# Combining Varenicline and Naltrexone for Smoking Cessation and Drinking Reduction

STUDY PROTOCOL

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## 1. INTRODUCTION

This study addresses medication development for nicotine dependence and alcohol misuse, highly significant public health problems for which only modestly effective interventions are currently available. This study builds upon compelling preliminary data from the PI's lab suggesting that the combination of varenicline and naltrexone may be superior to varenicline alone for heavy drinking smokers. The addition of naltrexone as an adjunct to varenicline seeks to break the link between higher smoking cessation relapse rates during drinking episodes [33, 103], which in turn may improve quit rates among this group of treatment-resistant smokers**.** Although naltrexone has been used as an adjunct to nicotine replacement therapy with some, although not uniform, benefit [79, 83-85, 87], to the best of our knowledge no clinical trials to date have combined varenicline and naltrexone. The study combines these two pharmacotherapies for a specific sub-group of smokers for whom heavy drinking represents an important risk factor for relapse in smoking cessation [7, 8]. This is a sizeable sub-group, representing at least 20-30% of all current smokers in the U.S. [3] and a group for whom the health consequences of smoking are exacerbated [4-6].

An important challenge in the treatment of nicotine and alcohol dependence is the development of effective treatments for patients with special needs [90]. The present study addresses this challenge by testing a combination of pharmacotherapies for a special needs group of heavy drinking smokers. In addition, this study examines the effects of the combination pharmacotherapy on alcohol use, among smokers who are willing to reduce their drinking. This aim will elucidate the effects of this combination on heavy drinking, which in addition to posing an obstacle to smoking cessation exacerbates the negative health consequences from smoking. By comparing the combination to the field standard for alcohol misuse (i.e., naltrexone), this study will advance treatment development for alcohol use disorders. In brief, this study has the potential to inform treatments that can target two important public health concerns, namely smoking and drinking. The secondary aim is designed to inquire whether the effects of medication on alcohol craving and alcohol use mediate their clinical efficacy. This is significant as it would allow us to elucidate clinically meaningful mechanisms of action of varenicline, naltrexone, and their combination for the treatment of nicotine dependence and alcohol misuse.

In summary, the significance of the study is high as it (a) addresses major public health concerns, namely nicotine dependence and alcohol misuse; (b) seeks to optimize treatment for a sizeable and treatment resistant sub-group of smokers, namely heavy drinking smokers; (c) builds upon a strong scientific rationale that encompasses both preclinical and clinical data on the co-use of nicotine and alcohol; (d) extends upon

compelling preliminary data supporting the combination of varenicline + naltrexone over monotherapy and placebo in the human laboratory; and (e) evaluates the effects of the combined pharmacotherapies on alcohol use outcomes in heavy drinkers who are willing to reduce their drinking, thereby informing treatment development for alcohol misuse. The successful completion of the study will inform clinical guidelines for the treatment of heavy drinking smokers, which currently consist simply of advising heavy drinking smokers to abstain from alcohol during their smoking quit attempt [19, 52]. Importantly, this study selects smokers who are motivated to change their drinking thus allowing for a meaningful evaluation of the combination of VAR + NTX for alcohol misuse, particularly in relation to the field standard for drinking (i.e., naltrexone alone).

## 2. BACKGROUND AND SIGNIFICANCE

### 2.1. Cigarette smoking and drinking: a bi-directional relationship

Alcohol and cigarettes are two of the most widely abused substances and are often used in combination. It was recently estimated that 6 in 10 adults in the U.S. are current drinkers and 1 in 5 are current smokers [20]. Levels of alcohol use are higher in smokers than non-smokers, and the prevalence of smoking is higher in heavy drinkers compared to non-drinkers [3]. Almost 20% of current smokers engage in hazardous drinking, consuming 5 or more drinks on one occasion (4 or more for females) at least once per month [21, 22], compared to about 6.5% of nonsmokers [21]. Moreover, just over 55% of those with an alcohol use disorder smoke compared to 22.5% of lifetime alcohol abstainers [3]. A recent study found that 56% of tobacco quitline callers reported drinking and 23% reported hazardous drinking using NIAAA guidelines [4]. Of note, heavy drinking smokers experience more negative health consequences, including impairments in brain morphology and function [5] and greater risk for various cancers [6], than drinkers only and smokers only.

Given the strong association between tobacco and alcohol use, researchers have attempted to elucidate the mechanisms underlying this relationship. In human laboratory studies, alcohol consumption is associated with increases in craving for cigarettes [23-25], in a dose-dependent fashion [26, 27]. Interestingly, acute nicotine administration increased alcohol consumption among occasional smokers [28] while intranasal nicotine enhanced alcohol's stimulant effects and attenuated its sedating effects [29]. More recently, a study has found that alcohol's effect on craving for smoking was partially mediated by its positive association with the self-reported stimulant effects of alcohol [27]; thus increases in stimulation may account, in part, for alcohol's effects on cigarette craving and smoking. In short, these studies highlight the complex, yet robust pharmacological interactions between alcohol and cigarettes.

Alcohol may also increase the rewarding properties of smoking. Pretreatment with alcohol was found to increase enjoyment from smoking [30], increase satisfaction with smoking, potentiate the stimulant and calming effects of smoking, and relieve cigarette craving when individuals smoke nicotine-containing cigarettes compared to

denicotinized cigarettes [31, 32]. Alcohol also offsets some of the effects of the nicotine antagonist mecamylamine, which reduces satisfaction with smoking [32]. Of clinical importance, greater alcohol use is associated with decreased odds of smoking cessation [7, 8] and it is estimated that smokers are 4 times more likely to experience a smoking lapse during drinking episodes. A recent study of tobacco quitline callers found that hazardous drinkers had lower smoking cessation rates compared to moderate drinkers [4]. Given the co-occurrence of smoking and drinking and the neurobiological interactions between alcohol and nicotine, it has been convincingly argued that heavy drinking smokers constitute a distinct sub-population of smokers with a unique clinical profile and treatment needs [2, 9]. Although practice guidelines recommend smokers be advised to reduce or avoid drinking alcohol when making a quit attempt [19], there are no available pharmacological treatments or guidelines tailored to heavy drinking smokers, a sizeable and treatment-resistant sub-group. And while a recent behavioral treatment study found some support for incorporating a brief alcohol intervention to improve smoking cessation among heavy drinking smokers [33], no pharmacological studies to date have combined medications for smoking and drinking for this population. Thus, treatment development for heavy drinking smokers represents a highly significant and understudied research area.

### 2.2. Varenicline: effective for smoking cessation and may reduce alcohol use

A number of pharmacological treatments have been developed for nicotine dependence. Nicotine replacement therapy appears to be modestly effective, presumably by decreasing withdrawal [34]. Bupropion is another medication with moderate effectiveness, although its mechanisms of action remain relatively unclear. It is thought that the effect of bupropion on dopamine, noradrenaline, or even its direct effects on nicotine receptors may be involved in its clinical efficacy [35]. More recently, varenicline has been approved for the treatment of tobacco dependence. Molecular studies have convincingly demonstrated that the α4β2 subtype is necessary for nicotine dependence [36, 37]. Developed to address the critical role of α4β2 in tobacco dependence, varenicline is a partial agonist at α4β2 receptors. The putative mechanisms of action of varenicline stem from the stimulation of dopamine release (as a partial nicotine agonist) [38] and with its ability to block the binding of nicotine to its site (an antagonist effect), which in turn results in reductions in nicotine craving and reward [39]. At the behavioral level, varenicline-induced blockade of α4β2 nAChRs reduces craving and withdrawal and attenuates the rewarding effects of smoking [39-43]. Functional neuroimaging studies found that varenicline increases activation of the dorsal anterior cingulate/medial frontal cortex, and dorsolateral prefrontal cortex during a working memory task [44] as well as during an emotional processing task [45]. Moreover, varenicline diminished smoking cue-elicited ventral striatum and medial orbitofrontal cortex responses compared to placebo [46]. Perhaps most importantly, a number of clinical trials found that varenicline is more effective than bupropion [10], superior to nicotine replacement therapy [47], and significantly more effective than placebo [10, 48-51] as a smoking cessation agent. As a result of this compelling clinical data, varenicline was advanced as a first line treatment for nicotine dependence [52]. It is to be noted, however, that abstinence rates on varenicline are about 43% at 12

weeks and 25% at one-year follow-up [53]. Thus, even though varenicline is superior to other treatments, there is a clear opportunity to improve upon these clinical outcomes, particularly among hard-to-treat sub-groups such as heavy drinking smokers.

In addition to the effects of varenicline on 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 [54-56]. Therefore, there is considerable enthusiasm for varenicline as a possible treatment for alcohol problems as well as the alcohol-nicotine co-abuse [2]. Preclinical studies have found that varenicline decreases ethanol self-administration in rats [57, 58]. Recent human studies of varenicline for alcohol use found that, compared to placebo, varenicline reduced alcohol self-administration in the human laboratory [11], as well as alcohol craving [12] and alcohol consumption [12, 13] 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 [59]. Together, these studies suggest that varenicline is an effective treatment for nicotine dependence and that it may have beneficial effects on alcohol use as well. Further, testing varenicline in combination with an alcoholism agent, such as naltrexone, may promote smoking cessation and drinking reductions over and above monotherapy.

### 2.3. Naltrexone: effective for alcohol problems and may improve smoking cessation outcomes

Naltrexone is an opioid receptor antagonist with established efficacy, albeit moderate, for the treatment of alcohol problems. Shortly after two initial trials suggested that naltrexone resulted in significantly fewer drinking days and lower rates of relapse after three months of treatment [60, 61], naltrexone was regarded as one of the more promising pharmacological interventions for alcohol dependence [62]. These initial results have been largely supported by more recent trials of naltrexone that generally demonstrate beneficial effects on heavy drinking rates, particularly among those who are compliant with the medication [63-66]. Studies have found that naltrexone reduces the occurrence of heavy drinking days [64, 67, 68], increases time to first relapse [66, 69, 70], yields lower relapse rates [60, 71, 72], reduces the number of drinking days [60, 61], the number of drinks per drinking episode [61, 63, 65, 69], and the latency to first and second drink among social drinkers [73]. However, the support for naltrexone is not uniform. A few trials found no significant outcome differences between naltrexone and placebo treated-patients [74, 75]. Most recently, naltrexone was tested in the large, multi-site, COMBINE Study and was superior to placebo when delivered in combination with medical management [14], which advanced naltrexone as a first line of treatment for alcohol misuse.

The neurobiological literature has recognized a role for the endogenous opioid system in modulating responses not only to alcohol, but to nicotine as well [76]. As such, naltrexone has been evaluated as a stand-alone as well as an adjunctive treatment to

smoking cessation. A study by O'Malley et al. found that naltrexone reduces drinking even among heavy drinking smokers who are not seeking treatment for alcohol problems [77] and similar results were recently reported by King and colleagues [78]. When naltrexone was used as an adjunct to smoking cessation, along with counseling and nicotine patches, naltrexone produced significantly higher quit rates than placebo but only at higher levels of depressive symptoms [79] or among females [80, 81]. While there is little support for naltrexone, and opioid antagonist broadly, as a stand-alone treatment for smoking cessation [82], studies found some support for the use of naltrexone as an adjunct to standard smoking cessation treatment, namely bupropion and nicotine patch [83, 84], while one study did not support combining naltrexone with bupropion [85]. No clinical trials to date have tested the combination of VAR and NTX for smoking cessation in general, and for heavy drinking smokers, in particular.

Although naltrexone is not an effective stand-alone treatment for smoking cessation, it is plausible that naltrexone may be a useful adjunct for a subgroup of smokers, particularly heavy drinking smokers. Results of laboratory studies have shown that naltrexone reduced cue-elicited withdrawal symptoms in combination with transdermal nicotine replacement [86] and that naltrexone alone attenuates smoking behavior [87] among heavy drinkers. Our own previous work with heavy drinking smokers revealed that naltrexone reduced urge to smoke during alcohol exposure [88]. Recent studies support the notion that naltrexone may be most useful in smoking cessation for a sub-group of patients who are heavy drinkers. In fact, a recent study found that naltrexone reduced drinking and improved smoking quit rates [15], particularly in heavy drinking smokers [16]. Interestingly, a re-analysis of the COMBINE Study found that naltrexone is more effective for the treatment of alcoholism in daily smokers than non-smokers [89]. In brief, there is no empirical support for naltrexone as a stand-alone treatment for nicotine dependence. However, results from recent human laboratory and clinical trials suggest that naltrexone may be effective among heavy drinking smokers trying to quit smoking. These studies, along with results from our recently completed human lab study testing the combination of naltrexone + varenicline on cigarette/alcohol reward and craving among heavy drinking smokers set the stage for testing this combination in a clinical trial. The rationale for adding naltrexone to varenicline for smoking cessation in heavy drinkers is based on the recognition that heavy drinkers are more prone to a smoking lapse during drinking episodes; hence a medication that helps patients reduce drinking may help them maintain smoking abstinence by preventing alcohol-related smoking lapses.

### 2.4. Combining pharmacotherapies: may optimize pharmacotherapy for smoking and drinking

It has been increasingly recognized that complex biobehavioral problems such as nicotine dependence and alcohol misuse require novel and multifocal treatment approaches. The existing monotherapies for smoking, including varenicline, have shown moderate efficacy at best [53, 90]. The current study is based on the assertion that a combination of pharmacotherapies may be more effective at addressing the complex nature of tobacco dependence, particularly among this treatment-resistant group of

heavy drinking smokers. The selection of treatment combinations requires careful evaluation of the actions of the therapies to be combined [91]. Specifically, effective treatment combinations may be composed of two pharmacotherapies with mechanisms of action (both behavioral and neuropharmacological) thought to be compatible with one another, and potentially additive or synergistic. Based on the known pharmacological and behavioral effects of both naltrexone and varenicline, these medications show great promise for their combined use, particularly among the high-risk group comprised of heavy drinking daily smokers. In our preliminary laboratory work, we decided to study the combination of varenicline and naltrexone, as opposed to nicotine replacement or bupropion, because it specifically targets the α4β2 receptor and has proven to be the most effective pharmacotherapy currently available [92, 93]. The effects of varenicline are also relatively independent of those of naltrexone and there is no potential for negative drug interactions. Additionally, we chose naltrexone because it is the most effective FDA-approved pharmacotherapy for alcoholism developed to date and has been found effective even among smokers who are not seeking treatment for alcohol problems [83]. Studies have shown that naltrexone attenuates the reinforcing value of alcohol preventing the transition from a lapse into a full-blown relapse [66, 94]. Similarly, varenicline has been shown to disrupt the transition from smoking lapse to relapse [95]. Therefore, we hypothesize that the combination of varenicline and naltrexone will have additive effects on relapse prevention, particularly in drinking situations which are problematic for heavy drinking smokers [8]. Likewise, there appears to be a benefit of varenicline over placebo for drinking reduction. Specifically, a large RCT by Litten et al. (2013) found that the varenicline group had significantly lower weekly percent heavy drinking days (primary outcome), drinks per day, drinks per drinking day, and alcohol craving compared with the placebo group [96].Thus the combination of varenicline plus naltrexone holds great promise to attenuate heavy drinking, which was selected as the primary outcome in this study.

Results from our human laboratory trial showed a benefit of combining varenicline and naltrexone on biobehavioral mechanisms of smoking relapse, namely cigarette craving and alcohol/smoking reward. We have argued that human laboratory studies serve an important role in medication development for addiction by allowing us to (a) screen promising medications, (b) identify doses, (c) elucidate mechanisms of action, and (d) test combined pharmacotherapies [97, 98]. Further, it is important to translate the mechanistic findings from human laboratory models by evaluating their clinical significance in smoking cessation outcomes [99-101]. Combining pharmacotherapies may offer significant advantages over monotherapies, such as permitting the use of lower doses of each component to achieve a given level of efficacy [102]. Lastly, combined treatments may facilitate tailoring of pharmacotherapies to the needs of individual patients, such as treatment augmentation in non-responders or patients with special needs (e.g., heavy drinkers, cancer patients, pregnant women) thereby addressing one of the challenges outlined by Lerman and colleagues (2005) [90]. To that end, the present study seeks to address this challenge by testing a combination pharmacotherapy for heavy drinking smokers who want to quit smoking and reduce their drinking.

# 3. STUDY OBJECTIVES

## 3.1. Primary Objectives

The primary aims of this project are to test:

**(1a)** Whether Varenicline (VAR) + Naltrexone (NTX) will result in higher rates of 7-day point prevalence smoking abstinence at 2, 4, 6, 8, 10, 12, 16, and 26 weeks post-quit date compared to VAR + Placebo (PLA).
**(1b)** Whether VAR + NTX will result in lower drinks per drinking day at 2, 4, 6, 8, 10, 12, 16, and 26 weeks post-quit date compared to VAR + PLA.

## 3.2. Secondary Objective

The secondary aim of this study is to test:

**(2a)** Whether the effects VAR + NTX on smoking cessation outcomes and milestones are mediated by reductions in alcohol use, measured over the course of the trial.

## 3.3. Supplemental Objectives

The supplemental aims of this study are to test:

**(s1a)** Whether men and women differ in reported side effects and treatment adherence (measured both by pill count and by study drop out) overall and between VAR + NTX and VAR only medication conditions.
**(s1b)** Whether men and women differ on rates of 7-day point prevalence smoking abstinence at 2, 8, 12, 16, and 26 weeks post-quit date overall and between VAR + NTX and VAR only medication conditions.
**(s1c)** Whether women and men differ in percentage of heavy drinking days at 2, 8, 12, 16, and 26 weeks post-quit date overall and between VAR + NTX and VAR only medication conditions.
**(s2a)** Whether E2 and P4 level, hormonal contraceptive use, and menstrual cycle phase at randomization and throughout the trial predict medication side effects and treatment adherence.
**(s2b)** Whether E2 and P4 level, hormonal contraceptive use, and menstrual cycle phase at randomization and throughout the trial predict smoking abstinence and heavy drinking days.

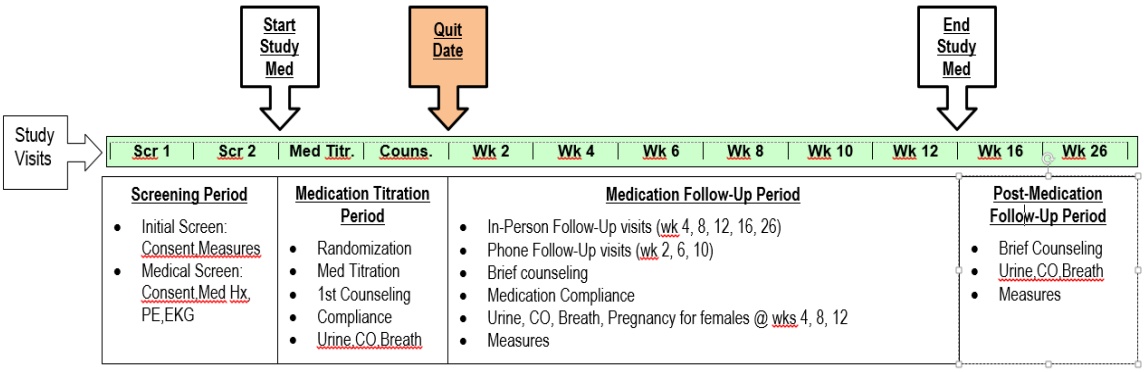
# 4. STUDY DESIGN

This study is a double-blind, randomized clinical trial using a two group medication design consisting of the combination of VAR (1 mg twice daily) + NTX (50 mg once daily) and VAR (1 mg twice daily) + PLA (matched to NTX), for smoking cessation in a sample of heavy drinking daily smokers who want to quit smoking and reduce drinking.

All participants will be daily smokers (≥ 5 cig/day) who are also heavy drinkers according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines: for men, > 14 drinks per week or ≥ 5 drinks per occasion at least once per month over the past 12 months; for women, > 7 drinks per week or ≥ 4 drinks per occasion at least once per month over the past 12 months. A total of 274 participants will be randomized, 137 to each medication group.

Interested individuals will come in to the laboratory for a two-part in-person screening visit. Eligible participants will then be randomized to either the combination of VAR (1 mg twice daily) + NTX (50 mg once daily) or VAR (1 mg twice daily) + PLA. Medication will be titrated over a 14-day period. Participants will attend a brain imaging session and receive an individual counseling session during week 2 of the medication titration period and the quit date will be set for day 14 of the medication regimen. All participants will be instructed to continue the study medications for 12 more weeks (14 weeks total) and will return to the laboratory for follow-ups 2, 4, 6, 8, 10, 12, 16, and 26 weeks post quit date. Follow-up visits at weeks 2, 6 and 10 may take place over the telephone as needed. At each follow-up, participants will complete questionnaires, receive brief smoking cessation counseling according to practice guidelines and will be encouraged to complete the online "Rethinking Drinking" program developed by NIAAA. Smoking abstinence [verified by CO level; 149] and alcohol use will be measured at each in-person follow-up to test whether the combination of VAR + NTX is superior to monotherapy for smoking cessation and drinking reduction.

### 4.1. Study Flow Diagram




## 5. PHARMACOTHERAPY INTERVENTIONS

### 5.1. Varenicline (VAR)

Varenicline will be used in this study for oral administration in two strengths:

- a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side

- a 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

Varenicline tablets will be provided by Pfizer and supplied in blister packs and should be stored at 77°F, with excursions permitted to 59–86°F.

## 5.2. Naltrexone (NTX)

NTX will be prepared by the UCLA pharmacy and packed into opaque capsules with 50 mg of riboflavin (B2) to aid in medication compliance procedures. Naltrexone will be provided for oral administration in three strengths:

- 12.5 mg capsules will be provided for the first 3 days, packaged in a blister pack.
- 25 mg capsules will be provided for days 4-7, packaged in a blister pack.
- 50 mg capsules will be provided for weeks 2-14 in amber child-resistant medication bottles.

## 5.3. Placebo (PLA)

Placebo tablets will be prepared by the UCLA pharmacy and packed into opaque capsules with 50mg of riboflavin (B2) to assess for medication compliance. Placebo capsules will be identical in appearance to Naltrexone tablets and will be provided in a blister pack for week 1 and in amber child-resistant medication bottles for weeks 2-14.

## 5.4. Study Medication Blinding

Naltrexone tablets and placebo tablets will be identically matched in appearance and the medication labels will not reveal the drug identity. The PI or designated approved study physician will make the decision to un-blind the identity of the study medication in the event that the study blind needs to be broken to make medical decisions regarding subject treatment (i.e. if necessary to assess AEs or SAEs for expedited reporting). Proper regulatory authorities will be notified if unblinding is required for a participant due to safety concerns.

## 5.5. Study Medication Handling

### 5.5.1. Medication Dispensing

At the medication titration visit, study medication will be dispensed as prescribed by the study physician. Drug accountability and compliance will be performed by the research staff at each clinic visit. The subject will be asked to bring all study medication and packaging (used and unused) to each subsequent visit for accountability. When study medications are dispensed, the subject will also be given a Medication Information Sheet for Varenicline and Naltrexone.

### 5.5.2. Medication Accountability

The PI or designated study personnel will maintain a log of the receipt of all study medications and record of dispensing of all study medications to the subject. Medication for each subject will be inventoried and accounted for throughout the trial. The PI or designated staff will count the tablets remaining at the end of the study and record the tablet count on the appropriate drug accountability form. Subject compliance with medication will be assessed by comparing unused tablet count to dispensing logs and dosing records (number of tablets dispensed, number of tablets prescribed, versus the number returned). Subjects will also be asked to account for any missing tablets. If the medication is not returned, the subject will be asked to report daily drug self-administration.

#### 5.5.3. Medication Compliance

Pill counts will be conducted at each visit. In addition, the naltrexone study medication will be packed into opaque capsules with 50 mg of riboflavin (B2). A urine sample will be tested for riboflavin content by examining it under an ultraviolet light at each visit. In addition, 20% of all participants may be randomly selected for a serum verification of medication content (varenicline and naltrexone) at each follow-up.

## 6. BEHAVIORAL INTERVENTIONS

### 6.1. Initial Smoking Cessation Counseling Session

All subjects will receive one smoking cessation counseling session to take place during week 2 of the medication protocol. Per published guidelines, session will focus on problem solving and relapse prevention skills training. All study staff will be equipped to deliver this intervention through training and ongoing supervision by the PI, a licensed clinical psychologist. Subjects will be encouraged to maintain abstinence and to take the study medication. However, eligibility to continue in the study or receive study compensation will not be affected if participants do not maintain abstinence and/or are not compliant with the medication. This session will last approximately 45 minutes.

### 6.2. Follow Up Smoking Cessation Counseling Sessions

Participants will also receive brief cessation counseling at each follow-up visit focusing on topics as described above.

### 6.3. Rethinking Drinking Program

In addition, all participants will be encouraged to complete the “Rethinking Drinking” program online (http://rethinkingdrinking.niaaa.nih.gov/default.asp) while in the study and will discuss their drinking with the counselor.

# 7. STUDY PROCEDURES

## 7.1. Recruitment of Subjects

Mass media advertisements will be placed in local newspapers and on local radio stations in the greater Los Angeles metropolitan area. Targeted recruitment will also take place through existing research databases from the Ray and Leventhal laboratories (each laboratory has contact information for over 500 daily smokers who completed previous studies and are interested in being called about future studies) as well as through the UCLA primary care clinics. In addition, we will employ snowball sampling. Participants who voluntarily agree will have an opportunity to forward a text message providing brief information about the study (drafted by the study team) to up to 5 acquaintances. Participants will earn an additional $1 in compensation for each text message they send, up to $5. Men and women of all ethnic backgrounds will be recruited into the study. We expect that the study will reflect the ethnic diversity of Los Angeles County. Given that the requirement of ≥5 cig/day may disproportionally exclude females and ethnic minorities, targeted recruitment will be carried out to ensure a balanced representation of these groups in our study.

## 7.2. Eligibility Criteria

### 7.2.1. Inclusion Criteria

To be included in the study, participants **must**:
1. Be treatment-seeking for smoking cessation and have a desire to reduce or quit drinking
2. Be between the ages of 21 and 65
3. Be able to provide informed consent
4. Smoke 5 or more cigarettes per day for the past year
5. Currently drink heavily according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines: for men, > 14 drinks per week or ≥ 5 drinks per occasion at least once per month over the past 12 months; for women, > 7 drinks per week or ≥ 4 drinks per occasion at least once per month over the past 12 months
6. Pass the physical exam and associated laboratory tests, as determined by study physician.

### 7.2.2. Exclusion Criteria

To be included in the study, participants **must not**:
1. Have clinically significant alcohol withdrawal, indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) and assessed at the in-person screening visits
2. Have lifetime DSM-V diagnosis of schizophrenia, bipolar disorder, a psychotic disorder, or any other psychiatric disorder as determined by the clinical interview

3. Have major depressive disorder within the past year requiring treatment as determined by the clinical interview using DSM-V criteria
4. Have a current DSM-V diagnosis of a substance use disorder, other than for alcohol or nicotine, as determined by the clinical interview
5. Have a prior history of taking FDA approved medications (i.e. varenicline or bupropion) for smoking cessation
6. Be currently using any forms of nicotine replacement therapy (past use is acceptable)
7. Have a serious medical illness (significant cardiovascular disease; uncontrolled hypertension; hepatic or renal disease) that would contraindicate participation, as determined by the study physician
8. Be currently taking opioid pain medications or any form of opioid agonist maintenance therapy (such as methadone or buprenorphine)
9. Be currently taking any psychoactive medications that would indicate serious or unstable mental illness, such as certain antidepressants, mood stabilizers or anti-seizure medications, sedatives-hypnotics, anxiolytics, stimulants, antipsychotics, as determined by the study physician.
10. Have self-reported use of cocaine, methamphetamine, heroin or other illicit drugs in the previous 60 days, verified by urine toxicology screen
11. For women, must not be pregnant (as indicated by self-report or a positive pregnancy test at any study visit), nursing, or planning to become pregnant while taking part in the study, and must agree to one of the following methods of birth control, 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

## 7.3. Screening Period

### 7.3.1. 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.

### 7.3.2. 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 for cotinine verification of smoking status and test for drugs of abuse and pregnancy (if female), be given a breath test of CO level and will complete a series of smoking and individual differences measures (described in detail below). This visit should take 1.5 to 2 hours.

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.

#### 7.3.3. Medical Screening Visit

Those participants who appear to be eligible after the initial screening visit, will then be scheduled for a second screening visit to take place at the UCLA Clinical and Translational Research Center (CTRC). This visit will be conducted by the study physician and will start with a breathalyzer test. 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 will conduct the second written (experimental) consent, medical history interview, physical exam, Comprehensive Metabolic Panel including liver function tests (LFTs) and blood chemistry, and EKG to screen for medical conditions that contraindicate taking naltrexone and/or varenicline. In addition, CO levels, and urine drug screen tests will be repeated. 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 smoking cessation treatment in the community.

### 7.4. Medication Titration/Stabilization Period

#### 7.4.1. Randomization and Medication Titration Visit

Participants who are eligible after the medical screening visit will be scheduled to come into the lab to be randomized and start study medication. Subjects will be urn randomized to one of two medication groups. Urn randomization will be used to balance the two medication groups by gender, number of cigarettes per day, and drinks per drinking day. At this visit, a quit date will be set for day 14 of the medication titration/stabilization regimen.

Female participants will be asked about their menstrual cycle and reproductive status and will answer questions about hormonal responses and symptoms (see Schedule of Assessments). In addition, female participants of child-bearing potential will provide a saliva sample for testing of progesterone and estradiol levels and urine will be tested for surges in luteinizing hormone (LH).

*7.4.1.1. Medication Titration Schedule*

| *Titration Day* | *VAR* | *NTX/PLA* |
|---|---|---|
| *1* | *.5 mg once per day* | *12.5 mg once per day* |
| *2* | *.5 mg once per day* | *12.5 mg once per day* |
| *3* | *.5 mg once per day* | *12.5 mg once per day* |
| *4* | *.5 mg twice per day* | *25 mg once per day* |
| *5* | *.5 mg twice per day* | *25 mg once per day* |
| *6* | *.5 mg twice per day* | *25 mg once per day* |
| *7* | *.5 mg twice per day* | *25 mg once per day* |
| *8+* | *1 mg twice per day* | *50 mg once per day* |

*All pills will be matched in number of pills and packaging across the two medication conditions (VAR + PLA and VAR + NTX). Participants will be asked to take the study medications for a period of 14 weeks and will complete regular follow-ups.*

7.4.2. Titration Follow Up Telephone Contact

The study physician will contact the participant via telephone once during the first week of the medication titration period to assess for side effects/adverse events and the potential need for dosage adjustments.

7.4.3. Initial Counseling Session

All subjects will receive one smoking cessation counseling session to take place during week 2 of the medication titration period. This session will last approximately 45 minutes, and will focus on preparation for the upcoming quit date.

#### 7.4.4. Brain Imaging Session

Participants found to be eligible for an MRI, as determined by the MRI Safety Screening form, will be asked to complete a brain imaging session after 9-12 days of taking the medication.

Participants will be asked to abstain from drinking alcohol prior to coming into the lab for the brain imaging session, which will be verified through a breathalyzer. Only participants with a blood alcohol concentration of zero will be allowed to complete the scanning visit. Female participants will be given a pregnancy test to make sure that they are not pregnant. We will also collect a urine sample on that day to verify compliance with the study medication. We will then ask participants to fill out a few questionnaires including information about your use of alcohol and tobacco.

After the initial questionnaires, participants will receive some training on how to complete questionnaires in the scanner. The scanning will be performed at the Brain Mapping Center or at the Center for Cognitive Neuroscience, both located on the UCLA campus. They will be asked to lie down on a padded table, with their head placed in the center of a large, metal doughnut-shaped magnet. While the machine is running, the participant will hear loud banging noises and will be offered earplugs to reduce the noise made by the magnet. Head and back support will also be provided to minimize discomfort. In the scanner, participants will watch brief videos of individuals smoking cigarettes or performing daily activities, such as driving And will view alcohol and neutral cues. They will also be asked to rate their urge to smoke cigarettes and drink after watching each of these videos and visual cues.

### 7.5. Medication Follow Up Period (Weeks 2, 4, 6, 8, 10, & 12)

Follow-up visits will occur at the UCLA Addictions Lab on weeks 4, 8, 12, 16, and 26. Telephone or in-person follow-up interviews will be conducted at weeks 2, 6 and 10. At each in-person follow up visit, participants will be asked to provide a urine specimen for cotinine level testing, perform an alcohol breathalyzer test, expired alveolar carbon monoxide (CO) levels test and complete measures as described in the Schedule of Assessments (Appendix 2). In addition, urine specimen will be assessed for pregnancy and LH and saliva sample will be collected to test for progesterone and estradiol levels monthly for female participants. Blood chemistry labs will be drawn at the last medication follow up visit at week 12. Participants will be asked to bring all study medication and used packaging to each visit to assess for medication compliance and will be dispensed study medication to last until the next scheduled visit.

Female participants will be asked about their menstrual cycle and reproductive status and will answer questions about hormonal responses and symptoms (see Schedule of Assessments). In addition, female participants of child-bearing potential will provide a saliva sample for testing of progesterone and estradiol levels and urine will be tested for surges in luteinizing hormone (LH).

## 7.6. Post-Medication Follow Up Period (Weeks 16 & 26)

At 16 and 26 weeks post quit date, participants will return to the UCLA Addictions Lab for post-medication follow up visits. At each visit, participants will be asked to provide a urine specimen for cotinine level testing, perform an alcohol breathalyzer test, expired alveolar carbon monoxide (CO) levels test and complete measures as described in the Schedule of Assessments (Appendix 2). Female participants of child-bearing potential will also be tested for pregnancy, LH levels and progesterone and estradiol levels.

## 7.7. Dose-adjustment Criteria

Participants who discontinue study medication should still continue in the study, and complete all assessments as scheduled. Females who become pregnant during the course of the study will be instructed to immediately discontinue use of the study medication and the pregnancy will be reported per required regulatory guidelines. Participants will need to be removed from study medication if they have a serious illness or a disabling condition that precludes them from taking the medication. If the participant experiences any AEs that are considered study drug related and for which the study physician has determined that continuation of the study drug could be detrimental to the health of the subject, then drug will be immediately discontinued as described above.

## 7.8. Subject Withdrawal or Discontinuation Procedures

Participants have the right to withdraw consent and withdraw from the study at any time. In addition, the investigator may find it necessary to discontinue a participant for any reason, including the occurrence of an AE or noncompliance with the protocol.
In the event that a participant withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded. A final follow up visit will be scheduled and collected if possible.

### 7.8.1. Stopping Criteria due to Safety Concerns

The following trial stopping rules have been established: If two subjects have unexpected serious life-threatening AEs (attempted/completed suicide, extreme psychosis, etc.) the study will be halted and the DSMB will determine if the study should continue or be terminated overall.

If at any time during study procedures, a participant develops any of the following stopping criteria, the study physician will abort study procedures, treat and/or observe the participant until stable, and discharge the patient from the study once stable with a 14-day post-discharge outpatient follow-up visit to complete additional safety assessments:

1. Abnormalities on liver function tests >3 times the baseline levels or any other clinically significant lab values or AEs.

2. Pregnancy: Both NTX and VAR are classified as Pregnancy Category C drugs by the FDA, and the drugs should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. As such, females who become pregnant during the course of the study will be instructed to discontinue the medication; the study physician will request a release of information to discuss the use study medication with their obstetrician. The participant will be followed through her pregnancy.
3. Psychiatric crises, including but not limited to the following:
   a. Acute psychosis (hallucinations, impaired reality testing, paranoid ideation, etc.) requiring medication and/or hospitalization or intensive outpatient intervention;
   b. Suicidal or homicidal ideation that results in a credible threat of violence directed at oneself or others;
   c. Hospitalization for psychiatric symptoms
4. A positive urine drug screen indicating illicit use of cocaine, methamphetamine, opiates, or other abused drugs at any visit during the trial.
5. Self-reported use of contraindicated medications (as listed in the inclusion/exclusion criteria)

Participants who report adverse reactions will be individually evaluated by the study physician. All participants will be clearly instructed that they may stop the study medication at any time. Upon physician evaluation, participants who reports either a severe side effect or any side effects that are not tolerable to them, whether severe or not, will be subjected to withdrawal by investigator and will be asked to discontinue the study medication immediately. In such cases, participants will be offered a follow-up visit with the study physician to re-evaluate symptoms upon discontinuation of the study medication.

### 7.9. Compensation for Participation

Participants will be compensated up to a total of $455 for their time and effort according to the following schedule:

| | |
|---|---|
| Initial screening visit: | $20 |
| Medical screening visit: | $20 |
| Medication Titration: | $20 |
| Initial Counseling Visit: | $20 |
| Brain Imaging Visit: | $50 (if eligible) |
| Follow up visit week 2: | $20 |
| Follow up visit week 4: | $20 |
| Follow up visit week 6: | $20 |
| Follow up visit week 8: | $20 |
| Follow up visit week 10: | $20 |
| Follow up visit week 12: | $50 |
| Follow up visit week 16: | $50 |

Follow up visit week 26: $75
Completion bonus week 26*: $50
*Only participants who have completed all 12 study visits will be eligible to receive the $50 completion bonus.

In addition, participants will have the opportunity to earn up to $5 additional at the initial screening visit for participating in snowball recruitment methods as described above. Participants who travel more than 10 miles from their home to attend visits on the UCLA campus will receive an additional $10 per visit to cover travel costs. All participants will be provided with free parking validation or bus tokens for attendance to each study visit.

Female participants will receive an additional $10 at each of the following visits for completing female-specific study procedures as described above: Medication Titration, FU week 4, FU week 8, FU week 12, FU week 16 and FU week 26, totaling $410 for completion of all study procedures.

Participants are free to discontinue participation at any time and will receive compensation for the amount of time that they participated.

## 8. 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 monitor, and DSMB.

### 8.1. 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 side effects will be collected in an open-ended way at each study visit. Vital signs, weight, and neuropsychiatric side effects, including depression and suicidal ideation, will be monitored at each study visit. The study physician will repeat all the clinical labs at the week 12 follow-up in order to verify that there were no changes associated with the 12-week medication regimen (+ 2 week titration/stabilization period). In the event that significant medical problems are encountered, the blind will be broken and appropriate medical treatment will be provided.

### 8.2. 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, perform drug accountability, 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, advise on storage of study records, and inspect the return and destruction records for unused study medication.

### 8.3. Data and Safety Monitoring Board (DSMB)

An independent DSMB of external advisors will meet prior to the start of the study, bi-annually during enrollment and follow-up and at trial end to review safety data. The Board will be blinded to subjects' actual randomized group assignments but may request at any time that the blind be broken by the data center, if concerns arise from the blinded data. In addition to bi-annual meetings, the DSMB will meet after half of the subjects (137) have been randomized to review safety data and the integrity of the study (i.e., an evaluation of the dropout rate and impact on the planned statistical analysis of the data) and make a formal recommendation to the PI on the continuation or early stopping of the study due to safety concerns. *Ad hoc* meetings will be convened if SAEs occur that are considered at least possibly related to the study medication.

## 9. ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Appendix 2); the following sections outline the details and procedures associated with the assessments. Most assessments will be recorded directly into the EDC system (MediaLab) with the exception of a few, which will be completed first on paper, then entered into the database as noted below.

### 9.1. Adverse Events (AE) and Serious Adverse Events (SAE)

The study physician and study site staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an AE or SAE. Adverse Events will be assessed at the medical screening visit and at each subsequent visit through the week 26 follow up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open ended question: "How have you been feeling since your last visit or the last time we spoke?"

Adverse Events will be recorded on the AE Log using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The study physician will assess all AEs for seriousness, relationship to study medication, and severity. When an event has not resolved by study closure, it will be documented on the AE Log as "ongoing".

If a woman has a positive or borderline pregnancy test after enrollment, the pregnancy will be recorded as an AE. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy (e.g., normal birth, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) will be recorded.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). All SAE's will be reported per requirements.

#### 9.1.1. Adverse Event (AE) Definition

An AE is any untoward medical occurrence in a participant who has been administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of the study medication, whether or not related to the medication. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

##### *9.1.1.1. Classification of Adverse Event Intensity and Relationship to Study Medication*

*For each recorded AE or SAE, the physician must make an assessment of severity based on the following criteria:*

- ***Mild:*** *An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.*
- ***Moderate:*** *An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.*
- ***Severe:*** *An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.*
- ***Life-threatening:*** *An event that puts the subject into imminent risk of death without intervention.*

*The physician must also make an assessment of relationship to the investigational product based on the following criteria:*

- ***Unrelated:*** *The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.*

- ***Unlikely:*** *There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE.*
- ***Possible:*** *There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.*
- ***Probable:*** *There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.*
- ***Definite*** *There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.*

#### *9.1.1.2. Outcomes and Actions Taken*

*All unresolved AEs will be followed for a minimum of 14 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 14-day period, or the subject is lost to follow-up. Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.*

*For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:*

- ***Fatal****: The subject died.*
- ***Resolved without Sequelae****: The AE or SAE has ended.*
- ***Resolved with Sequelae****: The AE or SAE has ended but changes are noted from baseline.*
- ***Unresolved – Ongoing****: The AE has not ended and is ongoing at the end of the reporting period (i.e., 14 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required*
- ***Unknown – Lost to Follow-up****: Lost to follow-up after repeated unsuccessful attempts to contact the subject.*

*Actions taken with respect to study medication (discontinuation or not) will also be recorded. In addition, if the AE was treated (medications or other physical measures), this will also be recorded.*

### 9.1.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

### 9.2. Alcohol Consumption Questionnaire (ACQ)

The Alcohol Consumption Questionnaire is measured with nine items assessing lifetime drinking history such as current drinking, age of onset, and attempts to quit/reduce drinking. This assessment will be completed directly by the participant at the initial screening visit.

### 9.3. Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test is used to identify persons with hazardous and harmful patterns of alcohol consumption. The AUDIT was developed by the World Health Organization (WHO) as a simple method of screening for excessive drinking. The AUDIT is a self-report measure that will be completed by the participant in MediaLab at the initial screening visit.

### 9.4. Barratt Impulsivity Scale (BIS-11)

The BIS-11 is a widely used measure of impulsiveness that includes 30 self-reported items that are scored to yield six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness). This questionnaire will be completed by the participant electronically during screening and at each follow up visit.

### 9.5. Breathalyzer

An alcohol breathalyzer will be administered at consent, and at every in-clinic 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.

### 9.6. Clinical Laboratory Tests

Clinical laboratory tests, including a chemistry panel and liver function tests, will be performed at CTRC during the medical screening and week 12 follow up visits. The total blood volume to be collected is approximately 72 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.

### 9.7. 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 on paper by appropriately trained staff during screening, at the medication titration visit, and at each follow-up visit. Participant responses will then be entered electronically.

### 9.8. 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 screening and at each follow up visit and will be administered by a trained staff member with responses recorded on paper first, then entered electronically.

### 9.9. Concomitant Medications

All medications taken by the participant 2-weeks prior to the start of screening and through the final follow-up contact at week 26 will be recorded. All medications reported by the participant will be recorded on a source document and later entered electronically.

### 9.10. Demographics

Demographics data include the participant's age, gender, race/ethnicity, marital status, education, employment pattern, occupation, and income level. These data will be collected by site staff at the initial screening visit on a source document and entered into an eCRF.

### 9.11. Drug Use Questionnaire (DUQ)

The Drug Use Questionnaire will collect information on frequency and quantity of drug use. Participants will directly enter responses into MediaLab at the initial screening visit.

### 9.12. Eating Disorders Inventory (EDI)

The EDI (Gerner, 1991) will be completed by all participants at the initial screening visit to assess for general weight concerns. Participants will directly enter responses into MediaLab.

### 9.13. EKG

A 12-lead resting ECG will be obtained at the medical screening visit. Any abnormalities will be noted and an assessment of clinical significance will be done by the study physician.

### 9.14. Alveolar Carbon Monoxide (CO) Levels

A Vitalograph CO monitor will be used to detect CO levels at screening to verify that participants are regular smokers and at follow up visits to assess for smoking abstinence. Test results will be recorded on the visit checklist and then entered into the database.

### 9.15. Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Test for Nicotine Dependence will be used to assess smoking status and motivation to change smoking behavior at screening. This questionnaire will be completed by the subject electronically.

### 9.16. Family Tree Questionnaire (FTQ)

Information on family history of alcohol problems will becollected 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 initial screening visit.

### 9.17. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale is a self-assessment tool to assess anxiety and depression levels. This measure will be completed at the initial screening visit and entered with participant responses entered directly into the database.

### 9.18. ImBIBe

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. This scale was adapted from the Drinker Inventory of Consequences (Drinc) questionnaire based on FDA recommendations on patient reported outcomes. This questionnaire will be completed by the participant electronically.

### 9.19. 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 contraindicate taking naltrexone and/or varenicline.

### 9.20. Menstrual Cycle Calendar

The Menstrual Cycle Calendar (Roche and King, 2015) is a calendar-based interview will estimate recent dates of menstruation, determine average menstrual cycle length, and estimate the onset of next menses. It will be administered to female participants at the medication-titration visit and follow-up visits at week 4, 8, 12, 16 and 26.

### 9.21. Menstrual Distress Questionnaire (MDQ)

The MDQ (Moos, 1968) will assess the level of menstrual cycle distress female participants of child-bearing potential experienced during their most recent cycle. This questionnaire will be completed by female participants at the medication titration visit, and at the week 4, week 8, week 12, week 16 and week 2 follow-up visits.

### 9.22. Minnesota Nicotine Withdrawal Scale (MNWS)

The Minnesota Nicotine Withdrawal Scale assesses signs and symptoms of nicotine withdrawal. The participant will respond to this 9-item assessment at the initial screening visit and all follow up visits.

### 9.23. Morisky Medication Adherence Questionnaire (MAQ)

The Morisky Medication Adherence Scale (MMAS) is a generic self-reported, medication-taking behavior scale, validated for hypertension but used for a wide variety of medical conditions. It consists of four items with a scoring scheme of “Yes” = 0 and “No” = 1. The items are summed to give a range of scores from low adherence to high adherence. This measure will be completed by the participant at the initial screening visit and at each of the medication follow up visits.

### 9.24. Opioid Receptor Antagonist Scale

Women will complete an opioid receptor antagonist-specific adverse effect scale that has been previously shown to be related to menstrual cycle related distress and

response to naltrexone (Epstein and King 2004; Roche et al., 2015). This measure will be completed at the medication titration, week 4, 8, 12, 16 and 26 visits.

### 9.25. Ovulation Predictor Test

A one step ovulation urine test will be used to determine when there is a surge in the (LH) luteinizing hormone, which will inform where female participants are in their menstrual cycle. This measure will be completed at the medication titration, week 4, 8, 12, 16 and 26 visits.

### 9.26. 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 initial screening and at each follow up visit.

### 9.27. 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. Abnormal findings will be reported as AEs, if appropriate.

### 9.28. Positive and Negative Affect Scale (PANAS)

The Positive and Negative Affect Scale comprises two mood scales, one that measures positive affect and the other which measures negative affect. The scale consists of 20 items using a 5-point scale that ranges from very slightly or not at all (1) to extremely (5). Participants will completed the PANAS initial screening and all follow up visits.

### 9.29. Pregnancy and Birth Control Assessment

An FDA approved rapid result urine pregnancy test will be used (i.e., dipstick test). 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. The Birth Control Assessment is designed to determine a female subject's compliance with the birth control specifications detailed in the inclusion criteria. The Pregnancy and Birth Control Assessment will be completed at the initial screening visit, the medication titration visit, and at the 4, 8 and 12 week follow up visits.

### 9.30. Questionnaire of Smoking Urges – Brief (QSU-Brief)

The Brief Questionnaire of Smoking Urges (QSU-Brief) consists of ten statements regarding the respondent's desire to smoke cigarettes at the time of assessment (i.e now). This ten item questionnaire measures agreement or disagreement with each statement by means of a 7-point scale where '1' indicates "strongly disagree" and '7' indicates "strongly agree." This assessment takes less than two minutes to administer and will be utilized at screening and all follow-up visits.

### 9.31. Readiness to Change (RTC) Ladder (cigarette use/alcohol use)

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

### 9.32. Saliva Collection

Normally-cycling and hormonal contraceptive using women will provide saliva samples for hormonal testing at medication titration and on each return to the laboratory for follow-ups 4, 8, 12, 16 and 26 weeks post quit date. Self-reported menstrual cycle phase will be confirmed by measuring levels of estradiol (E2) and progesterone (P4).

### 9.33. Self-Reported Habit Index Form (cigarette use/alcohol use)

The Self-Reported Habit Index Form is a 12-item index of habit strength for cigarette and alcohol use that will be completed at the initial screening visit. Responses will be self-reported by participants directly into the electronic data capture system.

### 9.34. Smoking History Questionnaire (SHQ)

The Smoking History Questionnaire will collect information on frequency and quantity of nicotine use. Participants will directly enter responses into the EDC system at the initial screening visit.

### 9.35. Structured Clinical Interview (SCID)

The SCID is a semi-structured interview for making the major DSM Axis-I diagnoses. It will be assessed by appropriately trained research staff to all participants at the initial screening visit to determine alcohol use disorder and rule out other exclusionary diagnoses.

### 9.36. 30-day Timeline Followback (TLFB)

The Time Line Follow Back will be administered for both alcohol use and cigarette smoking at initial screening, medication titration, and at all follow up visits. Information obtained in this interview will be recorded on the TLFB Calendar and transcribed to the database.

### 9.37. Urine Cotinine Levels

Participants will be asked to provide a urine specimen at the initial screening visit for testing of cotinine levels to verify that the participant is a regular smoker and at all follow up visits to assess for smoking abstinence.

### 9.38. Urine Drug Screen

An FDA cleared, CLIA waived urine drug test card will be used at the initial screening, medical screening and medication titration visits to assess candidates 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.

### 9.39. Vital Signs

Vital signs assessed at each visit include sitting blood pressure and pulse rate (after sitting for at least 3 minutes) and weight. Values will be recorded on the visit checklist and entered into the database.

### 9.40. Wisconsin Inventory of Smoking Dependence Motives (WISDM)

The Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) assesses 13 varied smoking motives in order to assess processes that may lead to nicotine dependence. Responses to this measure will be directly entered by the participant at the initial screening visit.

### 9.41. Wisconsin Predicting Patient's Relapse (WI-PREPARE)

The Wisconsin Predicting Patient's Relapse is a brief, seven-item questionnaire that taps physical dependence, environmental factors, and individual difference characteristics to suggest the nature of a patient's short- and medium-term relapse risk. The WI-PREPARE will be assessed at the initial screening visit with direct data entry by the participant.

### 9.42. Yale Craving Scale (YCS)

The Yale Craving Scale will be used to assess smoking and drinking urges at initial screening. This measure utilizes a generalized Labeled Magnitude Scale, which will be assessed by participants on paper and later scored and entered into the database.

## 10. ETHICS

### 10.1. 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.

#### 10.1.1. 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.

#### 10.1.2. 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.

### 10.2. 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.

#### 10.2.1. 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, sponsor officials, 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.

#### 10.2.2. 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.

### 10.2.3. 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.

### 10.2.4. 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.

### 10.2.5. 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.

# 11. 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 (MediaLab) 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.

## 11.1. 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 study sponsor, National Institute of Drug Abuse (NIDA), FDA, IRB, and the FDA 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.

## 11.2. 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. The investigator must provide key documents to the Sponsor prior to start of the study. 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. The Sponsor must be notified in writing of the name and

address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

### 11.3. Trial Registration

The PI will register the trial on the National Library of Medicine's Clinical Trials Registry at http://www.clinicaltrials.gov.

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## 13. APPENDICES

**13.1. Appendix 1: Schema of Study Procedures**
**13.2. Appendix 2: Schedule of Assessments**
**13.3. Appendix 3: Medication Information Sheets**
**13.4. Appendix 4: Smoking Cessation Counseling Manual**