Orexin Receptor Antagonists as Modulators of Threat Sensitivity in Individuals With Alcohol Use Disorder

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Orexin Receptor Antagonists as Modulators of Threat Sensitivity in individuals with Alcohol Use Disorder

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LIST OF ABBREVIATIONS

AE	Adverse Event
aINS	Anterior insula
AUD	Alcohol Use Disorder
BOLD	Blood Oxygen Level Dependent
BMI	Body Mass Index
CITI	Citi.gov Human subjects training
CRC	Clinical Research Center
dACC	Dorsal anterior cingulate cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EMG	Electromyography
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
HIPAA	Health Insurance Portability and Accountability Act
IDS	Investigational Drug Services
IRB	Institutional Review Board
ISI	Interstimulus Interval
MRI	Magnetic Resonance Imaging
N-	No
NPU	No-Predictable-Unpredictable
NIH	National Institutes of Health
ORX	Orexin
P-	Predictable
PBO	Placebo
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
SCID	Structured Clinical Interview for DSM-5
SUV	Suvorexant
U-	Unpredictable
U-Threat	Uncertain Threat

1.0 PROJECT SUMMARY/ABSTRACT

Alcohol use disorder (AUD) affects millions and is one of the leading causes of preventable death worldwide. In the US, pharmacotherapy for AUD is under-utilized; related to the fact that there are only three FDA-approved drugs to treat patients with AUD. These medications work well for some but have small to moderate effect sizes on drinking outcomes. The development of more efficacious pharmacotherapies for AUD is a top public health priority. A recent emphasis in psychiatric medication development is the use of reliable human laboratory measures of AUD dysfunction to test promising compounds to directly inform and power large-scale mechanistic clinical trials. PI Gorka and Co-I Phan have developed an assay of stress reactivity that is robustly related to drinking behavior and AUD. This assay reflects a negative reinforcement model of AUD and is reliably captured in the lab using complimentary objective psychophysiological (i.e., startle eyeblink potentiation) and functional neuroimaging measures. Using this model, we have uncovered that suvorexant (SUV) – a dual receptor antagonist of the orexin system, FDA-approved for insomnia – acutely modifies our AUD target in healthy adults, while sparing changes in other markers of stress reactivity. Compelling animal and human evidence together suggest that the orexin system is critically involved in stress-related alcohol use. The overarching goal of this study is to systematically advance this line of work to uncover if, how, and for whom orexin antagonism modifies brain-behavior stress targets of AUD to inform and power future large scale clinical trials. The study is a targeted double-blind, between-subjects, randomized clinical trial design with repeat lab assessment. A total of eighty subjects with AUD will complete our psychophysiological stress paradigm at baseline. They will return to the lab days later to repeat the protocol following administration of a single dose of either 10mg SUV or placebo (40 subjects/arm). Participants are then instructed to take daily 10mg capsules of SUV or placebo for the next 4-weeks before returning for a post-treatment lab assessment. Daily reports of medication adherence, side-effects, sleep, alcohol use, and mood will be collected via smartphones.

This multimodal design allows for a well-controlled test of whether an acute dose of SUV (Aim 1) and/or daily use of SUV (Aim 2) modifies brain-behavior targets of AUD dysfunction, particularly within individuals with high objective baseline stress reactivity. We will also examine whether daily SUV changes alcohol behavior, and whether this change in behavior is linked to brain-behavior change (Aim 3). Findings from this study will provide critical new knowledge regarding if and how orexin antagonism can be leveraged to treat AUD. The findings will also be used to inform and power a large-scale mechanistic clinical trial of SUV for AUD.

2.0 BACKGROUND/SCIENTIFIC RATIONALE

Alcohol use disorder (AUD) is a serious public health issue and a leading cause of preventable death worldwide[1]. In the US, there is a paucity of pharmacotherapies for AUD, related to the fact that there are only three FDA approved drugs used to treat patients[2-3]. These medications work well for some but have small to moderate effect sizes with ~50-60% relapsing within 12 weeks of treatment[4-5]. The development of more efficacious pharmacotherapies for AUD is urgently needed and a top public health priority[6-7]; though ushering compounds through the clinical testing process and into the AUD clinic has been a well-documented challenge.

A recent emphasis in medication development is the use of valid and reliable human laboratory measures of AUD pathophysiology to test promising compounds to inform and power targeted clinical trials[7-9]. The ultimate goal is to more quickly identify compounds deserving of clinical testing and accelerate the pace of mechanistic drug discovery. PI Gorka and Co-I Phan have developed a reliable assay of stress reactivity that is robustly associated with drinking behavior and AUD[10]. We have shown that greater brain (i.e., anterior insula [aINS] and dorsal anterior cingulate cortex [dACC]) and behavioral (i.e., startle eyeblink) reactivity to threats that are uncertain (U-threat) is associated with greater frequency of drinking, changes in drinking over time, and onset of AUD[11]. Individuals with AUD reliably exhibit greater brain-behavior reactivity to U-threat compared with controls, and magnitude of reactivity correlates with AUD severity[11-14]. These findings have been replicated by other labs and coincide with studies showing alcohol intoxication selectively and effectively dampens reactivity to U-threat (but not predictable threat; P-threat)[15-18]. We have therefore developed a negative reinforcement model of AUD that is reliably captured in the lab using objective, complimentary psychophysiological and neuroimaging measures. This paradigm is now being incorporated into several 'Fast-Fail' proof-of-concept medication trials.

Novel preclinical research indicates that the hypocretin/orexin (ORX) hypothalamic neuropeptide system plays a pivotal role in alcohol abuse. In rodents, antagonism of ORX receptors prevents alcohol-seeking behavior and binge-like alcohol drinking, while preserving motivation for natural rewards[19-22]. ORX receptor antagonism also robustly reduces behavioral and psychophysiological stress reactivity to threat and pharmacological challenge[23-24]. ORX antagonism may therefore be an effective strategy for disrupting the negative reinforcement cycle of addiction. Remarkably, using a within-subjects, placebo-controlled design our prelim data indicates an acute dose of suvorexant (SUV) – an FDA-approved dual ORX receptor antagonist for insomnia – robustly reduces behavioral reactivity to U-threat in adults, while sparing changes in other psychophysiological markers of threat sensitivity less relevant to AUD. ORX antagonism selectively engages the U-threat target, providing compelling evidence it is a promising pharmacological treatment for individuals with AUD and high U-threat reactivity, who frequently engage in stress-related alcohol use[22, 25-28].

No prior study has measured stress-related ORX target engagement in humans to uncover how ORX antagonism can be leveraged to treat AUD. The overarching goal of the current study is to advance ORX translation to the AUD clinic using a proof-of-concept

double-blind, between-subjects, randomized clinical trial design with repeat lab assessment.

All subjects will complete three lab visits of psychophysiological data collection. A subset of 20 subjects per arm (40 total) will also complete our stress task during simultaneous startle and functional magnetic resonance imaging (fMRI), pre- and posttreatment. This design allows us to address if, how, and for whom ORX antagonism modifies brain-behavior stress targets to inform and power future large scale mechanistic clinical trials.

3.0 Objectives/Aims

Aim 1. Does an acute dose of suvorexant decrease reactivity to U-threat? H1: Relative to placebo, SUV will acutely dampen psychophysiological reactivity to U-threat, but not P-threat.
Aim 2. Does daily use of suvorexant decrease reactivity to U-threat? H2a: 4-weeks of SUV will result in greater reductions in psychophysiological reactivity to U-threat compared with placebo, and these changes will be specific to U-threat. **H2b**: SUV-related change in U-threat reactivity will be greatest amongst those with higher baseline U-threat reactivity. Exploratory: Daily SUV will similarly result in decreases in aINS and dACC reactivity and connectivity during U-threat relative to placebo, and brain change will correlate with startle change.
Aim 3. Does daily use of suvorexant change alcohol behavior, and is this change linked to brain-behavior U-threat change? H3a: Daily SUV will result in greater reductions in proportion of heavy drinking days (PHDD) and drinks per drinking day (DPDD). **H3b**: SUV-related changes in PHDD and DPDD will be greatest in those with higher U-threat reactivity. **H3c:** In all subjects, changes in alcohol behavior will correlate with changes in brain-behavioral U-threat reactivity.

Study duration. Participants will complete a Screening Session and three to five in-person laboratory sessions (dependent upon randomization) over the course of 1.5 – 2 months.

4.0 Eligibility

4.1 Inclusion Criteria

Adults 18-65 years old will be enrolled in this study. Participants will be required to be generally medically and neurologically healthy. They will also be required to meet current DSM-5 diagnosis of moderate to severe AUD and engage in heavy alcohol use defined as drinking ≥14 standard drinks per week if male, and ≥7 standard drinks per week if female.

4.2 Exclusion Criteria

Exclusion criteria for all subjects will be: (a) clinically significant medical or neurologic condition or neurocognitive dysfunction that would affect function, and/or task performance, and/or interfere with the study protocol, and/or be contraindicated for suvorexant (SUV), including narcolepsy, complex sleep behaviors, severe hepatic impairment, and compromised respiratory function such as COPD, and severe obstructive sleep apnea; (b) current or past major DSM-5 psychiatric disorder including mania, schizophrenia, psychosis, suicidality (as defined by a score of 5 or higher on the Beck's Scale for Suicidal Ideation - Lifetime [SSI]), major depressive disorder (MDD), or obsessive-compulsive disorder (OCD); (c) current substance use disorder for any substance, except for mild cannabis use disorder; (d) treatment seeking for AUD due to the study design and experimental nature of SUV; (e) currently pregnant (positive pregnancy test), lactating, or not agreeing to use birth control methods during the duration of the trial (women); (f) recent (in the past 2 months) use of any psychoactive medications; (g) current antihistamines use; (h) current use of strong or moderate inhibitors of CYP3A liver enzymes; (i) current use of strong CYP3A inducers; (j) current use of digoxin; (k) night shift work; (l) smoke 5 or more cigarettes (or electronic equivalent) per day and are thus susceptible to acute nicotine withdrawal during lab visits; (m) obesity as defined by a body-mass index (BMI) greater than 35, as calculated from weight and height self-report; (n) lack of fluency in English; (o) acute alcohol withdrawal the day of the lab sessions, defined as a score >8 on the Clinical Institute Withdrawal Assessment of Alcohol Scale Revised (CIWA-Ar)[29]; (p) unwilling/unable to sign the informed consent document; (q) under 18 years old or over 65 years old at the time of enrollment; (r) history of traumatic brain injury (as defined by The American Congress of Rehabilitation as a traumatically induced physiological disruption of brain function - i.e., the head being struck, the head striking an object, and/or the brain undergoing an acceleration/deceleration movement, such as whiplash - without direct external trauma to the head), as manifested by at least one of the following: any loss of consciousness; any loss of memory for events immediately before or after the injury; any alteration in mental status at the time of the incident; or focal neurological deficits that may or may not be transient.

Additional exclusion criteria for all participants pertaining to the fMRI scan include: a) presence of ferrous-containing metals within the body (e.g., aneurysm clips, shrapnel/retained particles) or b) inability to tolerate small, enclosed spaces without anxiety (e.g., claustrophobia).

Acute alcohol intoxication, verified via breath test, will disqualify immediate participation for lab tasks; though subjects may be able to re-schedule the visit for a later date. Upon arrival to the lab sessions, individuals will provide a urine sample for drug screen and complete a corresponding detailed Timeline Follow-back (TLFB)[30] of their substance use. If individuals test positive for recreational substance use and self-report use within the past 24-hours their lab visit will be re-scheduled for a later date.

4.3 Excluded or Vulnerable Populations

No individuals will be allowed to participate in the study if they are < 18 years of age or > 65 years of age. This study will exclude children (<18 years of age).

This age range was chosen to minimize the potential for adverse medication side-effects. Limiting the sample to adults younger than 65 also reduces potential heterogeneity in brain structure and function, and psychophysiological stress reactivity, which could confound data interpretation in the current sample size.

Individuals younger than age 18 will be excluded because suvorexant is not FDA-approved for use in children.

The study will also exclude individuals who are pregnant, nursing, or are trying to get pregnant to ensure safety of the fetus/child during procedures. This study will exclude prisoners.

5.0 Subject Enrollment

- We propose to recruit from multiple sources with the intent to enroll a community sample.
- Participants will be recruited via print advertisements across the central Ohio area, word-of-mouth referrals (including through the OSU emergency department (ED)), and internet and social media postings (e.g., craigslist, Facebook, Snapchat, Instagram), and through OSU websites (such as Study Search) and electronic newsletters.
- We expect to recruit up to 120 participants in 2 years.
- Advertisements will include a QR code that when scanned will direct interested individuals to the study's online Recruitment Survey on REDCap. If the individual chooses, they will complete the online survey that assesses for initial eligibility criteria.
- The study staff will determine potential participants' eligibility for the research.
- If an individual meets this initial eligibility criteria on the survey, trained clinical research staff or investigators will call the individual and complete a phone screen to further assess eligibility for the research study. Data from participants not eligible for the study based on the initial phone screen will be destroyed once they are determined to be ineligible.
- In collaboration with Dr. Michael Lyons, Professor of Emergency Medicine at the OSU Wexner Medical Center, we propose to also recruit from the OSU ED. IRB approved and trained research specialists, employed by Dr. Lyons, who work in the OSU ED will assist in recruitment procedures by conducting the phone screen verbally in-person with interested participants.

The research specialists are a part of an established research initiative and are specifically trained to enroll individuals in the ED into IRB approved research studies. Thus, phone screening individuals in the ED is a part of the research specialists' routine job responsibilities.

- As outlined in the phone screen, the OSU ED research specialists will read a brief description of the study and if the individual is interested, the phone screen will be completed. Study staff will not access medical records at any point during the recruitment process.
- Following the completion of the phone screen, potentially eligible individuals will be scheduled for a Screening Session. Participants will be given the choice to complete the Screening Session online or in-person to accommodate potential limited access to the internet.
- During the Screening Session, participants will provide informed consent. Specifically, once the procedures are explained to them in detail, subjects will be given ample time to read the consent form, formulate questions and ponder the responses. Subjects will have time between initial contact and the scheduled testing to discuss participation with people of their choice; the initial laboratory session date will be scheduled for their convenience. We will emphasize to subjects the voluntary nature of their participation in the study. Subjects will also be told that they are free to drop out of the study at any time for any reason.
    - **Online Screening Sessions:** Consent will be collected via REDCap software. The authenticity requirements involve Remote Signing, Username & Password. During the phone screen, if participants are found to be eligible, they will establish a password with study staff. The study staff will enter the passcode in the participant's REDCap record. Participants are sent a link to sign the consent form in REDCap via email, which does not include the password. Participants are then asked for the password which is cross referenced with the password already on file in the REDCap project. The completed consent form will be downloaded and stored in the PI's laboratory in a locked cabinet and locked office. A copy of the signed consent is emailed to the participant by REDCap.
    - **In-person Screening Sessions:** Consent will be collected via REDCap software. The authenticity requirements involve in-person signing. Participants can provide ID, insurance card, name and date of birth, etc. for study staff to verify their identity. The completed consent form will be downloaded and stored in the PI's laboratory in a locked cabinet and locked office. A copy will be given to participants.
- At the Screening Session a clinically trained study staff member will perform the Structured Clinical Interview for DSM-5 (SCID-5)[31] and administer a small battery of questionnaires. MD level physician will review his/her medical and neurological history. Initial eligibility for the research will be

documented in the research record. Final determination of subject eligibility will be made by the PI or the PI in consultation with research staff.

- Following the Screening Session, eligible participants will be randomized to a treatment group (i.e., SUV or placebo) and protocol arm (i.e., EMG/EEG only or EMG/EEG + fMRI). Treatment group randomization will be double-blinded.
- Research study staff will monitor the participants throughout the course of the research to ensure that they still meet eligibility criteria, and their continuing eligibility will be documented by the research staff. This will include ensuring abstinence from alcohol at both laboratory visits. It will also ensure that no participant is pregnant at either session.
- Upon enrollment into the study, participants will be required to agree and consent to not operating heavy machinery, including driving a vehicle, for at least 24-hours after the Acute Drug Challenge visit due to day-time drug administration.
- Participants will also be instructed that they will be required to fast for at least 2-hours prior to the Acute Drug Challenge visit to avoid interactions between food and SUV metabolism. The Acute Drug Challenge visit will therefore begin at approximately 9-10am.
- Following the Acute Drug Challenge visit, participants will be instructed to take either SUV or placebo, dependent upon their randomized treatment group, once daily before bed for 4 weeks. Participants will complete daily online clinical assessments. The PI and study staff will monitor potential side effects and drug adherence throughout the duration of the 4 weeks.
- Participants will return to the lab at the end of the 4 weeks and complete a third EMG/EEG, and second fMRI (dependent upon randomization).
- Participants will be debriefed and provided AUD treatment referrals as appropriate at the end of their study participation.

- **Termination Criteria:** Participants may be terminated for any of the following: (a) completion of study; (b) participant request to exit or withdraw consent; (c) development of suicidal or homicidal ideation requiring hospitalization; (d) development of a systemic, medical, neurologic or psychiatric illness requiring treatment that would exclude participation; (e) clinical deterioration (see below); (f) non-compliance with study protocol requirements including refusing to consent to not driving for at least 24-hours after Lab Visit 2 (Acute Drug Challenge) due to day-time drug administration; (g) significant worsening of AUD symptoms that would require treatment; and (h) a positive pregnancy test. If alcohol tests are positive, participants will be given the option to reschedule. If breath tests are again positive, participation will be terminated.

6.0 Study Design and Procedures

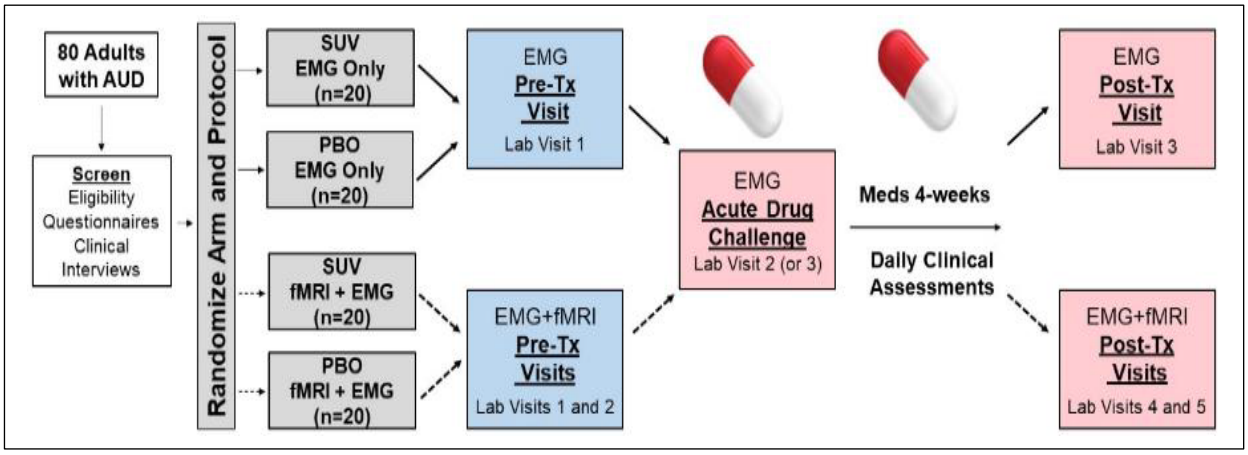
Participants. The sample size for the present study is 80 adults, ages 18-65 years old. However, to account for potential screen-fails, participants requesting to drop out of the study, and the PI withdrawing participants due to meeting termination criteria, approval for 120 participants is requested. Exclusion criteria are listed above. We will recruit

individuals who meet DSM-5 criteria for moderate or severe AUD. As noted above, we will not include individuals who meet DSM-5 diagnostic criteria for current or lifetime MDD, OCD, bipolar disorder, or psychotic disorder. All other lifetime psychiatric diagnoses will be assessed and examined as potential covariates in analyses. Individuals younger than age 18 will be excluded because suvorexant is not FDA-approved for use in children. Individuals older than 65 will be excluded to minimize the potential for adverse medication side-effects and prescription drug interactions. Limiting the sample to adults younger than 65 also reduces potential heterogeneity in brain structure and function, and psychophysiological stress reactivity, which could confound data interpretation in the current sample size.

Recruitment. Adults will be recruited via print advertisements, word-of-mouth referrals (including through the OSU ED), and internet postings (e.g., craigslist, social media sites). We expect to recruit all participants within 2 years, consistent with our prior psychophysiological and pharmacological challenge studies.

Entry Assessments. Inclusion/exclusion criteria. Potential participants will be screened using structured questionnaires (see Table 1 and Table 2). Exclusionary criteria will be those that would interfere with interpretation of brain and/or behavioral findings or increase risk of side effects/adverse events - see above for a complete list. After consent, if interested participants meet eligibility criteria, and are able to provide consent, they will be enrolled in the study.

Figure 1.



Study Overview. The study is a double-blind, between-subjects, randomized clinical trial with a multi-session lab paradigm (see Figure 1). Participants will first complete an initial Screening Session where they will complete an assessment of study eligibility (described above), a clinical interview, and questionnaires. If participants are found to be eligible, they will be randomized to a treatment group (SUV or placebo) and protocol arm (BEHAVIOR or BRAINS Group). Those in the BEHAVIOR Group will complete electromyography (EMG)/electroencephalography (EEG) only and those in the BRAINS Group will complete EMG/EEG + fMRI.

Therefore, participants have a chance of being randomized to four different groups (20 participants/group): 1) BEHAVIOR - SUV; 2) BEHAVIOR - Placebo; 3) BRAINS - SUV; and 4) BRAINS - Placebo.

BEHAVIOR Group Overview:
Following the Screening Session, participants randomized to the BEHAVIOR group will come in-person to Lab Visit 1 where they will complete the psychophysiological stress paradigm and Alcohol Cue Reactivity EEG task. Days later, they will return to the lab for Visit 2 (Acute Drug Challenge) and repeat the protocol during their first dose of medication (placebo or 10mg SUV). Next, they will be instructed to take a 10mg dose of SUV (or placebo) each night before bed for 4-weeks. Daily online assessments of medication compliance, side-effects, alcohol use, mood, and sleep will be collected. During the final week of the protocol subjects will return for Lab Visit 3 to repeat the paradigm (dose taken night prior, as prescribed).

BRAINS Group Overview:
Following the Screening Session, participants randomized to BRAINS Group will complete the same procedures as above with the exception of completing two additional fMRI visits pre- and post-treatment. Therefore, participants will complete: Lab Visit 1 (EMG/EEG), Lab Visit 2 (fMRI), Lab Visit 3 (Acute Drug Challenge), four weeks of SUV (or placebo) administration with daily online assessments, Lab Visit 4 (EMG/EEG), and Lab Visit 5 (fMRI).

Screening. During the Screening Session, participants will complete an assessment of study eligibility, the Structured Clinical Interview for DSM-5 (SCID-5)[31] with trained study staff, and a short battery of self-report questionnaires (see Table 1 and Table 2). Participants will be given the choice to complete the Screening Session online or in-person to accommodate potential limited access to the internet.

Measures of Alcohol and Other Substance Use: (1) Alcohol Use Disorders Identification Test (AUDIT)[32], (2) Timeline Follow-back (TLFB)[30]; (3) The Obsessive Compulsive Drinking Scale (OCDS)[33], (4) The Drinker Inventory of Consequences (Dr-InC)[34], (5) the CIWA-Ar[29], (6) Drinking Motives Questionnaire-Revised (DMQ-R)[35], (7) Drug Abuse Screening Test (DAST)[36], (8) Cannabis Use Disorder Identification Test (CUDIT)[37], and (9) the Fagerstrom Test for Nicotine Dependence (FTND)[38].

Measures of Psychiatric Symptoms and Personality: (1) Beck Depression Inventory (BDI-II)[39], (2) Beck Anxiety Inventory (BAI)[40], (3) Generalized Anxiety Disorder Questionnaire (GAD-7)[41], (4) Beck Hopelessness Scale[42], (5) Snaith-Hamilton Pleasure Scale (SHAPS)[43], (6) PTSD Checklist-Civilian Version (PCL-5)[44], (7) Life Events Checklist for DSM-5 (LEC-5)[45], (8) The Personality Inventory

for DSM-5 (PID-5)[46], and (9) Beck's Scale for Suicidal Ideation Lifetime (SSI)[47], (10) The Depression, Anxiety and Stress Scale (DASS-21)[48], (11) The Inventory of Depression and Anxiety Symptoms (IDAS-II)[49], (12) Childhood Trauma Questionnaire (CTQ)[50], (13) Anxiety Sensitivity Index (ASI), (14) Highly Sensitive Person Questionnaire (HSP).

Other Measures: (1) Pittsburg Sleep Quality Index (PSQI)[51], (2) Health Questionnaire, (3) Demographic Questionnaire, (4) Intolerance of Uncertainty (IUS)[52], (5) Contact Information Form, (6) Emotion Regulation Questionnaire (ERQ)[53], (7) Psychiatric Treatment History Form (clinician administered), (8) Medication History form (clinician administered); (9) Exclusionary Medication Checklist; (10) BMI Questionnaire.

Identifying and Monitoring Drug-Drug Interactions. The study physician will review the participant's self-report Health Questionnaire, self-report Exclusionary Medication Checklist, and clinician administered Medication History form prior to randomization in order to assess exclusionary criteria and identify potential drug-drug interactions. PI and the study physician will utilize Lexicomp to check drug-drug interactions and only interactions of minor severity will be allowed. Those found to have potential moderate or severe drug-drug interactions will be withdrawn from the study, consistent with study exclusionary criteria. Potential drug-drug interactions will continually be monitored throughout the duration of the study.

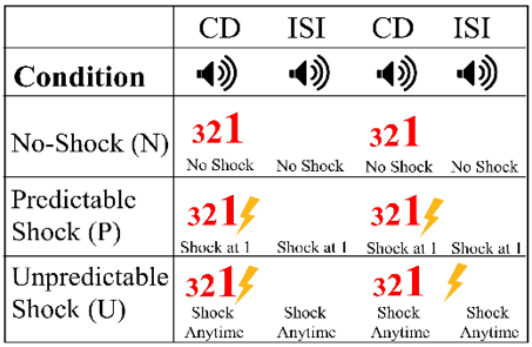
Randomization, Blinding, and Dosing. A computerized stratified block randomization will assign subjects to a treatment group and protocol arm. The randomization will be stratified by biological sex. The research team and participants will be blind to medication assignment. The PI will have the ability to unblind if needed. OSU Investigational Drug Services (IDS) staff and CRC medical staff will be unblinded.

Participants will receive either placebo or suvorexant (Belsomra®; 10mg; Merck & Co). This dose was chosen because it is the lowest clinical dose for sleep and arousal-related outcomes. We used 10mg in our pilot project and found significant change in reactivity to U-threat without adverse reactions (Protocol#: 2020H0285).

Laboratory Tasks. Participants will complete a startle response to threat task at the EMG/EEG, fMRI, and Acute Drug Challenge Visits (described below). The same paradigm will be administered during the EMG/EEG and Acute Drug Challenge Visit. The fMRI task is analogous to the original design; however, shock is administered to the left foot to minimize potential scanner interference and individual shock levels are re-calibrated. During the tasks, we will collect psychophysiological measures including startle eyeblink potentiation. At the EMG/EEG visit a second task, Alcohol Cue Reactivity[71] will be completed. These tasks are well-established, validated paradigms,

previously used in our laboratory for the past several years in both healthy and adults with AUD.

EMG/EEG Lab Visits. Task 1: Startle response to threat. Consistent with prior studies[54,55], participants will first complete a brief habituation task to prevent early exaggerated startle responding, during which a series of acoustic startle probes will be administered. For the threat task itself, a brief, mild electric shock will be used to elicit aversive responding. Importantly, the current shock equipment and shock protocol has previously been used in our laboratory. Prior to the task, shock electrodes will be placed on the participants' left wrist, followed by a shock work-up procedure in which they will receive increasing levels of shock intensity (max. = 5 mA) until they reach a level that they describe as feeling "highly annoying but not painful." Shock level will be determined ideographically to ensure equality in perceived shock aversiveness. The task itself includes three within-subjects conditions – no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the screen informs participants of the current condition. Conditions last 145-s, during which a 4-s visual countdown (CD) is presented six times. The interstimulus intervals (ISIs) range from 15 to 21-s during which only the text of the condition is on the screen. No shocks are delivered during the N condition. A shock is delivered every time the CD reaches 1 during the P condition. Shocks are delivered at random during the U condition. Startle probes are administered during both the CD and ISI. Each condition is presented two times in a randomized order. Participants receive 24 shocks (12 in P; 12 in U) and 60 startle probes (20/condition). This task will be conducted during all three EMG visits, including the Acute Drug Challenge Visit.



Startle Data Collection and Processing. Via Presentation software (Albany, CA), acoustic startle probes that are 40-ms duration, 103-dB bursts of white noise will be presented. Electric shocks will last 400-ms. Startle will be recorded using the PI's BioSemi Active Two system (BioSemi, Amsterdam, The Netherlands) and data collected and processed (e.g., filtering, rectification, smoothing, scoring blinks) according to published guidelines, as reported in the PI's publications[56-58]. Startle is processed using the PI's interactive 'batch' program in BrainVision Analyzer 2 (Brain Products). Consistent with the PI's work, and published recommendations[59], we will calculate standardized residual scores for the two forms of threat anticipation - U-threat and P-threat. This method has been shown to most accurately quantify the difference between threat and no-threat reactivity. Blinks will be scored as missing if the baseline period was contaminated with noise, movement artifact, or if a spontaneous or voluntary blink began before minimal onset latency. For each task, mean blink magnitude scores for each condition (N, P, U) will be calculated and used in primary analyses.

EMG/EEG Visits. Task 2: Alcohol Cue Reactivity. Participants will complete a modified Alcohol Cue Reactivity Task[71]. The task consists of four conditions: alcoholic

beverages, non-alcoholic beverages, pixilated control images, and fixation (rest) periods. Each of the 4 conditions consists of 22 stimuli each presented four times. Stimuli are presented sequentially in a pseudo-randomized order each for about 1 second with a 1250 ms inter-stimulus interval. Alcohol and non-alcohol beverage stimuli were previously standardized to ascertain adequate identification, and comparable valence, arousal, and visual characteristics between the two conditions[71]. Throughout the task, participants will be instructed to indicate their mood and the valence of the different stimuli.

Psychophysiology Data Collection and Processing. During the Alcohol Cue Reactivity task we will record continuous electroencephalography (EEG) readings using a 32 channel ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands).The data is recorded off the scalp, non-invasively, while participants are wearing a stretch lycra EEG cap. The EEG signal will be pre-amplified at the electrode to improve the signal-to-noise ratio. The data will be digitized at 24-bit resolution with a Least Significant Bit (LSB) value of 31.25nV and a sampling rate of 1024Hz, using a low-pass fifth order sinc filter with a -3dB cutoff point at 204.8Hz. Off-line analysis will be performed using Brain Vision Analyzer software (Brain Products), using conventional preprocessing steps. Data will be re-referenced to the average of the two mastoids and high-pass (0.1Hz) and low-pass (30Hz) filtered. Data will be segmented around event markers that correspond to the administration of task stimuli. Baseline correction for each trial will be performed and brain activity averages will be computed for each condition, for each task.

fMRI Data Collection. All scanning will be performed at the OSU Center for Cognitive and Behavioral Brain Imaging (CCBBI), using a Siemens 3T Prisma MR scanner with Total Imaging Matrix (TIM) system and a phase-array head coil for parallel imaging to minimize signal loss and image distortion. Prior to entering the fMRI scan, female participants will complete a urine pregnancy test. Each session will begin with an MP-RAGE high-resolution structural imaging of the whole brain (TI =950 ms; TR = 1950 ms; TE = 4.44 ms; flip angle 12o; 176 sagittal slices; 256 x 256 matrix size with spatial resolution as 1x1x1mm^3, slice partial Fourier of 6/8). fMRI signal measures will be acquired using a T2*-weighted Echo-Planar Imaging sequence with BOLD contrast to measure task-related effects, optimized to reduce susceptibility artifact in the ventral frontal cortex and medial temporal lobe (TR = 2000 ms; TE = 25 ms; flip angle =70o; 64 x 64 in-plane resolution; and 1906 Hz/pixel bandwidth). Thirty-five 3 mm axial slices will be acquired to cover the cerebrum and most of the cerebellum with no gap. Slices will be tilted about 20o clockwise along the AC-PC plane to obtain better signal in the orbitofrontal cortex. These parameters are used to minimize signal dropout, image distortion and susceptibility artifacts. Head movement is minimized through instruction, eye-tracking, and foam padding within the head coil. Participants will complete 2 tasks and spend 45 minutes in the bore of the magnet.

fMRI Lab Visits - Task 1: Startle response to threat. Stress reactivity will be probed using an fMRI version of the NPU threat paradigm, developed

and implemented by the PI[60]. The fMRI task is analogous to the original NPU design; however, shock is administered to the left foot to avoid scanner interference. Individual shock levels are re-calibrated.

The task uses threat-of-mild-electric-shock to elicit stress in two contexts: threat of a predictable electric shock (fear) and threat of an unpredictable electric shock (anticipatory anxiety). Shock level is determined ideographically using a pre-task shock work-up in which participants receive increasing levels of shock intensity (max 5mA) until they reach a level they describe as "highly annoying but not painful." The task includes three within-subjects conditions: no-threat (N), predictable threat (P), and unpredictable threat (U). Text at the bottom of the screen informs participants of the current task condition. Each condition includes a countdown (CD) that ranges 3-8s (M=5s). During N, no shocks are delivered. During P, a shock is delivered when the CD reaches "1". During U, shocks are delivered at random. Following each CD there is a fixation for 5-7s (M= 6s). N, P and U CDs are presented in blocks of 5 and each condition/block is administered in a randomized order 5 times over two runs for a total task time of 10 mins. Participants receive 20 shocks (10 in P, 10 in U) during each run. Electric shocks will last 400-ms. The rate of "Shock at 1" during the P condition is 60% to prevent an excessive number of total shocks during the task, consistent with the NPU version used by Grillon and colleagues[61]. Acoustic white noise startle probes that are 103bd, 40-ms duration will be administered via headphones during the NPU threat paradigm. Startle data is collected from two peripheral electrodes placed under the participant's left eye and recorded using Brain Vision Recorder software. Our data from two studies indicate that despite being shocked, participants are able to remain still and total motion is minimal (n=237; M translation=.03±.02mm and rotation=.02±.01degrees). PI Gorka's lab is currently recording simultaneous fMRI+startle in another IRB approved study (Protocol#: 2021H0039). After the task, self-report ratings of the threat, consistent with above, will be assessed.

During the NPU task, BOLD is the index of stress reactivity. The BOLD contrasts of interest will capture activation during threat anticipation: U-threat anticipation > No-threat anticipation and P-threat anticipation > No-threat anticipation. At the end of the task, participants rate how intense, arousing, and anxiety provoking the conditions and shocks were. Of note, our prelim data from two separate studies indicate that despite being shocked, participants are able to remain still and total motion is minimal (n=237; M age=19.3; M translation=.03±.02mm and rotation=.02±.01degree across runs).

fMRI Lab Visits - Task 2: The Resting State Task (RST). For this task participants will view a fixation cross on a blank background for approximately 10 minutes. Participants will be instructed to keep their eyes open and focused on the cross, and to try not to think of anything in particular.

fMRI Data Processing. Data preprocessing will involve well-tested, routine procedures used in our lab. Conventional steps (e.g., realignment, normalization, smoothing) will be executed using Statistical Parametric Mapping software (SPM8; Wellcome Trust Center for Neuroimaging, London). Strict quality control procedures will be in place to evaluate head motion (e.g., excluding subjects with >1.5 mm movement in any direction) and ensure proper normalization. Motion parameters will be included in all

first-level models as regressors of no interest. Statistical analyses will use the modified General Linear Model (GLM) in combination with a temporal convolution for block-related analyses in a random effects model. Statistical inference will use random field theory to account for non-independent observations within a smooth map. We will implement 2 complementary approaches to test regional activation: 1) hypothesis-driven region-of-interest (ROI)-based analysis of BOLD percent signal change (PCS) created from anatomy-based landmarks using small-volume correction ($p<.05$, FWE-corrected); and 2) whole-brain activation search at a threshold of $p<.05$ (FWE-corrected).

Suvorexant Accountability and Compliance. The compound pharmacy will prepare the study capsules and supply them to OSU Investigational Drug Services (IDS). Appropriate storage temperature of suvorexant will be maintained by IDS. IDS staff will maintain records of distribution to each subject. These records will include dates, quantities, batch, expiration dates, and unique code numbers assigned to the product and study subjects. Prior to distribution, the IDS will prepare each subject's study medication in blister packaging. Each blister is clearly marked with the date the capsule will be ingested.

Administration of Drug or Placebo (Acute Drug Challenge).

Overview. Following the initial EMG/EEG or fMRI visit (dependent upon randomization) participants will return to the lab for the Acute Drug Challenge Visit. Participants will first arrive to the Clinical Research Center (CRC) for drug or placebo administration. After 2-hours, participants will then be escorted to the PI's laboratory for the EMG assessment. After the assessment, participants will return to the CRC for further monitoring and discharge to assure that vital signs (heart rate, oximetry, blood pressure) are within normal limits and/or do not require immediate medical attention and that the participant can maintain wakefulness as demonstrated by a score of 7 or less on the Karolinska Sleepiness Scale (KSS)[62] (1="Very alert"; 5="Neither alert nor sleepy"; 7= "Sleepy, but no difficulty remaining awake; 9="Very sleepy, fighting sleep"). Participants will consent to not operating a vehicle for at least 24 hours after the Acute Drug Challenge Visit. A taxi voucher or Uber reservation will be provided by study staff for transportation home if participants do not have a means to transportation.

Placebo and suvorexant (i.e., Belsomra®; 10mg; Merck & Co., Inc.) will be obtained from the compound pharmacy and will be placed in opaque capsules with dextrose filler for each session. Placebo capsules will be identical in appearance but will contain only dextrose. All capsules will be administered to subjects in double-blind conditions at the CRC under medical supervision.

Administration Timing. Peak plasma concentration for suvorexant is 2 hours post-ingestion. Therefore, participants will receive the drug (or placebo) at the CRC upon arrival. After 1.5 hours (90 minutes post ingestion), participants will be escorted to the laboratory for EMG/EEG testing. Laboratory assessments will occur during peak concentration, ~2 hours post-ingestion.

Self-Report Assessments During Acute Drug Challenge. Throughout the Acute Drug Challenge Visit standardized questionnaires will be used to assess mood states and subjective drug effects: (1) Karolinska Sleepiness Scale (KSS)[62]; (2) Anxiety Visual Analog Scales (VAS)[63]; and (3) Drug Effects Questionnaire (DEQ)[64]; and Profile of Mood

States (POMS)[65]. The KSS, VAS and DEQ will be collected immediately before capsule ingestion (Time 0), and approximately 30, 60, 90, 120, 150, 180, and 210, and 240 minutes afterwards. The POMS will be completed immediately prior to capsule ingestion (Time 0), and approximately 60 minutes, 120 minutes, and 240 minutes afterwards.

Vitals Signs Measurements During Acute Drug Challenge. Physiologic measures will be collected throughout the study visit: (1) Blood Oxygen (O2) Saturation; (2) Heart Rate and (3) Blood Pressure will be taken before capsule ingestion (Time 0), and approximately 30, 60, 90, 120, 150, 180, and 210, and 240 minutes afterwards. Measurements will be performed at the CRC or in the PI's lab using portable blood pressure and finger oximeter. Measurements will be obtained using a finger oximeter and portable blood pressure cuff. Any participant who experiences excessive drowsiness, allergy symptoms, and/or adverse drug reactions will be assessed by the CRC and study physician and immediately withdrawn from the study as a safety measure.

Drug Trial and Monitoring. At the end of the acute challenge, subjects will be provided the rest of their prescription (SUV or placebo) in blister packaging, prepared by OSU IDS. The blister packaging will be labeled with each date of the protocol. Subjects will be directed to ingest one pill each night, as they get into bed (~30 mins prior to sleep time) to mitigate drowsiness, consistent with SUV's prescription.

Each morning for the 4-week medication trial period, subjects will be asked to complete a brief clinical assessment, sent directly to subjects' smartphones at 8:30am. The survey will capture: medication adherence (yes/no); timing of pill ingestion; time spent in bed and asleep; medication side-effects; number and timing of alcoholic beverages; alcohol craving; illicit substance use; mood; and new medication usage to monitor potential drug-drug interactions. If the survey is not completed, a reminder will be sent to the participant every 30 minutes for 150 minutes (5 total reminders). Responses will be collected, password-protected, and encrypted locally on smartphones.

Subjects who endorse medication side effects other than nighttime drowsiness will be contacted by the study physician for a review of symptoms and safety. Additionally, if subjects endorse taking new medications, the study physician will review the information and contact the subject if further information is needed. The study physician and PI will utilize Lexicomp to check drug-drug interactions and only interactions of minor severity will be allowed. Those found to have moderate or severe interactions will be withdrawn from the study, consistent with study exclusionary criteria.

Subjects will also be contacted if medication compliance falls below 80% or above 120%. At the final lab visit, subjects will be asked to bring their blister pack with them to verify compliance using the pill count method. Thus, medication compliance is tracked using both daily self-report, pictures, and objective pill count.

Post-Treatment Lab Visits. During the final days of the trial, subjects will return to the lab to repeat the lab protocol. Individuals enrolled in the BRAINS Group will come in for a separate visit to repeat the fMRI. At study conclusion, subjects will be debriefed and provided a list of AUD treatment referrals and resources.

Self-report Data Processing. All measures will be double entered, checked for discrepancies, and cleaned. Analyses will assume that 'missingness' occurred at random, with data imputed when necessary.

7.0 Expected Risks/Benefits

There will be no direct benefit to participants for participation in this study, other than they will be compensated for their time for participation in this study. The study will be used to further our knowledge on the potential utility of suvorexant for the treatment of AUD.

Diagnostic/Assessment Procedures: The diagnostic interview and questionnaires are time consuming and may be boring to some individuals. These are, however, necessary in order to determine eligibility for the study and test hypotheses. In addition, questions about alcohol/drug use, abuse/trauma history, and questions related to history of suicidal and/or homicidal behavior may be considered sensitive by some participants. The collection of such data poses a potential risk of loss of confidentiality around sensitive information such as psychiatric status and history of substance abuse. Participants will also be informed in the consent document that confidentiality will be limited in cases where the participant reveals intentions to harm themselves or others, and the investigator feels that the proper authorities may need to be notified in order to prevent the occurrence of harm to the participant, or others. Interviews will be conducted by experienced mental health workers who will maintain confidentiality and all data from interviews and questionnaires will be numbered so as to conceal the identity of the participant.

Tasks: Some subjects may feel anxiety in response to the acoustic startle probes during the startle task. The experience of mild, electrical stimulation during the threat task elicits temporary mild anxiety by design. Any distress experienced while participating in the study is unlikely to persist beyond completion of study procedures. It should be noted that neither the acoustic startle probes nor the electrical stimulation to be used in the study present greater than minimal risk. The startle probe is a 40ms, 103dB burst of white noise – 10,000 times lower than Occupational Safety and Health Administration guidelines for maximum daily acoustic energy exposure for adults. Moreover, studies have used more intense acoustic stimuli with infants with no adverse effects. The electrical stimulation lasts only 400ms, and the maximum stimulation level is 5 mA. This is in the ampere range used by physical therapists and chiropractors, but of a much shorter duration. This level of stimulation presents no risk of physical injury. The PI and/or Co-I will be available during all tasks in order to evaluate and recommend treatment for the emergence of any anxiety/panic attack or elevated levels of anxiety.

Magnetic Resonance Imaging: Magnetic resonance imaging is non-invasive, widely used, and safe. The potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life threatening. Additional minor and/or rare risks include: (a) discomfort or anxiety from being in the confined space of the MRI scanner; (b) fast imaging sequences, such as those employed

in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the subject; (c) risks of hearing damage due to loud noises produced by the scanner; (d) risk that the magnetic resonance image will reveal a minor or significant lesion in the brain, e. g. a tumor, previously unknown to the subject, and requiring additional follow-up; (e) risk of injury from objects accelerated by the strong magnetic field of the magnet, striking the subject; or metallic substances on the skin or foreign bodies implanted deliberately or accidentally in the subject that acquire kinetic or thermal energy from the magnetic or radiofrequency emissions of the MRI, causing tissue injury to the subject; (f) sometimes, subjects report a temporary, slight dizziness or light-headedness when they come out of the scanner; (g) potential risk for pregnant women: According to the NIMH Council Workgroup on MRI Research and Practices (September, 2005), "there is no known risk of MR brain scanning of a pregnant woman to the developing fetus for scanning at 4T or less, and no known mechanism of potential risks under normal operating procedures." Nevertheless, subjects should be warned about potential risks not yet discovered.

Discovery and disclosure of incidental finding or abnormality on MRI scans: During the formal consent process, all subjects will be informed about the potential risks of discovering an incidental finding or abnormality on their MRI scan. The Center for Cognitive and Behavioral Brain Imaging is a research center. It is NOT a Clinical MRI facility in a hospital. There are no neuroradiologists at the Center for Cognitive and Behavioral Brain Imaging, therefore the staff are unable to make any medical comments the scans. However, all structural scans obtained in normal research subjects are sent to a neuroradiologist for review. In addition, participants are given the structural images on a CD. In the event the neuroradiologist detects an abnormality, the Center staff will forward his findings to the participant primary care physician (PCP) within one month of the scan. The participant and PCP will receive information that the neuroradiologist has found some abnormalities that could be potentially significant. This will be communicated by a letter. The neuroradiologist will be available to consult with the PCP if it is necessary. Any costs associated with seeing the primary care physician will be participant responsibility. If participants cannot designate a primary care physician in the MRI Screening Form, they cannot participate in the study. Normal scan results will be available one month after the study and will not be communicated to a primary care physician.

Suvorexant-Related Risks: Suvorexant is a Drug Enforcement Administration (DEA) schedule IV-controlled substance in the United States because it is considered to have abuse liability similar to other approved sleep medications (e.g., zolpidem). Preclinical self-administration studies in rats and monkeys indicate suvorexant does not have positive reinforcing effects[65]. In previous clinical trials there has been no evidence of physical dependence with the prolonged use[66]. There is also no evidence of withdrawal or "discontinuation syndrome" following abrupt discontinuation[66].

Suvorexant is associated with some potential adverse side-effects including: sleepiness or drowsiness, headache, nausea, dizziness, diarrhea, dry mouth, and abnormal dreams. Next day drowsiness is considered the most common side-effect. All

other side-effects have an incidence between 1-10%. Rare but potentially serious side effects include: worsening of depression and increase of suicidal ideation, complex sleep behavior and sleep paralysis, and temporary weakness in legs. Taking a CNS depressant (e.g., benzodiazepines, opioids, some antidepressants and anxiolytics, other sleeping medication) increase the risk of side effects and should not be taken at the same time as suvorexant. Suvorexant should not be taken with grapefruit juice, as this may significantly increase the levels of medication in the blood. Suvorexant should not be taken unless individuals are able to stay in bed for a full night (at least 7 hours) before they must be active again. Individuals should also not drive, operate heavy machinery, or do other activities that require clear thinking immediately after taking suvorexant.

Co-I, Dr. Phan, M.D., is a Board-certified psychiatrist and physician, and will be available during the Acute Drug Challenge and Drug Trial in order to evaluate and/or recommend further evaluation and treatment for the emergence of any adverse events/side effects. Participants taking psychoactive/psychotropic medications or medications that would interact with suvorexant will be excluded. Pregnant participants will be excluded from participation because there is insufficient data to assure safety of the fetus during suvorexant exposure. As well, female participants who are not using acceptable methods of contraceptives or abstinence will be excluded. In addition, nursing mothers will be excluded from the study because the extent to which suvorexant is concentrated and excreted in human breast milk is unknown. Participants will be fully debriefed following the study. During debriefing, any questions participants may have will be answered.

Drug-Alcohol Interactions: To date, there have been at least three human laboratory studies that have directly investigated the pharmacokinetic (PK) and pharmacodynamic (PD) interactions between ethanol and orexin antagonists[67-69]. All three studies used the highest possible dose of orexin-based medication to robustly probe for the potential for ethanol interactions (e.g., 40mg of suvorexant). All three studies confirmed that coadministration with ethanol does not alter the PK of orexin therapeutics, apart from potentially prolonging time to reach maximum plasma concentration (t_{max}) by about 75 mins. There is no effect of orexin therapeutics on the ethanol concentration versus time profile. With regard to PD, co-administration produced additive impairment on measures of sustained attention/vigilance, balance, and working memory. There was no evidence of supra-additive effects. High doses of orexin antagonism alone, and in combination with ethanol, were well tolerated with no severe or serious AEs reported and no observed effects on clinical laboratory or cardiac variables. Mild to moderate treatment emergent adverse events (TEAEs) reported following co-administration included headache, fatigue, and sudden onset of sleep. There was no impact of co-administration on positive or negative mood. All three studies concluded that concomitant use of alcohol and orexin-based antagonists should be avoided due to the potential for additive psychomotor effects; though there are no serious concerns regarding safety and tolerability like with other sleep medications such as hypnotics. Participants will be informed of these risks during informed consent and at the Acute Drug Challenge Visit.

8.0 Data Collection and Management Procedures

- Sources of material from human subjects include: (a) written informed consent, (b) telephone screen form, (c) diagnostic interview, (d) self-report questionnaires, (e) urine drug screen, (f) urine pregnancy test (women only), (g) startle eyeblink data, (h) fMRI data, and (i) EEG data.
- Each subject is given a unique number and there is a password-protected master key database separate from study data linking the subject with the code only accessible to research team members. This file is a password-protected master key database, which links the participant with unique participant codes; it is stored on the password-protected server, and kept separate from study data. The information in this file could be used to *indirectly* identify participants. The record linking participants to the research codes will be destroyed 6 years after completion of the study, thereby anonymizing the data.
- All research materials from participants will be labeled with the unique participant code (not participant name).
- Paper forms with the participant code will be kept in a locked cabinet where only IRB approved key research personnel will have access.
- Data collected during the tasks and fMRI for each participant will be saved with a research identifier number only and stored in computer files without reference to any personally identifiable information. These files will be stored on the lab server. These measurements will be obtained solely for the purposes of research. All research materials will be maintained in strict confidentiality.
- To protect against, or minimize risk associated with participants using smart phones in an unsafe way (attempting to respond to smart phone survey questions while driving a car), participants will be trained to delay responding to the smart phone beeps when it is unsafe (e.g., when driving) or potentially embarrassing (e.g., during a religious service or at the movies). Data collection will be encrypted to prevent access of personally identifiable data should telephones be lost or stolen. The data will be stored on the device itself and can only be accessed by a password system. This means that no one, even the research participant, can see or review entered data.
- When daily clinical assessments are completed, the data will be transferred from the software platform and maintained on secure servers within Center for Human Resource Research (CHRR). CHRR maintains a secure data storage infrastructure. The procedures and infrastructure meet the stringent data protection requirements of the U.S. Census Bureau and the Bureau of Labor Statistics.
- Only IRB approved key research personnel have access to the data. If any member of the research study leaves, his or her access to the network and all files will be removed immediately, thereby terminating access to this file and other files associated with the study.

9.0 Data Analysis

- Startle Data Collection, Processing and Statistical Analysis: Stimuli will be administered using Presentation software (Albany, CA) and data collected using

Biosemi Actiview 2 system. Acoustic startle probes will be 40-ms duration, 103-dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. For the threat task, electric shocks will last 400-ms. Startle responses will be recorded and data collected and processed (e.g., filtering, rectification, smoothing, scoring blinks) according to published guidelines. The startle data will be processed using an interactive 'batch' program that the PI developed in BrainVision Analyzer (BrainProducts). The PI's data indicate that ~7% of blinks are "missing" and thus, we will administer a large number of startle probes (72) to ensure that missing responses do not bias analyses. Consistent with prior studies, we will create startle potentiation scores for U and P, which account for individual differences in baseline reactivity by subtracting responses during the N condition. All variables will be checked for inter- and intra-measure consistency, and frequency distributions will be examined for outliers. Data transformations will be employed as necessary.

- EEG Data Collection, Processing and Statistical Analysis: During the Alcohol Cue Reactivity task we will record continuous electroencephalography (EEG) readings using a 32 channel ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands).The data is recorded off the scalp, non-invasively, while participants are wearing a stretch lycra EEG cap. The EEG signal will be pre-amplified at the electrode to improve the signal-to-noise ratio. The data will be digitized at 24-bit resolution with a Least Significant Bit (LSB) value of 31.25nV and a sampling rate of 1024Hz, using a low-pass fifth order sinc filter with a -3dB cutoff point at 204.8Hz. Off-line analysis will be performed using Brain Vision Analyzer software (Brain Products), using conventional preprocessing steps. Data will be re-referenced to the average of the two mastoids and high-pass (0.1Hz) and low-pass (30Hz) filtered. Data will be segmented around event markers that correspond to the administration of task stimuli. Baseline correction for each trial will be performed and brain activity averages will be computed for each condition, for each task.

- fMRI Data Collection, Processing and Statistical Analysis: All MR scanning will be performed on a 3.0 Tesla GE Discovery MR750 System (Milwaukee, WI) using a state-of-art 8-channel radiofrequency coil and updated software (Discovery 20.0, Neuro-optimized gradients), optimized to reduced susceptibility artifact in the ventral frontal cortex and medial temporal lobe. A high-resolution T1 scan (Bravo 3D IR-prepped fast SPGR: Axial 22 x 22cm FOV, 1mm slice thickness, 13º flip, TI = 450 ms, matrix = 256 x 256 matrix, 186 slices, NEX=0.75, 25kHz rBW, minimum TR/TE [~8-9ms/3-4ms]) will provide precise anatomical localization. Participants will be instructed on tasks and will be acclimated in an MRI simulator. Whole-brain fMRI BOLD-related signal measures will be acquired using a T2*-weighted echo-planar imaging sequence with BOLD contrast (gradient-echo axial EPI with 22 x 22cm FOV, 3 mm slice thickness, 0 gap, TR=2s, TE=minFull [~25ms], 90º flip, 250 kHz rBW, Parallel imaging (ASSET) =ON, Number of Slices: 43+ (optimal for normal coverage), 64 x 64 matrix) to measure task-related effects and designed to minimize susceptibility artifact (signal loss).

- Functional data will be processed and analyzed using conventional methods (GLM, event-related design, random effects) with Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm). Analysis will implement two complementary approaches: 1) a hypothesis-driven, anatomically focused region of interest (ROI)-based analysis; and 2) exploratory whole-brain voxel-wise analysis.
- The Data Analysis Plan for each aim is presented in the "Statistical Considerations" section.

10.0 Quality Control and Quality Assurance

- Please see bullet below for description on how startle and fMRI data is evaluated for adherence with the protocol. As noted above, all self-report data will be double entered, checked for discrepancies, and cleaned. Analyses will assume that 'missingness' occurred at random, with data imputed when necessary. Type 1 error rates will be adjusted using Bonferroni corrections.
- The PI of the study and her research staff are responsible for the monitoring of the research and the evaluation of the data quality. After each session data is transferred to the lab storage drive. The data is closely reviewed to ensure its quality and that nothing is missing.
- Both startle and fMRI data are processed using automated scripts; however, the PI and study staff examine each blink file by hand to ensure acceptability and high-quality data.

11.0 Data and Safety Monitoring

- We have developed a formal data safety and monitoring plan to ensure the ongoing safety of participants (as well as the integrity of the study). The plan involves weekly meetings that will be used to communicate any concerns or issues with safety, confidentiality, or progress.
- Suicidal Ideation: The PI is a clinician and has extensive experience in the assessment of acutely depressed and anxious patient volunteers at screening and in the context of lab assessments. The PI routinely evaluates for suicidal ideation, behavior and risk, and will consult with and closely oversee the clinical monitoring and suicide assessment during the study. If suicidality is endorsed by a participant at any point during the assessment or experimental portion of the study, appropriate steps will be taken. Specifically, the PI or trained study staff member will a) obtain a more detailed assessment of intent, plan and method, including using the gold-standard, empirically-validated Columbia Suicide Severity Rating Scale (CSSRS)[70]; b) discuss the situation with the participant, the participant's emergency contact, and/or members of the mentorship team as warranted; c) consult with the PI and/or CO-Is; and d) make an appropriate treatment referral for the participant. If the PI believes that the participant is in imminent danger, they will call 911 or will walk the participant over to the emergency room at the Ohio State University hospital, only 1 block away.

- Once enrolled, participants who show deterioration between assessment and the lab tasks (e.g., increased anxiety, depression, mania, psychosis, or suicidality) may be removed from the study and referred to our outpatient psychiatry clinic or emergency psychiatric evaluation, if necessary. Participants who are deemed to be at high risk during either the assessment or experimental session may need to be psychiatrically hospitalized. If the CSSRS indicates suicidal thinking or if suicidal behavior is present, or if there is any concern about current suicide risk, the PI will evaluate suicide risk and decide what level of care is sufficient. The PI will then facilitate follow-up visit, Emergency Room/emergency department visit or inpatient admission if necessary.
- Weekly meetings of the research staff of this study will be conducted that will include review of accrual, consenting procedures, protocol adherence, adverse events, and quality control of all data obtained from the study in the previous week. All changes in protocol design will be reviewed by the IRB before such changes in protocol design take place.
- All AEs occurring during the course of the study will be reported to the PI. Serious adverse events (SAEs) will be reported by the PI to the IRB within 5 business days of the PI (or her team's) knowledge of the SAE. Moderate adverse events (AEs) that are unexpected and indicate that the research is associated with a greater risk of harm to participants or others than previously known will be reported to the IRB within 15 business days of the PI's (or her team's) knowledge of the event. All mild AEs and moderate AEs that are expected or are not associated with a greater risk of harm to participants or others than previously known will be reported to the IRB at the scheduled Continuing Review.

12.0 Statistical Considerations

13.0 Aim 1. Does a single dose of SUV decrease reactivity to U-threat? Hypothesis 1: Relative to PBO, SUV will acutely dampen startle reactivity to U-threat, but not P-threat. We will conduct a multilevel mixed model with startle magnitude as the dependent variable. Startle to U-threat and P-threat will be included as a within-subjects factor, to test for specific changes in U-threat. Time (baseline vs. acute challenge) and treatment arm (SUV vs. PBO) will be included as within-subjects and between-subjects factors, respectively, and we expect a time x treatment arm x task condition interaction on startle. Models will include a random effect for participant.

14.0 Aim 2. Does daily use of SUV decrease reactivity to U-threat? Hypothesis 2a: 4-weeks of SUV will result in greater reductions in reactivity to U-threat compared with PBO, and these changes will be specific to U-threat. **Hypothesis 2b**: SUV-related change in U-threat reactivity will be greatest amongst those with higher baseline U-threat reactivity. **Exploratory Analysis**: SUV will similarly result in decreases in aINS and dACC reactivity and connectivity during U-threat relative to PBO, and brain change will correlate with startle change. For H2a, we will conduct a multilevel mixed model that is nearly identical to the model described for H1. However, the time variable will be modeled as baseline vs. post-treatment. For H2b,

we will include baseline startle to U-threat as a predictor in our model and test for a baseline startle by treatment arm interaction. Lastly, for our exploratory fMRI analyses, we will first extract activation and functional connectivity parameter estimates from anatomical aINS and dACC during U-threat (and P-threat) > No-threat contrast maps. fMRI variables will be tested as dependent variables in the model used for H2a. Magnitude of brain change will be directly correlated with magnitude of startle change.

15.0 **Aim 3**. **Does daily use of SUV change alcohol behavior, and is this change linked to brain-behavior U-threat change? Hypothesis 3a:** Daily SUV will result in greater reductions in PHDD and DPDD compared with PBO. **Hypothesis 3b**: SUV-related changes in PHDD and DPDD will be greatest in those with higher U-threat reactivity. **Hypothesis 3c**: In all subjects, changes in brain-behavioral U-threat reactivity will correlate with changes in drinking behavior. For H3a, linear mixed models will be used to assess the impact of treatment arm (SUV vs. PBO) on changes in drinking behavior over the 4-week follow-up period (daily reports). If the assumptions of linear models are violated due to skewed residual errors, we will explore the use of Poisson and negative binomial generalized linear mixed models to model drinking behavior. For H3b, baseline startle potentiation to U-threat (and in secondary models, aINS, dACC, and BNST parameter estimates) will be entered as a covariate/predictor and we will test for a baseline startle to U-threat by treatment arm interaction on drinking behavior outcomes. Lastly, the hypothesis for H3c will be tested using a linear mixed model that includes magnitude of U-threat and P-threat reactivity (startle and brain, separate models), time, and treatment arm as predictors and PHDD and DPDD as the outcomes. We expect a startle by time interaction such that regardless of treatment arm, a change in U-threat reactivity will correspond to a change in drinking behavior.

Sample Size. Our key hypothesis testing involves treatment arm by session interactions on startle eyeblink potentiation. Assuming a medium to large effect size, which is supported by our preliminary data, a sample size of 40 individuals per treatment group would conservatively yield 91% power (a total sample size of 80 individuals). To account for potential screen-fails, participants requesting to drop out of the study, and the PI withdrawing participants due to meeting termination criteria, approval for 120 participants is requested.

13.0 Regulatory Requirements

13.1 Informed Consent

- During the initial assessment, the nature of the research project will be described to participants. A written summary, in lay terms, of the research project will be provided to the participants in the written informed consent document that the participants will review. The consent document will inform

the participants of the voluntary nature of the study procedures, the purpose of the study, the procedures to be followed, the duration of the study, the risks associated with suvorexant, the risks associated with startle and fMRI procedures such as exposure to loud noise bursts, as well as the potential benefits to the community at large. Women will agree that they are not pregnant, nursing, or planning to become pregnant. Participants will be informed that a urine sample for a pregnancy/toxicology screen and a breathalyzer will be obtained at both sessions. Written informed consent will be obtained by the PI or designated research staff and the participant will receive a copy of the signed consent form. Participants will be informed that they can discontinue participation at any time without penalty.

- Each member of the research team will complete the HIPAA and CITI human subjects trainings and will be trained in the research protocol and will have reviewed the informed consent document and assent forms themselves.
- The informed consent document will be stored in a separate locked file cabinet from any other research files in a locked office. Only research staff on this specific research study will have access to the informed consent documents.

13.2 Subject Confidentiality

- All data from subjects will be marked with a research identifier number only and kept in locked cabinets. No data will have subject names on them, except for consent forms, which will be stored separately from other questionnaires in a locked file cabinet. Paper records will be kept in locked file drawers in a locked room, to which only authorized research personnel have access. Confidentiality of subject's records is assured by assigning each subject a research identifier number/code, and such data, as well as fMRI and startle data, are stored in computer files (except for a single tracking file) without reference to name, or any other type of personally identifiable information. Data that may be reported in scientific journals will not include any information that identifies any person as a subject in this study.
- Location and storage of computer files, which will store the startle/fMRI data: These files will be stored on the lab server.
- Single tracking file: This file is a password-protected master key database, which links the participant with unique participant codes; it is stored on the password-protected server, described above, and kept separate from study data. The information in this file could be used to *indirectly* identify participants. Only research study personnel directly involved with the project (e.g., the PI, her research assistants and the project manager) will have access to this file. If any member of the research study leaves, his or her access to the network will be removed immediately, thereby terminating access to this file and other files associated with the study. The record

linking participants to the research codes will be destroyed 6 years after study completion, thereby anonymizing the data.

- Limits of Confidentiality on Clinical Information: Confidentiality is limited, however, when a danger to self or others is present. If the subject is discovered to be acutely homicidal or suicidal during the evaluation period, the subject will be evaluated for hospitalization in a mental health facility (either voluntarily or involuntarily as necessary). If, for whatever reason, the subject is not hospitalized when it is determined that he/she is either homicidal or suicidal (e.g., we receive a phone call from the subject or another person) the police may be alerted to bring the subject to a psychiatric emergency room.
- Confidentiality of Drug Tests Prior to Scans or Assessment:
  The results of the urine drug and pregnancy screens will remain confidential. The only individuals who will have knowledge of the results of these tests are research staff directly working on the project.
- The only PHI we are collecting in this study include the participants name and contact information (phone number, email address, home address). The reasons that we are collecting this information include: the participants name for the informed consent document, phone number and email address to schedule lab appointments.

13.3 Unanticipated Problems

- Any unanticipated problems (its occurrence, frequency or severity is new or greater than previously known or as expected based on subject characteristics, including natural progression of disease). They are always unanticipated by definition and will be reported to the IRB within 5 business days of the PI's (or her team's) knowledge of the event.

14.0 References

1. World Health Organization. (2019). Global status report on alcohol and health 2018. World HealthOrganization.
2. Kranzler, H.R., & Soyka, M. (2018). Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA, 320(8), 815-824.
3. Morley, K.C., Perry, C.J., Watt, J., Hurzeler, T., Leggio, L., Lawrence, A.J., & Haber, P. (2021). New approved and emerging pharmacological approaches to alcohol use disorder: a review of clinical studies. Expert Opinion on Pharmacotherapy, 1-13.
4. Maisel, N.C., Blodgett, J.C., Wilbourne, P.L., Humphreys, K., & Finney, J.W. (2013). Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction, 108(2), 275-293.
5. Agabio, R., Sinclair, J. M., Addolorato, G., Aubin, H. J., Beraha, E. M., Caputo, F., et al. (2018). Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. The Lancet Psychiatry, 5(12), 957-960.
6. Litten, R.Z., Falk, D.E., Ryan, M.L., & Fertig, J.B. (2016). Discovery, development, and adoption of medications to treat alcohol use disorder: goals for the phases of medications development. Alcoholism: Clinical and Experimental Research, 40(7), 1368-1379.
7. Ray, L. A., Bujarski, S., Roche, D.J.O., & Magill, M. (2018). Overcoming the “Valley of Death” in medications development for alcohol use disorder. Alcoholism: Clinical and Experimental Research, 42(9), 1612-1622.
8. Williams, L.M., & Hack, L.M. (2020). A precision medicine–based, ‘fast-fail’ approach for psychiatry. Nature Medicine, 26(5), 653-654.
9. Kranzler, H.R., Smith, R.V., Schnoll, R., Moustafa, A., & Greenstreet-Akman, E. (2017). Precision medicine and pharmacogenetics: what does oncology have that addiction medicine does not? Addiction, 112(12), 2086-2094.
10. Schmitz, A., & Grillon, C. (2012). Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nature Protocols, 7(3), 527-532.
11. Gorka, S. M., Kreutzer, K. A., Petrey, K. M., Radoman, M., & Phan, K. L. (2020). Behavioral and neural sensitivity to uncertain threat in individuals with alcohol use disorder: Associations with drinking behaviors and motives. Addiction Biology, 25(3), e12774.
12. Gorka, S.M., Nelson, B.D., & Shankman, S.A. (2013). Startle response to unpredictable threat in comorbidpanic disorder and alcohol dependence. Drug and Alcohol Dependence, 132(1-2), 216-222.
13. Gorka, S.M., Lieberman, L., Phan, K.L., & Shankman, S.A. (2016). Association between problematic alcohol use and reactivity to uncertain threat in two independent samples. Drug and Alcohol Dependence, 164, 89-96.
24. Gorka, S. M., Hee, D., Lieberman, L., Mittal, V.A., Phan, K.L., & Shankman, S.A. (2016). Reactivity to uncertain threat as a familial vulnerability factor for alcohol use disorder. Psychological Medicine, 46(16), 3349-3358.
15. Moberg, C.A., Bradford, D.E., Kaye, J.T., & Curtin, J.J. (2017). Increased startle potentiation to unpredictable stressors in alcohol dependence: Possible stress neuroadaptation in humans. Journal of Abnormal Psychology, 126(4), 441-453.
16. Moberg, C.A., & Curtin, J.J. (2009). Alcohol selectively reduces anxiety but not fear: startle response during unpredictable versus predictable threat. Journal of Abnormal Psychology, 118(2), 335-347.
17. Hefner, K.R., Moberg, C.A., Hachiya, L.Y., & Curtin, J.J. (2013). Alcohol stress response dampening during imminent versus distal, uncertain threat. Journal of Abnormal Psychology, 122(3), 756-769.
18. Bradford, D.E., Shapiro, B.L., & Curtin, J.J. (2013). How bad could it be? Alcohol dampens stress responses to threat of uncertain intensity. Psychological Science, 24(12), 2541-2549.
19. Moorman, D. E., James, M. H., Kilroy, E. A., & Aston-Jones, G. (2017). Orexin/hypocretin-1 receptor antagonism reduces ethanol self-administration and reinstatement selectively in highly-motivated rats. Brain Research, 1654, 34-42.

20. Dhaher, R., Hauser, S. R., Getachew, B., Bell, R. L., McBride, W. J., McKinzie, D. L., & Rodd, Z. A. (2010). The orexin-1 receptor antagonist SB-334867 reduces alcohol relapse drinking, but not alcohol-seeking, in alcohol-preferring (P) rats. Journal of Addiction Medicine, 4(3), 153.
21. Anderson, R. I., Becker, H. C., Adams, B. L., Jesudason, C. D., & Rorick-Kehn, L. M. (2014). Orexin-1 and orexin-2 receptor antagonists reduce ethanol self-administration in high-drinking rodent models. Frontiers in Neuroscience, 8, 33.
22. Moorman, D. E., & Aston-Jones, G. (2009). Orexin-1 receptor antagonism decreases ethanol consumption and preference selectively in high-ethanol–preferring Sprague–Dawley rats. Alcohol, 43(5), 379-386.
23. Bayerlein, K., Kraus, T., Leinonen, I., Pilniok, D., Rotter, A., Hofner, B., et al. (2011). Orexin A expression and promoter methylation in patients with alcohol dependence comparing acute and protracted withdrawal. Alcohol, 45(6), 541-547.
24. von der Goltz, C., Koopmann, A., Dinter, C., Richter, A., Grosshans, M., Fink, T., et al. (2011). Involvement of orexin in the regulation of stress, depression and reward in alcohol dependence. Hormones and Behavior, 60(5), 644-650.
25. Moorman, D. E. (2018). The hypocretin/orexin system as a target for excessive motivation in alcohol use disorders. Psychopharmacology, 235(6), 1663-1680.
26. Hopf, F. W. (2020). Recent perspectives on orexin/hypocretin promotion of addiction-related behaviors. Neuropharmacology, 168, 108013.
27. Campbell, E. J., Marchant, N. J., & Lawrence, A. J. (2020). A sleeping giant: Suvorexant for the treatment of alcohol use disorder?. Brain Research, 1731, 145902.
28. Lawrence, A. J., Cowen, M. S., Yang, H. J., Chen, F., & Oldfield, B. (2006). The orexin system regulates alcohol-seeking in rats. British Journal of Pharmacology, 148(6), 752-759.
29. Sullivan, J.T., Sykora, K., Schneiderman, J., Naranjo, C.A., & Sellers, E.M. (1989). Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). British Journal of Addiction, 84(11), 1353-1357
30. Sobell, L.C., & Sobell, M.B. (1992). Timeline follow-back. In Measuring alcohol consumption (pp. 41-72). Humana Press.
31. First, M.B., Williams, J.B.W., Karg, R.S., & Spitzer, R.L. (2015). User's guide for the Structured Clinical Interview for DSM-5 Disorders, research version (SCID-5-RV). Arlington, VA: American Psychiatric Association.
32. Babor, T.F., De La Fuente, J.R., Saunders, J., & Grant, M. (1989). AUDIT: The Alcohol Use Identification Test. Guidelines for use in primary healthcare. World Health Organization Geneva, Switzerland.
33. Anton, R. F., Moak, D. H. & Latham, P. (1995). The obsessive compulsive drinking scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcoholism: Clinical and Experimental Research, 19, 92–99.
34. Miller, W. R. (1995). The Drinker Inventory of Consequences (DrInC): An instrument for assessing adverse consequences of alcohol abuse: Test manual (No. 95). US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism.
35. Grant, V.V., Stewart, S.H., O'Connor, R.M., Blackwell, E., & Conrod, P.J. (2007). Psychometric evaluation of the five-factor Modified Drinking Motives Questionnaire—Revised in undergraduates. Addictive Behaviors, 32(11), 2611-2632.
36. Skinner, H. (1982). The Drug Abuse Screening Test. Addictive Behaviors, 7, 363-371.
37. Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, & Sellman D. (2010). An improved brief measure of cannabis misuse: The Cannabis Use Disorders Identification Test-Revised (CUDITR). Drug and Alcohol Dependence, 110, 137-143.
38. Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K.O. (1991). The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. British Journal of Addiction, 86(9), 1119-1127.
39. Beck, A., Steer, R., & Brown, G. (1996). Manual for the BDI-II. Psychological Corporation, San Antonio, TX.

40. Beck, A. T., & Steer, R. A. (1990). Manual for the Beck Anxiety Inventory San Antonio, TX Psychological Corporation.
41. Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of Internal Medicine, 166(10), 1092-1097.
42. Beck, A.T. & Steer, R.A. (1988). Beck Hopelessness Scale manual. San Antonio, TX: The Psychological Corporation.
43. Franken IH, Rassin E, & Muris P. (2007). The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith–Hamilton Pleasure Scale (SHAPS). Journal of Affective Disorders, 99(1-3), 83-89.
44. Weathers, F., Huska, J., & Keane, T. (1991). The PTSD Checklist-Civilian Version (PCL-C). Available from FW Weathers. National Center for PTSD, Boston Veterans Affairs Medical Center, 150, 02130.
45. Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). The life events checklist for DSM-5 (LEC-5).
46. Krueger, R.F., Derringer, J., Markon, K.E., Watson, D., & Skodol, A.E. (2011). Initial construction of a maladaptive personality trait model and inventory for DSM-5. Psychological Medicine, 42, 1879–1890.
47. Beck, A. T., Kovacs, M., & Weissman, A. (1979). Assessment of suicidal intention: The Scale for Suicide Ideation. Journal of Consulting and Clinical Psychology, 47, 343-352.
48. Osman, A., Wong, J. L., Bagge, C. L., Freedenthal, S., Gutierrez, P. M., & Lozano, G. (2012). The depression anxiety stress Scales—21 (DASS-21): further examination of dimensions, scale reliability, and correlates. *Journal of clinical psychology*, 68(12), 1322-1338.
49. Watson, D., O'Hara, M. W., Naragon-Gainey, K., Koffel, E., Chmielewski, M., Kotov, R., & Ruggero,C. J. (2012). Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). Assessment, 19, 399-420.
50. Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., et al. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse & Neglect, 27(2), 169-190.
51. Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research, 28(2), 193-213.
52. Carleton, R. N., Norton, M. P. J., & Asmundson, G. J. (2007). Fearing the unknown: A short version of the Intolerance of Uncertainty Scale. Journal of Anxiety Disorders, 21(1), 105-117.
53. Sala, M. N., Molina, P., Abler, B., Kessler, H., Vanbrabant, L., & van de Schoot, R. (2012). Measurement invariance of the Emotion Regulation Questionnaire (ERQ). A cross-national validity study. *European Journal of Developmental Psychology*, *9*(6), 751-757.
54. Gorka, S. M., Lieberman, L., Shankman, S. A., & Phan, K. L. (2017). Association between neural reactivity and startle reactivity to uncertain threat in two independent samples. *Psychophysiology*.
55. Gorka, S. M., Lieberman, L., Shankman, S. A., & Phan, K. L. (2017). Startle potentiation to uncertain threat as a psychophysiological indicator of fear-based psychopathology: An examination across multiple internalizing disorders. *Journal of Abnormal Psychology*, *126*(1), 8.
56. Gorka, S. M., Lieberman, L., Shankman, S. A., & Phan, K. L. (2017). Startle potentiation to uncertain threat as a psychophysiological indicator of fear-based psychopathology: An examination across multiple internalizing disorders. Journal of Abnormal Psychology, 126(1), 8-18.
57. Gorka, S. M. (2020). Interpersonal trauma exposure and startle reactivity to uncertain threat in individuals with alcohol use disorder. Drug and Alcohol Dependence, 206, 107727.
58. Lieberman, L., Petrey, K., Shankman, S. A., Phan, K. L., & Gorka, S. M. (2020). Heightened reactivity to uncertain threat as a neurobehavioral marker of suicidal ideation in individuals with depression and anxiety. International Journal of Psychophysiology, 155, 99-104.
59. Meyer, A., Lerner, M. D., De Los Reyes, A., Laird, R. D., & Hajcak, G. (2017). Considering ERP difference scores as individual difference measures: Issues with subtraction and alternative approaches. Psychophysiology, 54(1), 114-122.

60. Gorka, S.M., Lieberman, L., Klumpp, H., Kinney, K.L., Kennedy, A.E., Ajilore, O., et al. (2017). Reactivity to unpredictable threat as a treatment target for fear-based anxiety disorders. Psychological Medicine, 47(14), 2450-2460.
61. Schmitz, A., & Grillon, C. (2012). Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). Nature Protocols, 7(3), 527-532.
62. Shahid, A., Wilkinson, K., Marcu, S., & Shapiro, C. M. (2011). Karolinska sleepiness scale (KSS). In *STOP, THAT and one hundred other sleep scales* (pp. 209-210). Springer, New York, NY.
63. Williams, V. S., Morlock, R. J., & Feltner, D. (2010). Psychometric evaluation of a visual analog scale for the assessment of anxiety. *Health and quality of life outcomes*, *8*(1), 1-8.
64. Morean, Meghan E., et al. "The drug effects questionnaire: psychometric support across three drug types." *Psychopharmacology* 227.1 (2013): 177-192.
65. Curran, S. L., Andrykowski, M. A., & Studts, J. L. (1995). Short form of the profile of mood states (POMS-SF): psychometric information. *Psychological assessment*, *7*(1), 80.
65. Born, S., Gauvin, D. V., Mukherjee, S., & Briscoe, R. (2017). Preclinical assessment of the abuse potential of the orexin receptor antagonist, suvorexant. Regulatory Toxicology and Pharmacology, 86, 181-192.
66. Michelson, D., Snyder, E., Paradis, E., Chengan-Liu, M., Snavely, D. B., Hutzelmann, J., et al. (2014). Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. The Lancet Neurology, 13(5), 461-471.
67. Sun, H., Yee, K. L., Gill, S., Liu, W., Li, X., Panebianco, D., et al. (2015). Psychomotor effects, pharmacokinetics and safety of the orexin receptor antagonist suvorexant administered in combination with alcohol in healthy subjects. Journal of Psychopharmacology, 29(11), 1159-1169.
68. Hoch, M., Hay, J. L., Hoever, P., de Kam, M. L., te Beek, E. T., van Gerven, J. M., & Dingemanse, J.(2013). Dual orexin receptor antagonism by almorexant does not potentiate impairing effects of alcohol in humans. European Neuropsychopharmacology, 23(2), 107-117.
69. Berger, B., Brooks, S., Zuiker, R., Richard, M., Muehlan, C., & Dingemanse, J. (2020). Pharmacological interactions between the dual orexin receptor antagonist daridorexant and ethanol in a double-blind, randomized, placebo-controlled, double-dummy, four-way crossover phase I study in healthy subjects. CNS Drugs, 34(12), 1253-1266.
70. Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., ... & Mann, J. J. (2011). The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry, 168, 1266-1277.
71. Pulido, C., Brown, S. A., Cummins, K., Paulus, M. P., & Tapert, S. F. (2010). Alcohol cue reactivity task development. Addictive behaviors, 35(2), 84-90.

Appendices.

Table 1. Administration of Questionnaires for BEHAVIOR Group.

Interviews and Questionnaires	Screening Session	Lab Visit 1: Pre-Tx (EMG #1)	Lab Visit 2: Acute Drug Challenge (EMG #2)	Daily Clinical Assessments	1-Month Follow-up	Lab Visit 3: Post-Tx (EMG #3)
SCID-5 Diagnostic Interview	x					
C-SSRS*	x					
Contact Information Form	x					
NIAAA GUID Information	x					
Health Questionnaire	x					
BMI Questionnaire	x					
Exclusionary Medication Checklist	x					
Medication History Questionnaire (clinician administered)	x					
Psychiatric Treatment History Form (clinician administered)	x					
Demographic Information Form	x					
BDI-II	x				x	
BAI	x				x	
SSI *(timeframe: lifetime)*	x					
IUS	x				x	
GAD	x				x	
ASI	x				x	
BHS	x					
PID-5	x					
DASS-21	x				x	
SHAPS	x					

PSQI	x				x	
IDAS-II	x				x	
ERQ	x					
CTQ-SF	x					
PCL-5	x					
LEC-5	x					
AUDIT	x				x	
Dr-InC	x				x	
DMQ-R	x				x	
OCDS	x				x	
DAST	x				x	
FTND	x				x	
CUDIT	x				x	
TLFB *(timeframe: past 3-months)*		x				
TLFB *(timeframe: since Lab Visit 1)*						x
CIWA-Ar – Clinician Administered		x	x			x
KSS			x *(9 times)*			
VAS			x *(9 times)*			
DEQ			x *(9 times)*			
POMS			x *(4 times)*			
Daily Clinical Assessment Form				x		
**CSSRS will be completed as necessary based upon participant reports of suicidal ideation.*						

Table 2. Administration of Questionnaires for BRAINS Group.

Interviews and Questionnaires	Screening Session	Lab Visit 1: Pre-Tx (EMG #1)	Lab Visit 2: Pre-Tx (fMRI #1)	Lab Visit 3: Acute Drug Challenge (EMG #2)	Daily Clinical Assessments	1-Month Follow-up	Lab Visit 4: Post-Tx (EMG #3)	Lab Visit 5: Post-Tx (fMRI #2)
SCID-5 Diagnostic Interview	x							
C-SSRS*	x							
Contact Information Form	x							
NIAAA GUID Information	x							
Health Questionnaire	x							
BMI Questionnaire	x							
Exclusionary Medication Checklist	x							
Medication History Questionnaire (clinician administered)	x							
Psychiatric Treatment History Form (clinician administered)	x							
Demographic Information Form	x							
BDI-II	x					x		
BAI	x					x		
SSI *(timeframe: lifetime)*	x							
IUS	x					x		
GAD	x					x		
ASI	x					x		
HSP	x					x		
BHS	x							
PID-5	x							
DASS-21	x					x		
SHAPS	x							

PSQI	x					x		
IDAS-II	x					x		
ERQ	x							
CTQ-SF	x							
PCL-5	x							
LEC-5	x							
AUDIT	x					x		
Dr-InC	x					x		
DMQ-R	x					x		
OCDS	x					x		
DAST	x					x		
FTND	x					x		
CUDIT	x					x		
TLFB *(timeframe: past 3-months)*		x						
TLFB *(timeframe: since Lab Visit 1)*							x	
CIWA-Ar – Clinician Administered		x	x	x			x	x
MRI Screening Form			x					x
KSS				x *(9 times)*				
VAS				x *(9 times)*				
DEQ				x *(9 times)*				x
POMS				x *(4 times)*				
Daily Clinical Assessment Form					x			
**CSSRS will be completed as necessary based upon participant reports of suicidal ideation.*								