A NOVEL HUMAN LABORATORY MODEL FOR SCREENING MEDICATIONS FOR ALCOHOL USE DISORDER

STUDY PROTOCOL

NCT #04249882

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1. INTRODUCTION

Alcohol use disorder (AUD), as defined in DSM-5, represents a highly prevalent, costly, and often untreated condition in the United States [1]. Pharmacotherapy offers a promising avenue for treating AUD and for improving clinical outcomes for this debilitating disorder [2]. While developing novel medications to treat AUD remains a high priority research area, there are major opportunities to refine the process of screening novel compounds [3]. To that end, a key question in clinical studies of novel compounds for AUD is how to efficiently determine whether a novel medication has sufficient evidence of initial treatment efficacy to warrant proceeding to clinical trials. The process of screening novel compounds for initial efficacy, known as the early phase 2 of medications development, often consists of human laboratory studies assessing constructs of putative clinical relevance, such as alcohol craving, subjective response to alcohol, and alcohol self-administration under laboratory conditions [2-4]. Nevertheless, these controlled human laboratory models lack the ecological validity of clinical trials in which medication efficacy is established via clinically meaningful endpoints in individuals motivated to change their drinking behavior [5]. The scientific premise of this study is that screening novel AUD medications can be more efficient and clinically meaningful if early efficacy (phase 2) studies combine the internal validity of laboratory testing with the external validity of clinical trials. To that end, we propose to develop and validate a novel early efficacy paradigm informed by the smoking cessation medication development literature [6], to screen AUD medications in humans. Specifically, the proposed early efficacy paradigm consists of a study in which individuals with current AUD reporting intrinsic motivation to change their drinking (i.e., wanting to quit or reduce their drinking within the next 6 months) will complete a week-long “practice quit attempt” while on study medication. The primary outcomes of the practice quit attempt are (a) percentage of days abstinent and (b) drinks per drinking day. The proposed laboratory protocol has been carefully developed and validated for screening smoking cessation pharmacotherapies [6-10]. The objective of this proposal is to develop, refine, and validate this novel approach to screen pharmacotherapies for AUD.

In order to advance this novel early efficacy detection paradigm to AUD medication development, two critical issues were carefully considered: (a) which medication(s) to use and (b) how to best validate the novel procedure against a well-established model. First, we decided that the use of an established, well-known, and FDA-approved medication for AUD would be ideal as a probe of this new model. Thus, we propose to use naltrexone (NTX), a well-known pharmacotherapy for AUD [11]. Second, we decided to include varenicline (VAR), a medication approved for smoking cessation that may have beneficial effects on alcohol use as well [12, 13], as an additional probe of this new model. Third, we believe that having an alcohol cue-reactivity paradigm conducted at each medication condition would allow us to detect medication effects on cue-elicited alcohol craving and in turn validate the sensitivity of the novel paradigm for detecting medication effects. In brief, we propose to test this novel paradigm (i.e., practice quit attempt) in combination with a well-established paradigm (i.e., alcohol cue-reactivity), using an established and well-known pharmacotherapy for AUD (NTX) and an experimental, but promising pharmacotherapy for AUD (VAR).

Building upon the need to develop more effective models for screening novel medications for AUD, we propose a randomized, double-blind, placebo-controlled, 3-arm, parallel-group study. A total of 108 men and women with current AUD (moderate or severe) and reporting intrinsic motivation to change their drinking will be randomly assigned to receive NTX (50 mg QD), VAR (1 mg BID), or matched placebo (PLA). Post-randomization, all participants will complete an alcohol cue-reactivity paradigm prior to the initial dose of study medication. After a week-long medication titration period, participants will be asked to come in to the laboratory to receive their second pack of medication and to begin a 7-day practice quit attempt, during which they will have daily virtual (online and phone) visits where they will report on their alcohol use. Additionally, a second cue-reactivity paradigm and behavioral economics procedure will be conducted 90 minutes following study drug administration on final day of the practice quit attempt (Day 14).

The successful completion of this study will advance medications development for AUD by developing and validating a novel early efficacy model for screening AUD pharmacotherapies, which in turn can serve as an efficient strategy for making go/no-go decisions as to whether to proceed with clinical trials. Specifically, a valid model of initial efficacy will allow us to reliably detect an initial efficacy signal for AUD pharmacotherapies and in turn decide whether to proceed to the full-scale efficacy (Phase 2) testing.

2. BACKGROUND AND SIGNIFICANCE

2.1. Medications for AUD are only modestly effective and developing novel treatments is crucial.

Although treatments for alcoholism have improved in past decades [14], there is still great need to develop more effective interventions. Pharmacotherapies for alcoholism are used less often than psychosocial interventions [15]. The limited use of pharmacotherapy for alcoholism is due, in part, to the relative lack of pharmacological options to treat AUD. The only pharmacotherapies currently approved by the Food and Drug Administration (FDA) for the treatment of AUD are disulfiram (Antabuse®), naltrexone, acamprosate, and Vivitrol, an injectable extended-release formulation of naltrexone. Psychotherapy is generally used more often than these pharmacotherapies [15], but alcohol produces impairments in neurocognitive functioning that are theorized to limit the effectiveness of cognitive-based treatments for many individuals with AUD [16]. Given the potentially limited efficacy of both psychosocial interventions and the available pharmacological treatments, NIAAA has identified medication development for the treatment of AUD as a top research priority and has highlighted the need for the testing of new molecular targets and novel compounds [2, 3, 17]. In line with these research priorities, the proposed project seeks to develop and validate a novel early efficacy model for screening AUD pharmacotherapies.

2.2. Human laboratory models are ideal for screening novel compounds but lack clinical validity.

Human laboratory methods have been proposed as efficient approaches to medications development by simultaneously addressing two important endpoints: (1) safety/tolerability, and (2) medication early efficacy in clinically-relevant phenotypes (e.g. subjective responses to alcohol, cue-induced craving, and alcohol self-administration) [3, 18, 19]. The success of a

human laboratory study with a well-established laboratory paradigm is believed to inform go/no-go decisions regarding large scale clinical trials. For example, it has been proposed that a medication's ability to blunt the positive subjective effects of alcohol (i.e. "block the buzz") or potentiate the aversive aspects of alcohol intoxication predicts clinical efficacy [20, 21]. Supporting this claim is the broad literature linking subjective responses to alcohol and alcoholism etiology [22, 23], as well as the effects of a small number of exemplar medications, most notably naltrexone [24], which blunts the rewarding effects of alcohol and have established, albeit modest, clinical benefit. However, while medication effects in the laboratory are generally believed to predict clinical efficacy, this hypothesis has never been subjected to the rigorous quantitative analysis necessary to establish translational validity. It remains unknown whether medication effects observed in the human laboratory reliably predict clinical efficacy.

The practice quit attempt model used by Perkins and colleagues initially tested FDA-approved smoking cessation medications in order to validate their model [8, 9, 25]. These studies found that in individuals with high motivation to quit, there was a significant increase in number of days abstinent when on active medication compared to placebo; the same pattern of findings was not evident in individuals with low motivation to quit [8, 9, 25]. Further, when modafinil, a medication that has not shown efficacy as a smoking cessation aid, was added as a study arm, they demonstrated model specificity, as bupropion was effective at improving abstinence, while modafinil was not [25]. More recently, Perkins and colleagues have moved to testing novel medications using their practice quit attempt model [26, 27]. They did not find a significant reduction in days abstinent when testing a novel fibrate medication [27] or a novel positive allosteric modulator of nicotinic receptors [26], which provides a critical "no-go" signal for both medications. In summary, the development of the practice quit attempt model for medication development in nicotine dependence provides strong "road map" for the development of a similar approach modified to AUD and strengthens the scientific premise of this study.

2.3. Developing valid and efficient screening paradigms will optimize medication development.

Medications development, particularly for CNS disorders is a cumbersome process, taking nearly 20 years from discovery to market, and costing nearly $2 billion [3, 18]. Alcoholism treatment development appears especially difficult with over 20 medications having been tested in humans yet only three compounds have received FDA approval, the last of which was granted over a decade ago [5]. There is a pressing need to develop valid and efficient methods for shepherding novel compounds from initial discovery and safety testing through RCTs and ultimately approval/dissemination. While traditional human laboratory methods have been proposed to serve these aims, at present no human laboratory method has demonstrated translational validity. To address this central limitation in the alcoholism medications development field, we are proposing to expand the traditional laboratory methodology to more closely mirror actual treatment processes. Through combining a well-established laboratory paradigm (i.e. cue-reactivity), with an abbreviated "practice" quit attempt in intrinsically motivated individuals with AUD, this proposal reduces the conceptual distance between the lab and the clinic, thus reducing the possibility for laboratory effects to "fade" when applied to the clinical context.

2.4. Established medication should be used to test a novel model.

Naltrexone is the most widely studied of the FDA-approved medications for AUD. NTX is an opioid antagonist, with the highest affinity for the mu-opioid receptor. The neurobiological basis for the use of NTX stems from the neurocircuitry through which alcohol exerts its effects [28, 29]. Alcohol increases release of endogenous opioids in the mesolimbic dopamine system contributing to the pleasurable effects of alcohol [28, 29], thus an opioid antagonist is proposed to block these reinforcing effects. Oral NTX was approved by the FDA in 1994 after initial trials suggested that NTX resulted in significantly fewer drinking days and lower rates of relapse, defined as drinking 5 or more drinks on an occasion for men or four or more drinks on an occasion for women (23% relapse rate for NTX versus 54% relapse rate for placebo) following three months of treatment [30, 31]. These initial results have been largely supported by more recent trials of NTX that have generally demonstrated NTX reduces the subjective pleasurable effects of alcohol [32, 33], craving for alcohol [34, 35], drinks per drinking day [36], rates of relapse [37, 38], and time to first relapse [39, 40]. However, the support for NTX is not uniform. A few trials, including a large multisite trial, have reported no significant outcome differences between NTX and placebo treated patients [41-43]. Moreover, the effect sizes of previous findings are often modest even when they reach statistical significance. Extended-release injectable NTX was developed to address poor medication adherence with oral NTX [44]. A multi-site trial of long-acting NTX identified significant reductions in the number of heavy drinking days over a period of 6 months compared to placebo [45]; however this effect was only significant for men [45]. Improvements in drinking outcomes were greater in individuals who were abstinent for at least 4 days prior to randomization [45, 46]. In sum, studies of NTX suggest a moderate effect on the reduction of alcohol use. While we considered using a novel compound and are aware that new studies of NTX are not encouraged by NIAAA, we agree with the comments of the reviewers which argued for the use of an established medication to test the novel paradigm. As such, we propose to use NTX in this study. We would like to clarify that this is not a NTX study per se, but instead is a study of a novel experimental approach to screen pharmacotherapies for AUD and that NTX is used simply because it is a well-known medication, ideal for testing a novel paradigm.

2.5. Varenicline is a promising novel compound for AUD.

Varenicline is a partial agonist at the α4β2 receptor and a full agonist at the α7 nicotinic acetylcholine receptor, and is FDA-approved for smoking cessation. A number of studies have highlighted the role of the nicotinic acetylcholine receptor (nAChR) system in alcohol dependence phenotypes. Studies have suggested that alcohol produces mesolimbic activation through its effects on nAChRs [47-49]. Therefore, there is considerable enthusiasm for varenicline as a possible treatment for alcohol problems. Preclinical studies have found that varenicline decreases ethanol self-administration in rats [50, 51]. Recent human studies of varenicline for alcohol use found that, compared to placebo, varenicline reduced alcohol self-administration in the human laboratory [52], as well as alcohol craving [53] and alcohol consumption [53, 54] in smoking cessation trials. Interestingly, one study found that varenicline increased dysphoria and tended to reduce alcohol liking ratings following a controlled alcohol administration in the laboratory, suggesting that varenicline may potentiate the aversive effects of alcohol [55]. A recent multisite RCT of varenicline in individuals with AUD found that varenicline reduced the percentage of heavy drinking days, and the number of drinks per drinking day and alcohol craving [12]. Together, these studies suggest that varenicline may have beneficial effects on alcohol use. Including varenicline, a widely studied, promising AUD pharmacotherapy as a third arm in this study will enable us to further validate this novel alcohol quit paradigm.

2.6. Medication effects on behavioral economic measures.

The Sponsor's laboratory completed a proof-of-concept study assessing naltrexone efficacy in terms of alcohol demand [45]. Participants were 35 heavy-drinking (AUDIT ≥ 8) Asian Americans. A within-subjects cross-over medication design was used along with an intravenous alcohol challenge completed after four days of both naltrexone and placebo. At baseline and with a BrAC = 0.06 g/dl, participants completed an Alcohol Purchase Task, which assessed estimated alcohol consumption along escalating prices. Results revealed a medication main effect such that naltrexone, relative to placebo, significantly reduced three indices of alcohol demand.

2.7. Varenicline effects on behavioral economic measures.

The laboratory has also conducted a randomized placebo-controlled, crossover study aimed to examine effects of varenicline on cigarette demand using hypothetical cigarette purchase tasks [46]. Non-treatment seeking (n = 37) daily smokers (>10 cigarettes per day) completed a measure of subjective craving for cigarettes and the Cigarette Purchase Task following overnight nicotine abstinence. Participants completed these measures after 10 days on varenicline (1 mg twice per day) and matched placebo. There was a Medication main effect such that varenicline, compared to placebo, reduced maximum expenditure. Taken together, these studies demonstrate the Sponsor's experience in medications development, including the application of behavioral economics. They also suggest that behavioral economic measures are sensitive to the effects of AUD medications.

3. STUDY OBJECTIVES

3.1. Specific Aims

Primary Aim #1: To test whether NTX (50 mg) or VAR (2 mg) results in a (a) higher percentage of days abstinent and (b) lower number of drinks per drinking day during the 7-day practice quit attempt, as compared to placebo.

Primary Aim #2: To test whether NTX (50 mg) or VAR (2 mg) reduces cue-induced craving for alcohol, as compared to placebo. This aim allows us to confirm NTX effects using an established and widely studied paradigm.

Primary Aim #3: In order to validate this early efficacy paradigm, we will test the association between medication effects on cue-reactivity in the laboratory and drinking behavior during the practice quit attempt.

Secondary Aim #1: To determine whether the effects of medication on the multiple-choice paradigm are mediated by changes in discounting or demand for alcohol.

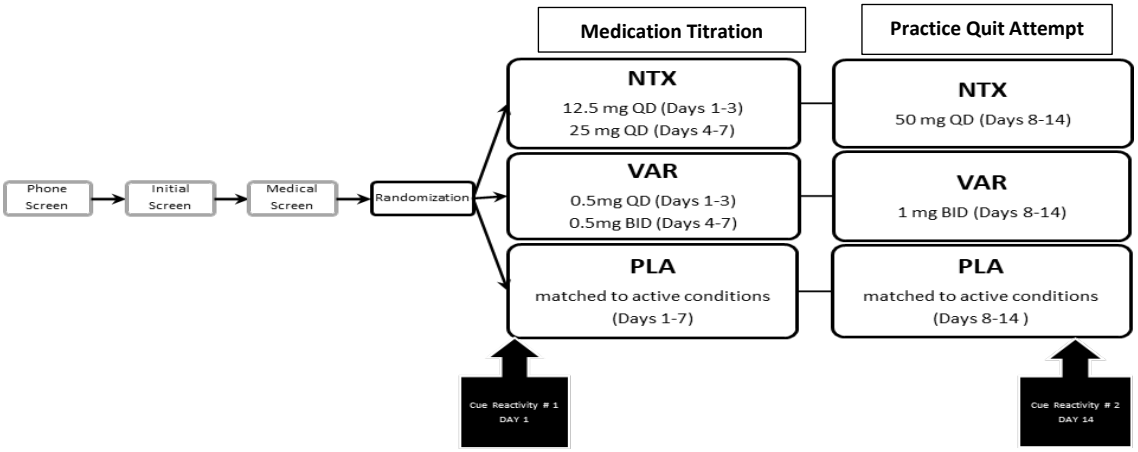
Secondary Aim #2: To determine whether the number of drinks per drinking day and percentage of days abstinent during the practice quit attempt predict alcohol choice.

Exploratory Aim: In order to test medication efficacy, we will directly compare NTX and VAR on percentage days abstinent and number of drinks per drinking day during the 7-day practice quit attempt.

4. STUDY DESIGN

4.1. Design Overview

This study design consists of a randomized, double-blind, placebo-controlled, 3-arm, parallel-group study of naltrexone (50 mg QD) and varenicline (1 mg BID). A total of 108 men and women with current AUD (moderate or severe) and reporting intrinsic motivation to change their drinking, will be randomly assigned to receive naltrexone (50 mg QD), varenicline (1 mg BID) or matched placebo. Post-randomization, all participants will complete an alcohol cue-reactivity paradigm prior to the initial dose of study medication. After a week-long medication titration period, participants will be asked to come in to the laboratory to receive their second medication blister pack and to begin a 7-day practice quit attempt, during which they will have daily virtual (online and phone) visits where they will report on their alcohol use. Additionally, a second cue-reactivity paradigm will be conducted 90 minutes after study drug administration, followed by a behavioral economics paradigm on the final day of the practice quit attempt (Day 14).



5. STUDY PROCEDURES

5.1. Recruitment of Subjects

Participants will be recruited from the community through online and newspaper advertisements. Campaigns in local buses and print publications (e.g., LA Weekly) will also be implemented. Targeted recruitment will also take place through a lab database of previous study participants who agreed to be contacted for future studies.

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

To be included in the study, participants must:
(1) Be between the ages of 21 and 65
(2) Meet current (i.e., past 12-month) DSM-5 diagnostic criteria for AUD moderate or severe
(3) Have intrinsic motivation to reduce or quit drinking (defined as self-reported intention to reduce or quit drinking within the next 6 months)

(4) Report drinking at least 14 drinks per week if male (7 drinks per week if female) in the 28 days prior to the initial consent
(5) Have reliable internet access

5.2.2. Exclusion Criteria

To be included in the study, participants must not:
(1) Have a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine
(2) Have a lifetime DSM-5 diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder
(3) Have a positive urine screen for drugs other than cannabis
(4) Have clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-R)
(5) Have an intense fear of needles or have had any adverse reactions to needle puncture
(6) Be pregnant, nursing, or planning to become pregnant while taking part in the study; and must agree to one of the following methods of birth control (if female), unless she or partner are surgically sterile:
- Oral contraceptives
- Contraceptive sponge
- Patch
- Double barrier
- Intrauterine contraceptive device
- Etonogestrel implant
- Medroxyprogesterone acetate contraceptive injection
- Complete abstinence from sexual intercourse
- Hormonal vaginal contraceptive ring

(7) Have a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes)
(8) Be currently taking any psychotropic medications that, in the opinion of the investigators, compromises participant safety
(9) Be currently taking either naltrexone or varenicline
(10) Have any other circumstances that, in the opinion of the investigators, compromises participant safety

5.3. Screening Phase

5.3.1. Telephone Screen

Individuals who call the lab (in response to flyers and advertisements) expressing interest in the study will receive detailed information about the study procedures, and if they remain interested they will complete a telephone screen performed by a trained research assistant for self-reported inclusion and exclusion criteria. Those who appear eligible will be invited to the laboratory for an initial in-person screening session.

5.3.2. Initial Screening Visit

Prior to conducting any research related procedures, research staff will conduct the informed consent process, which details the procedures to take place during the screening visit.

Informed consent will be a three-part process. First, participants will be asked to read and provide verbal consent for breathalyzer. If the breathalyzer is above 0.000, the visit will be stopped and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the written informed consent form will be reviewed and signed by the participant and study staff outlining procedures for the initial screening visit. A second written consent form will be reviewed and signed in the presence of the study physician at the medical screening visit if the participant is found eligible to continue to that visit.

At the initial screening visit, subjects will be asked to provide a urine sample to test for drugs of abuse and pregnancy (if female), and will complete a series of questionnaires and interviews (described in detail below) to determine initial eligibility. This visit will take approximately 1 hour.

Following the initial in-person screening, the study coordinator will meet with the PI to determine if the participant is eligible to continue to the medical screening based on study inclusion/exclusion criteria.

5.3.3. Medical Screening Visit

Those participants who appear to be eligible after the initial screening visit, will then be scheduled for a second screening visit, which will start with a breathalyzer test administered by study staff. If the breathalyzer is above 0.000, the visit will be stopped and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the physician or nurse practitioner will conduct the second written (experimental) consent. The experimental consent process will be conducted in person or remotely via the UCLA HIPAA-compliant Zoom meeting platform. In cases where the web-based consent process occurs, both participant and physician will provide electronic signatures on the consent form via DocuSign, following guidance set forth by the UCLA Compliance Office. After informed consent, the physician will conduct a medical history interview and physical exam. In addition, a urine sample will be obtained for repeat drug screen and pregnancy tests. The participant will then be accompanied by research personnel to the CTRC for blood specimen collection including Comprehensive Metabolic Panel and Complete Blood Count to evaluate overall health; and EKG to screen for medical conditions that could make study participation medically unsafe. The study physician will review each participant's medical history, vital signs, weight, review of systems, and laboratory tests, including liver function tests (LFTs), drug screen, chemistry screen, and urine pregnancy screen to determine if it is medically safe for the participant to take the study medication.

Any subject who is excluded from the study will be compensated for their time in the screening session and will be offered referrals for alcohol treatment in the community.

5.4. Medication Phase

5.4.1. Randomization and Medication Titration

Participants who are eligible after the physical exam will be randomized to one of three treatment conditions (VAR, NTX, or PLA). Urn randomization will be used to balance the groups by gender, smoking status (as reported on question 1 of the Fagerstrom Test for Nicotine Dependence), and drinking status ('heavy' drinker defined as 14 or more drinks per week for

males/7 or more drinks per week for females, or 'very heavy' drinker, defined as 35 or more drinks per week for males/28 or more drinks per week for females). The UCLA Research Pharmacy will manage the blind. The three treatment conditions will not be different in appearance or method of administration. All participants will undergo a week-long medication titration period prior to the onset of the practice quit attempt.

5.4.2. Practice-Quit Attempt

During the practice-quit attempt, participants will be instructed to abstain completely from drinking alcohol during a 7-day practice quit period. This period will begin on Day 8 of study medication dosing. During this period, participants will complete daily online and phone visits to report on their drinking, mood and craving for alcohol during the previous day in a daily diary assessment (DDA). For each virtual visit, participants will be contacted over the phone by research staff. Participants will first be asked about adverse events (open-ended) and about use of concomitant medications. Research staff will then administer the CIWA-Ar to measure alcohol withdrawal. Next, they will ask participants to report on their past day drinking as well as cigarette and marijuana use. Finally, while participants are still on the phone, research staff will send a link to the daily diary assessment (administered via Qualtrics). Research staff will request that participants' report the completion of this assessment via phone call or text message. Upon confirmation of assessment completion, staff will schedule a time for the following day's virtual visit. Depending on interest and eligibility, participants may be asked to wear a sleep tracking wristband during the 7-day practice quit period. Participants will be reminded to sync wristband data to an app during the daily calls and instructed to only use the wristband for sleep tracking purposes. Staff will also request a picture of the medication blister pack to monitor medication compliance. This procedure has been designed to maintain study integrity while reducing participant safety burden by limiting direct, in-person contact.

5.4.3. Study Medication

On Day 1, participants will report to the laboratory to complete the alcohol cue-reactivity paradigm and receive their first medication dose under direct observation of study staff. They will receive a 7-day supply of study medication in blister packs with AM and PM dosing clearly distinguished for the titration procedure. After reaching full medication dose at the end of one week, participants will come to the laboratory on Day 8 to receive their second, 7-day supply of study medication and to begin the 7-day practice quit attempt. Participants will be asked to take AM dose of study medication on Day 8 in the lab under direct observation of study staff. All study medication will be prepared by the UCLA Research Pharmacy and will be identically matched in appearance (opaque capsules) and the medication labels will not reveal the drug identity.

5.4.3.1. Dosing Schedule

Group:	**NTX**		**VAR**		**PLA**	
Day:	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
Medication Titration						
1	1 capsule (12.5mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)	1 capsule (placebo)
2	1 capsule (12.5mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)	1 capsule (placebo)
3	1 capsule (12.5mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)	1 capsule (placebo)

4	1 capsule (25mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)
5	1 capsule (25mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)
6	1 capsule (25mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)
7	1 capsule (25mg NTX)	1 capsule (placebo)	1 capsule (0.5mg VAR)	1 capsule (0.5mg VAR)	1 capsule (placebo)	1 capsule (placebo)
Practice Quit Attempt						
8	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
9	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
10	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
11	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
12	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
13	1 capsule (50mg NTX)	1 capsule (placebo)	1 capsule (1mg VAR)	1 capsule (1mg VAR)	1 capsule (placebo)	1 capsule (placebo)
14	1 capsule (50mg NTX)	-	1 capsule (1mg VAR)	-	1 capsule (placebo)	-

5.4.4. Alcohol Cue Reactivity Sessions (CR)

Randomized participants will complete a cue-exposure paradigm at two time points during the study, once on Day 1 prior to ingesting the first dose of study medication, and again on Day 14, approximately 90 minutes after study drug administration. Alcohol cue exposure will follow well-established experimental procedures. Sessions will begin with a 3-minute relaxation period. Participants will then hold and smell a glass of water for 3 minutes to control for the effects of simple exposure to any potable liquid. Next, participants will hold and smell a glass of their preferred alcoholic beverage for 3 minutes. Order is not counterbalanced because of carryover effects that are known to occur. Participants (who are smokers) will be allowed a smoke break immediately prior to the CR assessment. After every 3 minutes of exposure, participants will rate their urge to drink on the Alcohol Urge Questionnaire (AUQ) and their mood on the Profile of Mood States (POMS). AUQ score (alcohol minus water) is the primary outcome for the CR.

5.4.5. Behavioral Economics Procedure

Participants will complete the behavioral economic protocol at the final day of the practice quit attempt (Day 14). Specifically, the multiple-choice procedure and measures will be completed after the cue-reactivity procedure in order to maintain the scientific integrity of the trial. The primary behavioral economic measure is the multiple-choice protocol. The multiple-choice protocol consists of choices between immediate alcohol (a single standard-sized drink of the participant's preferred alcoholic beverage, available today) and 17 delayed monetary reward amounts in the form of cash or electronic gift card (1¢, 5¢, 10¢, 25¢, 50¢, $1, $1.50, $2, $3, $4, $5, $6, $8, $10, $15, $20, and $30, available after one week). Participants will receive one randomly selected choice from the multiple-choice protocol. Participants will select a poker chip from a bowl containing chips pertaining to all of their choices on the multiple-choice protocol. A computerized random number generator program may be used in lieu of the poker chips if COVID safety regulations require. If the participant's choice on that item is for alcohol, they will receive one standard drink at that moment. If their choice is for the delayed money, they will

receive the money in cash or electronic gift card after one week. All participants will remain in their respective visit room for a 15-minute consumption period. Participants who receive alcohol are permitted to consume their beverage during this time. This will be followed by a recovery period in a laboratory lounge. The order of presentation will be multiple-choice procedure, hypothetical delay discounting task (Monetary Choice Questionnaire), and the hypothetical purchase task (Alcohol Purchase Task). Completion of the multiple-choice paradigm and hypothetical measures will take approximately 30 minutes. All participants will be required to stay in the laboratory for at least 1.5 hours after completing measures and the multiple-choice procedure. This will be done to standardize the procedure and prevent participants from choosing money instead of alcohol to limit the amount of time spent in the laboratory. Participants will be required to remain in the laboratory until BrAC reaches 0.00 g/dl.

5.4.6. Brief Counseling Session

All participants will meet in-person or via an online platform with a trained study counselor briefly after the behavioral economics procedure, either on Day 14 or scheduled on a separate day shortly after the Day 14 visit depending on participant and counselor availability. This brief intervention draws from motivational interviewing and SBIRT models. It uses the therapeutic stance of motivational interviewing which is collaborative and client-centered. Consistent with the literature on brief intervention, the therapist will seek opportunities to engage in- and to amplify change talk. Together, the combination of evidence-based practices and principles applied to AUD, coupled with the experience of change in the context of study participation, is expected to result in an opportunity for health behavior change (i.e., reductions in alcohol use).

5.5. Compensation for Participation

Participants will be compensated up to $325 for their time and effort as follows:

Initial Screening:	$40	Day 11 Online Visit:	$5
Medical Screening:	$40	Day 12 Online Visit:	$5
Cue-Exposure #1:	$20	Day 13 Online Visit:	$5
Day 1 In-person Visit:	$30	Day 14 In-person Visit:	$30
Day 8 In-person Visit:	$50	Sleep Tracking Wristband:	$20
Day 9 Online Visit:	$5	Cue-Exposure #2:	$20
Day 10 Online Visit:	$5	Completion Bonus:	$50

In addition, participants will have the opportunity to earn between 1¢ and $30 in the form of cash or electronic gift card one week after the behavioral economics paradigm described above. All participants will be provided with free parking validation, round-trip bus fare or transportation via Uber for attendance to each study visit. Participants are free to discontinue participation at any time and will receive compensation for the amount of time they participated. The completion bonus will be given to participants who complete at least 7 of the 8 in-person and online study visits.

6. ASSESSMENTS

6.1. Schedule of Assessments Table

STUDY VISIT:	Initial Screening	Medical Screening	CR Sessions (Days 1 & 14)	Randomization (Day 1)	Practice Quit (Days 8-14)
SCREENING/INDIVIDUAL DIFFERENCE MEASURES:					
Alcohol Dependency Scale (ADS)				x	
Beck Anxiety Inventory (BAI)				x	x*
Beck Depression Inventory (BDI)				x	x*
Brief AUD Severity Scale				x	
Cannabis Use Disorder Identification Test (CUDIT)				x	
Demographics	x				
Fagerstrom Test for Nicotine Dependence (FTND)	x				
Family Tree Questionnaire (FTQ)				x	
Graded Chronic Pain Scale				x	
ImBIBe				x	
Inventory of Drinking Situations (IDS)				x	
Locator Form	x				
Monetary Choice Questionnaire (MCQ)				x	x*
Obsessive Compulsive Drinking Scale (OCDS)				x	x*
Penn Alcohol Craving Scale (PACS)				x	x*
Perceived Stress Scale (PSS)				x	
Pittsburgh Sleep Quality Index (PSQI)				x	x*
Readiness to Change (RTC) Ladder				x	
Self-Report Habit Index (SRHI) Drinking & Smoking				x	
Structured Clinical Interview for DSM-5 Screener & AUD Module	x				
Timeline Follow Back (TLFB)	x	x		X	x
UCLA Reward Relief Habit Drinking Scale (UCLA RRHDS)				X	
UPPS-P Impulsive Behavior Scale				X	
SAFETY MEASURES/BIOMARKERS:					
Adverse Events/SAFTEE					x
Alcohol Breathalyzer	x	x	x	X	x
Birth Control Assessment	x				
Clinical Institute Withdrawal Assessment (CIWA-AR)	x	x		X	x
Columbia Suicide Severity Rating Scale (C-SSRS)	x				
Comprehensive Metabolic Panel/Complete Blood Count		x			
Concomitant Medications	x	x		X	x
Electrocardiogram (EKG)		x			
Medical History/Physical Exam		x			
Urine Ethyl Glucuronide (EtG) Test					x
Urine Drug Screen	x	x		X	
Urine Pregnancy Test	x	x		X	x*
Vital Signs	x	x		X	x
EXPERIMENTAL MEASURES:					
Alcohol Purchase Task (APT)					x*
Alcohol Urge Questionnaire (AUQ)			x		
Daily Diary Assessment					x
Multiple Choice Procedure (MCP)					x*
Profile of Mood States (POMS)			x		

Sleep Tracking Wristband					x

*Measure collected on Day 14 only

6.2. Description of Assessments

6.2.1. Alcohol Dependency Scale

The Alcohol Dependency Scale is a 25-item scale that measures alcohol dependence symptoms over the past 12 months. The ADS is a self-report measure that assesses problems that are relevant for alcohol dependent drinkers and will be completed by the participant electronically at the randomization visit.

6.2.2. Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI) surveys anxiety symptomatology including physical and cognitive indicators of anxious mood. The BAI will be completed electronically at the randomization and final (Day 14) visit.

6.2.3. Beck Depression Inventory (BDI-II)

The Beck Depression Inventory, Revised (BDI-II) captures depressive symptomatology. The BDI-II will be completed at the Day 1 (randomization), and Day 14 visits.

6.2.4. Brief AUD Severity Scale (BASS)

The Brief AUD Severity Scale (BASS) is a 9-item self-report measure used to assess alcohol use disorder severity. The BASS will be completed at the randomization visit.

6.2.5. Cannabis Use Disorder Identification Test (CUDIT)

The Cannabis Use Disorder Identification Test (CUDIT) is an 8-item measure used to screen for cannabis use disorders (CUD) and will be completed at the randomization visit.

6.2.6. Demographics

Demographics data include the participant's age, gender, race/ethnicity, marital status, education, employment pattern, occupation, and income level. This questionnaire will be administered electronically at the initial screening visit.

6.2.7. Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Test for Nicotine Dependence will be used to assess smoking status at the initial screening visit. This questionnaire will be completed by the subject electronically.

6.2.8. Family Tree Questionnaire (FTQ)

Information on family history of alcohol problems will be collected using the Family

Tree Questionnaire. The questionnaire provides subjects with a family tree listing of relatives to identify blood relatives with alcohol problems. This questionnaire will be completed by the subject electronically at the randomization visit (Day 1).

6.2.9. Graded Chronic Pain Scale

The Graded Chronic Pain scale is a 7-item measure used to evaluate an individual's overall severity of chronic pain if they have suffered from chronic pain that has lasted at least six months. The measure assesses on two dimensions: pain severity, and pain-related disability. This questionnaire will be completed by participants electronically at the randomization visit.

6.2.10. ImBIBe

The ImBIBe is a 15-item questionnaire in which the subject responds on a 5-point scale responses to questions on the consequences of alcohol use. The ImBIBe will be completed at the randomization visit (Day 1).

6.2.11. Inventory of Drinking Situations (IDS)

The Inventory of Drinking situations (IDS) is a questionnaire developed to characterize the particular high-risk situations of a problem drinker. The IDS will be completed by the participant electronically at the randomization visit.

6.2.12. Locator Form

The Locator Form asks participant to provide his/her name, address, and phone number and to provide names, addresses, and phone numbers of friends and family members who can be contacted if the subject cannot be located. This information is essential and will be collected during the initial screening, and will be updated throughout the study as necessary.

6.2.13. Monetary Choice Questionnaire (MCQ)

The Monetary Choice Questionnaire is a 27-item self-administered questionnaire in which the participant chooses between a smaller, immediate monetary reward and a larger, delayed monetary reward. The MCQ will be completed at randomization and Day 14 visit, as part of the behavioral economics paradigm.

6.2.14. Obsessive Compulsive Drinking Scale (OCDS)

The 14-item Obsessive Compulsive Drinking Scale (OCDS) is a quick and reliable self-rating instrument that provides a total and two subscale scores that measure some cognitive aspects of alcohol craving. The OCDS will be completed at the randomization and Day 14 visits.

1.1.1. Penn Alcohol Craving Scale (PACS)

The PACS is a five-item, self-report measure that includes questions about the frequency, intensity, and duration of craving, the ability to resist drinking, and asks for an overall rating of craving for alcohol for the previous week. Each question is scaled from 0 to 6. Participants will complete this scale at randomization and Day 14.

1.1.2. Perceived Stress Scale (PSS)

The PSS is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The PSS will be completed at randomization.

1.1.3. Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a self-report questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce one global score, and takes 5-10 minutes to complete. The PSQI will be completed at the randomization and Day 14 visits.

1.1. Readiness to Change (RTC) Ladder

The Readiness to Change Ladder is a measure with 11 response items designed to assess motivation to reduce or cut back on drinking. This assessment will be completed at the randomization visit.

1.1.1. Self-Report Habit Index Form (SRHI)

The Self-Report Habit Index (SRHI) is an instrument that measures self-reported perceptions of habit strength for an identified behavior. In addition to measuring prior behavior and automaticity, the SRHI measures identity expression as a component of habit. The SRHI will be assessed for drinking and smoking and will be completed at the randomization visit.

1.1.4. Sleep Tracking Wristband

The Fitbit Charge 5 is a health tracker used as a passive sleep tracking device. Interested participants will be asked to wear the sleep tracking wristband every night during the practice quit attempt (Days 8 – 14). Sleep data from the previous day will be synced to the Fitbit app every day.

1.1.5. Structured Clinical Interview for DSM-5 Disorders

The SCID is a semi-structured interview for making the major DSM-5 diagnoses. The SCID screener assessment and alcohol module, used to assess current (past 12-month) AUD diagnosis will be completed by appropriately trained research personnel. Any positive responses on the SCID screener will be further assessed by the study physician to determine eligibility.

1.1.6. Timeline Follow Back (TLFB)

The Time Line Follow Back will be administered to assess quantity and frequency of alcohol, cigarette and marijuana use and will be completed at the initial screening (for the 30 days prior to that visit) and at each subsequent visit, including phone visits, to gather data for every day prior to and including the last visit. Information obtained in this interview will be recorded on the TLFB Calendar and transcribed to the database.

1.1.7. UCLA Reward Relief Habit Drinking Scale (UCLA RRHDS)

The UCLA RRHDS is a 4-item self-report questionnaire to assess reward, relief and habit drinking sub-types. It will be completed electronically at the randomization visit.

1.1.8. UPPS-P Impulsive Behavior Scale

The UPPS-P Impulsive Behavior Scale is a 59-item self-report that assesses five subscales (urgency, premeditation, perseverance, sensation seeking, and positive urgency) that are used to measure 5 distinct dimensions of impulsive behavior. This measure will be completed electronically at the randomization visit.

1.1.9. Adverse Events/SAFTEE Assessment

On each day of the practice-quit attempt (Days 8-14) participants will be asked by study staff if they have experienced any symptoms or side effects since the last visit. With guidance from the study physician, each participant response will be coded into one of the listed items on the SAFTEE (Systematic Assessment of Treatment Emergent Effects).

1.1.10. Alcohol Breathalyzer

An alcohol breathalyzer will be administered at consent, and at every in-person study visit as a safety measure. BrAC must be equal to 0.000 prior to performing any study assessments. Results will be recorded on the paper checklist, and later entered into the database.

1.1.11. Birth Control Assessment

The Birth Control Assessment is designed to confirm a female subject's compliance with the birth control specifications detailed in the inclusion criteria. Birth Control Assessment information will be recorded on the checklist at the initial screening visit for participant safety purposes.

1.1.12. Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

The CIWA-AR is a brief 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome. The CIWA-AR has been used both in clinical and research applications and has demonstrated both reliability and validity. This questionnaire will be administered by appropriately trained staff during the initial and medical screening, and at each visit during the medication phase. Participant responses will then be entered electronically.

1.1.13. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 4-page form asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute. This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia University Medical Center. Those completing the training are certified to administer the C-SSRS, and will receive a training certificate. This scale will be used to assess current

suicidal ideation at each visit and will be administered at the initial screening visit by a trained staff member with responses recorded on paper first, then entered electronically.

1.1.14. Comprehensive Metabolic Panel/Complete Blood Count

Blood will be drawn for a comprehensive metabolic panel and complete drug count during the medical screening to assess for participant safety. The total blood volume to be collected is approximately 8 mL. Additional laboratory samples may be taken at the discretion of the study physician if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety.

1.1.15. Concomitant Medications

All medications taken by the participant 2-weeks prior to the start of screening and through the final visit, collected via participant self-report will be recorded on a source document and later entered electronically.

1.1.16. Electrocardiogram (EKG)

A 12-lead resting EKG will be obtained at the medical screening visit to assess for medical safety. Any abnormalities will be noted and an assessment of clinical significance will be made by the study physician.

1.1.17. Medical History

A Medical History interview will be conducted by the study physician at the medical screening visit and will screen for medical conditions that would make participation unsafe.

1.1.18. Physical Exam

A physical examination of the oral cavity, head, eyes, ears, nose, and throat, cardiovascular system, lungs, abdomen, extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed during the medical screening visit.

1.1.19. Urine Ethyl Glucuronide Test (EtG)

The ethyl glucuronide (EtG) test is widely used to detect the presence in the urine of ethyl glucuronide, a breakdown product of ethanol, the intoxicating agent in alcohol. A urine EtG test will be conducted during the practice quit attempt on day 8 and day 14 to assess for recent alcohol use.

1.1.20. Urine Drug Screen

An FDA cleared, CLIA waived urine drug test card will be used at all visits to assess for recent use of opioids, cocaine, amphetamines, methamphetamine, THC, buprenorphine, methadone or benzodiazepines. Subjects must be negative for all substances except THC. Results will be recorded on the visit checklist first and then entered into the database.

1.1.21. Urine Pregnancy Test

An FDA approved rapid result urine pregnancy test will be used (i.e., dipstick test) to assess for pregnancy in female participants at each screening visit and on Day 1 and Day 14 of the medication phase. If applicable, participants will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study.

1.1.22. Vital Signs

Vital signs include sitting blood pressure, pulse rate (after sitting for at least 3 minutes) and weight. Values will be recorded on the visit checklist and entered into the database. Vital signs will be collected at every in-person visit.

1.1.23. Alcohol Purchase Task (APT)

The Alcohol Purchase Task (APT) will be used to assess state-level alcohol demand during the behavioral economics paradigm at Day 14. The APT is a hypothetical assessment wherein participants report how many standard drinks they would immediately consume at 17 price points: free, 5¢, 10¢, 25¢, 50¢, $1, $1.50, $2, $3, $4, $5, $6, $8, $10, $15, $20, and $30. A hypothetical APT will be used given evidence that derived alcohol demand indices correlate with both self-reported drinking measures and alcohol consumption during actual purchase tasks.

1.1.24. Alcohol Urge Questionnaire (AUQ)

The Alcohol Urge Questionnaire (AUQ) is comprised of eight items rated on a 7-point Likert scale with items related to the subjective experience of alcohol craving. The AUQ has demonstrated high reliability in experimental studies of state alcohol craving and will be completed after every 3 minutes of exposure during the cue exposure paradigm on Days 1 and 14.

1.1.25. Daily Diary Assessment (DDA)

Participants will complete daily diary assessments reporting on their mood, alcohol and cigarette craving, motivation to change, self-efficacy, pain, and drinking behavior from the previous day. Participants will complete the DDA electronically during the practice quit attempt (days 8-14). Research staff will distribute the link to the online daily diary assessment during each in-person and virtual visit.

1.1.26. Multiple Choice Procedure (MCP)

The Multiple Choice Procedure (MCP) is the primary behavioral economic measure. The multiple-choice protocol consists of choices between immediate alcohol (a single standard-sized drink of the participant's preferred alcoholic beverage, available today) and 17 delayed monetary reward amounts (1¢, 5¢, 10¢, 25¢, 50¢, $1, $1.50, $2, $3, $4, $5, $6, $8, $10, $15, $20, and $30, available after one week). Participants will receive one randomly selected choice from the multiple-choice protocol. Participants will select a poker chip from a bowl containing chips pertaining to all of their choices on the multiple-choice protocol. A computerized random number generator program may be used in lieu of the poker chips if COVID safety regulations

require. If the participant's choice on that item is for alcohol, they will receive one standard drink at that moment. If their choice is for the delayed money, they will receive the money in cash after one week. All participants will remain in their respective visit room for a 15-minute consumption period. Participants who receive alcohol are permitted to consume their beverage during this time. This will be followed by a recovery period in a laboratory lounge.

1.1.27. Profile of Mood States (POMS)

The POMS measures dimensions of mood and will be completed during the cue reactivity sessions.

2. SAFETY MONITORING PLAN

Safety monitoring will be conducted throughout the study; therefore, safety concerns will be identified by continuous review of the data by the PI and study physician, internal quality assurance checks, and DSMB.

2.1. PI and Study Physician Safety Monitoring

Participants will be given a 24-hour telephone number for calling the physician to discuss side effects, and physician office hours will be available as needed. Adverse events, including signs of sickness will be collected in an open-ended way at each in-person and phone study visit. Vital signs will be monitored at multiple time points during the experimental study visits. Alcohol withdrawal will be monitored at each visit through administration of the CIWA, and any significant withdrawal, as indicated by a score of 10+ on the CIWA will be reported to the study physician immediately. In the event that significant medical problems are encountered, the study blind will be broken and appropriate medical treatment will be provided.

2.2. Internal Quality Assurance Monitoring

The PI will designate appropriately qualified personnel to periodically perform quality assurance checks at mutually convenient times during and after the study. These monitoring visits provide the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitor will assure that data are accurate and in agreement with any paper source documentation used, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, verify that study procedures are being conducted according to the protocol guidelines, monitor review AEs and SAEs, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed. At the end of the study, they will confirm that the site has the appropriate essential documents on file, and advise on storage of study records.

3. STATISTICAL METHODS AND POWER CONSIDERATIONS

3.1. Statistical Power

Power analyses were conducted using G*Power 3.1.9.2. In order to conduct a one-way ANOVA with fixed effects, we estimated a medium-to-large effect size (f=0.40 and an alpha error probability of 0.05). Specifically, with 3 groups a sample size of 90 completers, the proposed

study has an actual power of 0.91%. Therefore, we propose to randomize 108 individuals (36 in each group) to reach a final sample of 30 completers per group. This will allow us the statistical power to detect a medium-to-large effect size as projected.

3.2. Data Analytic Plan

Descriptive statistics will be computed for continuous outcome variables, and frequencies for categorical variables to summarize the study data. Box plots, histograms, and Q-Q plots will be used to check for skewness and normality for continuous variables. Transformations of continuous outcome variables will be performed as necessary to ensure that the normality assumptions in parametric tests are met. The models described below will test whether medication effects in reducing drinking behavior during the practice quit attempt are associated with concurrent blunting of cue reactivity. To improve model fit and hypothesis testing, we will consider covariates, such as age, sex, ethnicity, medication order, and AUD symptom count.

3.2.1. Primary Aim 1: To test that NTX and VAR will reduce drinking during the practice quit attempt as compared to placebo.

A series of repeated measures ANCOVAs will be conducted using PROC GLM in SAS Statistical Software. Specifically, we will conduct repeated measures ANCOVAs on Percent Days Abstinent (PDA), and Drinks per Drinking Day (DPDD), our two co-primary outcomes, as predicted by Medication (NTX vs. PLAC and VAR vs. PLAC) a between-subjects factor and the covariate of baseline PDA and DPDD.

3.2.2. Primary Aim 2: To test that NTX and VAR will reduce cue-induced craving for alcohol as compared to placebo.

We will conduct a series of repeated measures ANOVAs on Alcohol Cue – Water Cue change scores on the AUQ as predicted by Medication condition (NTX vs. PLAC and VAR vs. PLAC).

3.2.3. Primary Aim 3: To test that medication effects on cue-reactivity are associated with medication effects on drinking outcomes during the quit attempt.

A series of regression analyses will be conducted testing whether medication effects on drinking (indicated by NTX – PLAC and VAR – PLAC change scores) are predicted by medication effects on cue reactivity (indicated by NTX – PLAC and VAR – PLAC change scores on the cue reactivity outcomes described for Aim #2).

3.2.4. Secondary Aim 1: Medication Effects on Alcohol Choice, Delay Discounting, and Alcohol Demand.

One-way Analysis of Covariance (ANCOVAs) will be used to determine significant mean differences in crossover points on the multiple-choice paradigm, delay discounting, and alcohol demand between the medication groups (naltrexone, varenicline, and placebo). Mediation analyses will be used to determine whether the effects of medication on the multiple-choice paradigm were mediated by changes in discounting or demand for alcohol. Baseline covariates such as age, sex, and smoking status will be included in the model.

3.2.5. Secondary Aim 2: Alcohol Choice and Drinking Behavior During Practice Quit Attempt.

Multiple regression analyses will be used to determine whether the number of drinks per drinking day and percentage of days abstinent during the practice quit attempt predict alcohol choice. Regression analyses will also include medication condition (naltrexone, varenicline, placebo) as a moderator of the relationship between alcohol drinking behaviors during the practice quit attempt and alcohol choice. Baseline covariates such as age, sex, and smoking status will also be included in the model.

3.2.6. Exploratory Aim

We will conduct direct comparisons between the two active medications (VAR vs. NTX) as part of the exploratory analyses for the study.

4. ETHICS

4.1. IRB Review

The study will be conducted under a protocol reviewed by the UCLA IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

4.1.1. Protocol Modifications

All necessary protocol changes will be submitted in writing as protocol amendments to the IRB by the PI for approval prior to implementation.

4.1.2. Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the UCLA IRB.

4.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice. The procedures set out in this study are designed to ensure that all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR). The PI confirms this by signing FDA Form 1572.

4.2.1. Confidentiality of Data and Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff, and other required regulatory representatives will have access to the records. Subject information will not be released without written permission. The PI has received a Certificate of Confidentiality for this study.

4.2.2. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash. Compensation will be provided at each subject visit and is detailed in the informed consent form.

4.2.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the IRB and prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50. The consent document indicates that by signature, the subject, permits access to relevant medical records as described above. A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for each subject. All potential subjects for the study will be given a current copy of the Informed Consent Form to read. All aspects of the study and informed consent will be explained in lay language to the subject by either the investigator, or a medically trained designee. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation. All study subjects will be given a copy of the signed informed consent.

4.2.4. Delegation of Responsibilities and Adequate Resources

The PI should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The term “investigator” used throughout this protocol refers to the PI and/or qualified Sub-investigators. The PI may delegate responsibilities to other study site personnel. The PI shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The PI shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The PI is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

4.2.5. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR §54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

5. DATA HANDLING AND RECORD KEEPING

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. This study will use an electronic data capture (EDC) eCRF system (Qualtrics) and paper source documents. Data will be transcribed from source documentation directly into a statistical program such as SPSS. Only questionnaire data will be entered directly into eCRF (i.e., without prior written or electronic record of data). Paper copies of the eCRFs will be available in the event that the EDC is not accessible at the time the questionnaire is being completed. The transcribed data will be consistent with the source documents or the discrepancies will be explained. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. The EDC system maintains a full audit trail of data entry, data corrections, and data queries.

5.1. Subject Identification and Confidentiality

Subjects will be identified on eCRFs and paper source documents by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. Regulatory bodies, such as the FDA and IRB, are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

5.2. Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by Title 21 Code of Federal Regulations (21CFR) Parts 50, 54, 56, and 312, ICH E6 section 8, as well as any other documentation defined in the protocol. Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.

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