI on severity and attribution using the above coding and appropriate reporting procedures will be followed. Serious Adverse Events (SAEs) will be defined on the basis of the NIH Guidelines on Data and Safety Monitoring for Intervention Trials. An SAE will be any fatal event, any immediately life-threatening event, any permanent or substantially disabling event or any event that requires or prolongs inpatient hospitalization (a severity rating of 3 or above). Any Unexpected Event that suggests a significant hazard, contra-indication, side effect or precaution will also be reported.

The project PI and the Data Safety Monitoring Board will promptly report all Unexpected SAEs to Stony brook IRB and to the NIH program officer within 48 hours, using the Stony Brook IRB adverse events reporting form. The completed SAE Form will include demographic information, a narrative explanation of the event, and photocopies of any relevant source documents from the patient's case report forms. The project PI will also address whether there is a need to re-design or amend the protocol, or a need to change the description of risk, either in the consent form or in the protocol.

Reporting of other study-safety events: The project PI will inform the Data Safety Monitoring Board, the Stony Brook IRB committee and the NIAAA program officer promptly of any change in recruitment or other changes in this project that are relevant to safety, as well as any action taken by the Stony Brook IRB committee as a result of continuing review of this project**.** The NIH Project Officer will also be informed of any change in the status of the study protocol, including amendments to protocols, changes in informed consent process, or other problems that could affect the human subjects in the study.

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STATISTICAL ANALYSIS PLAN

Aim1: To evaluate the safety and tolerability of GXR (3mgs/day) in women with Alcohol Use Disorder (AUD). All potential adverse effects from both treatment groups were recorded twice weekly and classified. Descriptive statistics are displayed in a frequency table.

Aim2: To determine the preliminary efficacy of 10-week GXR (3mgs/day) versus PBO treatment on outcome measures in women with AUD: Linear Mixed Effects (LMEs) models were used to analyze data from the intent-to-treat sample where, for all Dependent Variables (% no. of heavy drinking days, % no. of days abstinent, % drinks consumed on any one occasion, alcohol craving, depressive symptomatology, anxiety and emotion regulation), the Between Group Factors of Group (GXR, PBO) and Within Group Factors of Time-points (12-weeks), represented the Fixed Effects and Subjects represented the Random Effects. Demographic and drug use variables differing between Treatment Groups and associated with the Dependent Variables were entered as covariates into the models and a Compound Symmetry covariance structure was applied to the model. Descriptive statistics were additionally conducted on % no. of negative urines collected across the trial.