"Effect of Prazosin and Naltrexone on Personalized Script Induced Alcohol Craving in Individuals with Alcohol Use Disorders with and without Comorbid PTSD"

NCT02322047

PaN Study Protocol (8-17-2020)

Design Overview

This is a 7-week double-blind, double-dummy, placebo controlled study of prazosin and naltrexone for Veterans with an AUD that includes two imaginal craving inductions at the final study visit, one oriented towards relief craving and the other towards reward craving. After passing an initial telephone screen, participants are seen for an in-person eligibility appointment that includes a physical and psychiatric examination, labs, and self-report measures. One hundred twenty individuals who meet study inclusion/exclusion criteria will enter the medication phase of the study within 14 days of the initial assessment initiating prazosin/placebo as well as 50mg naltrexone/placebo treatment. Randomization is blocked by gender, PTSD status, and desire to abstain vs. desire to cut down. Prazosin is titrated to three times daily dosing (9 am: 4mg; 3pm: 4 mg; 9pm: 8mg) at the end of two weeks. Naltrexone is taken once daily 50 mg/day with no titration schedule. The stable dose of both medications continues for four more weeks and medication compliance is evaluated through pill counts and riboflavin trace in urine analysis. On approximately day 42 participants come into the lab for the craving inductions (there is a two-week window after day 42 in which participants may still be seen if scheduling issues arise). The order of the craving inductions is counterbalanced, and their administration separated in time by 30 minutes to minimize carry over between them. Subjective responses to the craving inductions is obtained via relief oriented craving items and reward oriented craving items from the Desire for Alcohol Questionnaire. Participants are then assisted in returning their craving levels to baseline prior to debriefing. They are all offered DoD, VA, or community referrals to treatment. Both prazosin and naltrexone can be safely discontinued without tapering.

Setting, Recruitment, Participants, and Inclusion/Exclusion Criteria

Study Setting:

There are three VAPS study sites including the Seattle Division VA, the American Lake Division VA, and the Mt Vernon CBOC VA. Clinical backup in case of emergencies is available at all sites.

Participants and Recruitment:

Potential subjects are Veterans with a DSM-V Alcohol Use Disorder (AUD) recruited from the VA, the community, and other local alcohol treatment programs via letters, flyers, VA TV monitors, and advertising in the local media. Potential Veteran subjects will also be identified via Corporate Data Warehouse or VISTA fileman pull.

CDW/VISTA fileman: Access to the Corporate Data Warehouse is used to identify Veterans in the VAPSHCS area with an ICD-10 code for an active alcohol use disorder or a positive VA mandated alcohol screen (AUDIT-C) and without exclusionary diagnoses and/or medications. We retrieve potential participants' names and current mailing addresses and, after reviewing key information regarding additional inclusion/exclusion criteria in CPRS, we mail those who are likely eligible a recruitment letter with an "opt out" card. A $2 bill is included in each envelope to thank Veterans for reading the letter. Those who indicate they are interested in the study are screened on the telephone under an already approved waiver of documentation of consent. Those who do not return the opt out card and do not call the study are contacted by phone with up to three messages left to ascertain whether they are interested in learning more about the study and possibly completing the telephone screen.

Alcohol Clinical Reminder flag: IRB approval is in place to add the study as a treatment referral option for patients who screen positive on the annual AUDIT-C clinical reminder so that providers can discuss the study with patients at the time of screening and communicate with study staff regarding patients who are interested in learning more about the study.

We anticipate conducting approximately 1500 telephone screens and enrolling approximately 240 participants, approximately 70 of whom will fail to meet the study inclusion/exclusion criteria during the initial screen, and an additional 50 who will fail to meet the criteria later due to lab values that are of concern or poor compliance with the IVR monitoring. We plan to randomize 120 men and women with a current 12-month history of AUD who have recently consumed alcohol (see inclusion/exclusion criteria below) and want either to abstain or reduce their alcohol consumption.

Inclusion and Exclusion Criteria:

To move on from the in-person screening appointment, the following Inclusion/Exclusion criteria need to be met:

Inclusion: To be enrolled in the study participants need to meet the following inclusion criteria: Veteran of the U.S. military or National Guard Reserve; current AUD by DSM-V criteria; ≥ 14 drinks per week for females OR ≥ 21 drinks per week for males for at least 2 weeks in the last 3 months **and** some drinking during the past two weeks immediately prior to in-person screening OR 3+ binge drinking days in the last month as defined by 4+ SDUs for females and 5+ SDUs for males; at least mild alcohol craving as assessed by the Pennsylvania Alcohol Craving Scale (PACS; score ≥ 10) at baseline; age 18-80; English fluency and literacy; trying or planning to try to cut down on or abstain from alcohol; good general medical health, and capable of giving informed consent.

Exclusion Criteria: The following characteristics exclude potential participants from being randomized into the study: DSM-IV* diagnosis of an uncontrolled psychiatric disorder with psychotic symptoms or cognitive impairment; *if* taking psychiatric medication, **NOT** on a stable dose for at least 30 days prior to randomization; any suicidal ideation in the past 7 days, plan or intent past 6 months, or suicide attempt past year; homicidal ideation with plan and intent in the past 30 days; PHQ-9 endorsement of hopelessness or self-harm/SI and/or sum score ≥ 19 on items 1-9; any use of prazosin or naltrexone past 30 days; currently taking disulfiram or acamprosate *OR* planning to take any of these medications (including prazosin or naltrexone) during the 8 weeks of the study; current moderate or greater level of substance use disorder (past 30 days) on any psychoactive substance other than alcohol, nicotine, or cannabis; current diagnosis of any opioid or amphetamine use disorder, *OR* use of any amphetamine or opioid-containing medications during the previous 30 days; UDA screen positive for amphetamine, opioids; significant acute or chronic medical illness including unstable angina, recent myocardial infarction, history of congestive heart failure, preexisting hypotension (sys <100) or orthostatic hypotension (sys drop of > 20 mmHg; after two minutes of standing, or any drop w/dizziness); insulin-dependent diabetes mellitus; chronic renal or hepatic failure; pancreatitis; Meniere's disease; benign positional vertigo or narcolepsy; liver enzymes aspartate aminotransferase (AST), cirrhosis, alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), > 8 x the upper limit of normal or total bilirubin >2 mg/dL (in the absence of Gilbert's disease); allergy or previous adverse reaction to naltrexone, prazosin, quinazolines, or other α-1 adrenergic blockers or use of other α-1 adrenergic blocker; women who are pregnant, breastfeeding, or of childbearing potential and not using a contraceptive method judged by the investigator to be effective; legal involvement that could interfere with study participation including being court ordered for treatment; signs or symptoms of withdrawal at time of initial consent, or any participation in an experimental drug study or any addiction study past 30 days (See Appendix 1 for Initial Inclusion/Exclusion Checklist).

*DSM-IV criteria are used to determine these aspects of eligibility because we did not have access to the new DSM-5 criteria for these disorders at the start of the study.

Additional Inclusion/Exclusion Criteria:

To proceed to randomization participant lab values will need to indicate that it is safe for them to take the study medications (See Appendix 1 for Additional Inclusion/Exclusion Checklist).

Study Visits and Procedures

Telephone Screen: Interested callers are provided an overview of the study procedures either immediately if they reach someone when they call or their call is returned in two to three business days. Those who remain interested undergo a 15-20 minute telephone screen to ascertain basic inclusion/exclusion criteria under a waiver of documentation of consent. Those who are eligible and remain interested are scheduled for an in-person screening assessment. Please see the attached Study Flow Chart for a schematic overview of study activities.

Consent, Screening Assessment, and IVR Initiation (Visit 1; Study Day 1):

Consent Procedures: During Visit 1 (Study Day 1) the Study Clinician (Advanced Registered Nurse Practitioner (ARNP), Physician Assistant (PA), or physician) explains the study in detail by reviewing the study

consent with the patient, and if the individual is interested in proceeding, written informed consent and HIPAA authorization is obtained.

Participants are then asked to complete the UCSD brief assessment consent quiz to insure adequate comprehension of the consent and study procedures. If any items on the consent quiz are missed, the information pertaining to the items in question are reviewed and those items are re-administered. This measure is used to ensure that the potential participant can read well enough to be able to adequately read the written directions regarding the medication regimen and other study activities. If the clinician determines that the potential participant is likely to have adequate cognitive capacity to participate safely in the study, she/he reviews the quiz items missed and re-administer those items. If one or more of these items are missed again, the person is deemed unable to adequately understand study procedures, and the interview will be terminated. Those who able to answer the items correctly move on to the screening assessment.

Screening Procedures: The Study Clinician administers the substance use disorders section of the Mini International Neuropsychiatric Interview (MINI) to confirm DSM-V AUD and to assess for other potential substance use disorder diagnoses, any suicidal ideation in the past 7 days, plan or intent past 6 months, or suicide attempt past year, and homicidal ideation with plan and intent in the past 30 days (see *Study Instruments Table* below for an overview of assessment measures and materials). Recent drinking will be determined during the AUD assessment to determine whether participants meet drinking inclusion requirements. Presence of at least mild craving will be assessed via the self-report instrument "Pennsylvania Alcohol Craving Scale (PACS);" a score of at least 10 is required. Participants undergo a complete medical history and a physical examination with the Study Clinician. Participants who are found to be in good medical health from the initial exam complete the Clinician-Administered PTSD Scale for DSM-5 (CAPS) –to determine current PTSD diagnostic status. Participants complete a self-report demographic questionnaire that includes a forced choice item regarding their goals for their alcohol use over the next month (i.e., no change, reduce or cut down on amount of drinking, abstain completely). Those who indicate no desire to change their drinking are excluded from the study.

Those who are found to be initially eligible are asked to complete a short battery of self-report measures regarding craving, PTSD symptom severity, and characteristics that may moderate response to prazosin and naltrexone.

Data Capture: The interview data are recorded on paper or entered directly into an ACCESS database and self-report measures are entered online into a Survey Monkey form. Research staff remain in the room with participants while they complete the self-report measures to ensure that they do not leave the Survey Monkey website. Note: there are paper forms available in the event there is a problem with either the ACCESS or Survey Monkey systems or if a participant prefers to complete measures off-line.

Laboratory Procedures: Women of childbearing potential provide urine for a pregnancy test at screening and again at weeks 4 and 8. Laboratory evaluation of blood samples includes CBC, routine liver function tests, and routine serum chemistries. Specimens are also sent to a lab in Minnesota, MedTox, for assessment of the alcohol biomarker phosphatidylethanol – Peth. The lab procedure differs slightly by site as follows:

Seattle VA: The Clinical Research Unit (CRU) draws the blood samples and ship the specimens to MedTox. Either the Clinical Research Unit (CRU) or study staff deliver the remaining vial(s) to the Seattle VA lab for processing. Study participants are escorted by study staff to the CRU at the end of the initial study visit.

American Lake VA: Clinical Studies Unit staff (CSU) draws the blood samples and ships the specimens to MedTox. A member of the Clinical Studies Unit (CSU) or study staff delivers the remaining vial(s) to the lab for processing. Study participants are escorted by study staff to a room in the CSU at the end of the initial study visit.

Mt. Vernon CBOC VA:Blood specimens are drawn by lab personnel in the on-site lab. Specimens are then transported to the Seattle VA via a courier service. Mt Vernon CBOC VA specimens for MedTox are held at an identified location in the Seattle VA lab and then picked up by Clinical Research Unit (CRU) staff to be shipped to MedTox.

Safety and Comfort Call by Study RA (Safety and & Comfort Call #1): The RC calls the participant the next business day following the initial screen to assess any symptom exacerbation stemming from the visit, to provide support.

Randomization, Baseline Assessment, and Initial Medication Administration (Visit 2; Study Day 8):

Randomization: In this double-blind, double-dummy design participants are randomized to one of four study conditions: prazosin + naltrexone; prazosin + naltrexone placebo; naltrexone + prazosin placebo, and double placebo. Randomization is blocked by gender, PTSD status, and alcohol consumption goal (abstention vs. reduction). Random assignment to study condition is conducted by the VAPSHCS Research Pharmacist with randomization tables supplied by the study PIs. The Research Pharmacist distributes study medications appropriate to the randomization condition. The Research Pharmacist will have no contact with participants. Study medications will have been prepared ahead of time and will be available at Study Visit 2.

Baseline Assessment: Approximately one week after the screening visit (Study Day 8) the RC or Study Clinician contacts each participant to inform her/him as to whether she/he continues to fit the study inclusion criteria. Note: If issues arise while attempting to contact participant, there may be up to an additional week between the initial screen and the baseline appointment. At the outset of this visit, blood pressure and suicidality are rescreened to ensure that participants are safe to start the study medications. Those that are eligible and wish to continue are asked to complete the Form-90 to evaluate drinking history over the past three months. They also complete the Script Preparation Form to provide details for the craving induction paradigm (see below). They also complete a battery of self-report measures as well as complete the two craving measures (Desire for Alcohol Questionnaire and Obsessive Compulsive Drinking Scale) again.

Form-90 Details. The RC or Study Clinician administers the Form-90 to ascertain drinking history over the last three months as well as involvement in various types of health care and mental health treatment.

Script Preparation Details. Participants complete the Script Preparation Form to provide details regarding two different recent situations that led to alcohol craving or actual use, including physiological and emotional reactions and specific information on the type of alcohol craved or consumed. One situation will have evoked anxiety, concern, or worry that led to craving or consumption, and the other will have involved craving or consumption meant to lead to or enhance positive emotional reactions in a situation or that pertain to desired effects of alcohol (e.g., feeling high, intoxicated, "good," etc.). These materials are used by study staff to write brief, personalized, imaginal craving inductions using a standard format that portrays each experience in the second person, present tense, and incorporates between five and seven different visceral and muscular reactions. The imaginal scene leads the person through the situation up to the acquisition of the alcohol and bringing the drink to her/his lips (but not consuming it). Each induction is 1 minute long (approximately 214 words) and is recorded in a neutral tone by someone other than the Study Clinician or RC for replay during the induction procedures at session 8

Self-report Details. In addition, participants complete self-report measures on craving, drinking motives, and social networks. In addition, potential phenotypic moderators of interest will be examined, including family history of AUD, age of onset of drinking and AUD, drinking motives, depression, PTSD severity, anxiety sensitivity, emotional reactivity, disinhibition/impulsivity, and sensitivity to reward and punishment. They also complete the Stroop, another measure of impulsivity, which is administered by the RC or Study Clinician.

Medication Administration: Upon completion of the questionnaires the Study Clinician meets with the participant and orients him/her to the medication regimen. A two-week supply of the study medications loaded into a 14-day, 3-compartment Mediset is provided along with written instructions with visuals (i.e., pictures of the capsules) regarding dosing. Safety precautions regarding the medications are reviewed and participants are reminded to call the study telephone number should they experience any concerning side-effects or have any questions. The two-week prazosin titration schedule detailed in Table 1 is followed. Naltrexone does not require a titration period; participants are instructed to take the naltrexone/matched placebo capsule at the 9pm dosing time. Participants are given a pre-printed index-size card with study contact information and an alert that they could be taking naltrexone should they need emergency medical care involving pain medication (i.e., opiates).

Titration Schedule.

Prazosin Dosing:	**9 AM**	**3 PM**	**9 PM**	**Naltrexone 9 PM Dosing:**
Days 1-2			1 mg	50mg
Days 3-4	1 mg	1 mg	1 mg	50mg
Days 5-7	2 mg	2 mg	2 mg	50mg
Day 8-10	2 mg	2 mg	8 mg	50mg
Day 11-14	4 mg	4 mg	8 mg	50mg
Day 15-42	4 mg	4 mg	8 mg	50mg

Study Clinician Safety and Comfort Call (Safety and Comfort Call #2): The Study Clinician calls each participant the day immediately following the initial dose of study medications to assess whether any concerning side effects were experienced, including any suicidal ideation.

Vital Signs and Adverse Events Checks (Visits 3-7; Safety Calls # 3 & 4):

In-person Visits: To assure that participants are tolerating the study medications they are scheduled for five brief visits after the initial medication administration visit and before the final visit. Study days 12, 19, 29, 36, and 42 are the target (± 3 days) days for these in-person visits. At each of the in-person visits, sitting and orthostatic BP and HR are obtained. Participants are queried for adverse events using the open-ended question "How have you been feeling since you were last here?" Any elicited adverse events are recorded and rated for severity, duration, action taken, and relatedness to study medication. 20 mmHg drop in systolic BP accompanied by dizziness, lightheadedness or syncope at time of measurement or blood pressure systolic reading <100 with reported dizziness, lightheadedness or syncope at the time of measurement or between visits are considered unacceptable side effects and the titration is slowed or decreased to the last tolerated dosage or medication discontinued and study participation terminated as clinically appropriate. When the titration is adjusted, new study medications are requested from the pharmacy immediately and dispensed before the participant leaves.

In addition, participants complete a brief battery of measures to assess depression, anxiety, pain, and sleep and wake disturbance at each in-person visit. Participants are administered the PHQ-9 to screen for depression and suicidal ideation; the PHQ-9 was adapted for a one week timeframe.

Safety Calls: Study days 16 and 22 will be the target (± 3 days) days for the telephone calls 2 and 3. Participants are queried for adverse events using the open-ended question "How have you been feeling since we last saw you in the research clinic?" If safety concerns are apparent, participants are either be told to discontinue study medications or to adjust their dosing. An in-person study visit is scheduled as soon as possible in either case. The PHQ-9 suicide screen question is asked during each call with the timeframe adapted to cover since the participant last had contact with study staff.

Final Assessment and Craving Induction (Visit 8; Study day 42):

Final Visit Timing: Participants are scheduled to come back for their final visit approximately 7 weeks after their screening visit (Note: if scheduling difficulties arise there may be up to a two-week delay following the target end of the medication period in completing the final visit).

Final Assessment: Participants will complete the CAPS, PHQ-9, PROMIS measures, Form-90 (adapted for the 7-week time interval), and the Stroop with the study RC or Study Clinician, as well as the same paper-and-pencil measures collected at Visit 2 and during the weekly visits. They then undergo the two craving inductions in counterbalanced order (see below). At the conclusion of the craving induction procedures, the Study Clinician checks the participants' vital signs and adverse events as per Visits 3-7, and questions will be answered about medication discontinuation. Level of craving is reassessed and if the participant indicates a strong desire to actually drink, the Study Clinician will work with him/her to identify alternatives or ways of drinking moderately. Laboratory evaluation of blood samples is repeated and again includes CBC, routine liver function tests, and routine serum chemistries. Specimens are sent to a lab in Minnesota, MedTox, for assessment of the alcohol biomarker phosphatidylethanol – Peth. The same blood draw procedures indicated above for Visit 1 are repeated at the final visit.

The portion of the visit with the Study Clinician may take place before the craving induction depending on scheduling and room availability. At the end of the appointment participants are thoroughly debriefed, and provided community or VA referrals for alcohol treatment. This portion of the visit may be conducted by either the RC or the Study Clinician.

Craving Induction Procedures: At approximately 1pm or later participants are oriented to the craving induction procedures by the study RC or Study Clinician. Participants are seated in a comfortable chair in a quiet, undecorated room and fitted with headphones. The craving inductions are presented in counterbalanced order. Immediately prior to the first induction participants rate their current craving using the abbreviated Desire for Alcohol Questionnaire (DAQ). Current positive and negative affect are also assessed with the PANAS. Participants are then be instructed to close their eyes and imagine that they are in the situation they are about to hear. Their personalized reward oriented or relief oriented craving scene is played over the headphones. At the end of the scene the participants imagine the scene for an additional three minutes following which they are asked to complete the same ratings as before. Participants then relax for 30 minutes with engaging but not

provocative reading material and puzzle books prior to completing the second induction, the procedures of which parallels the first.

Study Medications

Prazosin: Prazosin HCl or identical matched placebo capsules are dispensed as 1, 2, and 4 mg capsules prepared by Kelley-Ross Pharmacy, a compounding pharmacy in Seattle. A 25mg riboflavin trace will be added to each capsule to evaluate medication compliance.

Naltrexone: 50 mg naltrexone or identical matched placebo capsules prepared by Kelley-Ross Pharmacy (tablets are ground and then compounded with the 25mg riboflavin trace).

Procedures for Maximizing Research Integrity

Maintaining the Study Blind: Only the VAPSHCS research pharmacist will have access to the randomization schedule, and she will have no contact with study participants. The blind may be broken by the PIs in case of safety concerns and for the purposes of interim analyses, but the information will not be shared with study staff except in the event of clinically significant safety concerns.

Maximizing Retention: We update contact information at each clinical and assessment visit. Participants will be paid $15 for each of the two blood draws.

Study Instruments

Study Construct/ Variables	Study Phase	Purpose
Inclusion/Exclusion Criteria and Blocking Factors		
Demographic information	V1	sample description, blocking (gender)
Medical history interview	V1	exclusion
Medical Exam	V1, V8	exclusion; safety
Lab values	V1, V8	exclusion; safety
MINI International Psychiatric Interview (DSM-V AUD & SUD onset of drinking and alcohol problems as well as recent drinking; DSM-IV Psychosis; suicidality, homicidality)	V1	inclusion and exclusion
Alcohol use goal (embedded in MINI AUD)	V1	inclusion, blocking, treatment moderator
Desires for Alcohol Questionnaire (DAQ)	V2, V8	, outcome
Life Events Checklist	V1, V8	blocking
Penn Alcohol Craving Scale	V1, V2, V8	inclusion
Clinician-Administered PTSD Scale For DSM-5 (CAPS)	V1, V8	blocking, treatment moderator (Aim 3)
Tracking		
Contact form	V1-V7	retention
Primary Outcomes		
Alcohol Biomarker (Peth)	V1, V8	outcome
Alcohol Craving (DAQ)	V8	outcome (Aim 2)
Alcohol use	V8	outcome (Aim 2)
Reward Craving for Craving Inductions from DAQ	V8	outcome (Aim 1)
Relief Craving for Craving Inductions from DAQ	V8	outcome (Aim 1)
Hypothesized Moderators		
State Trait Anxiety	V1, V8	moderation (Aim 3)
Anxiety Sensitivity Inventory	V1, V8	moderation (Aim 3)
Sensitivity to Reward/Punishment Scale	V1, V8	moderation (Aim 3)
PHQ-9 Depression	V1-V8	moderation (Aim 3); safety
Family History of AUD	V2	moderation (Aim 3)
Drinking Motives (Card Sort)	V2, V8	moderation (Aim 1)
Secondary Measures (Descriptive and/or Exploratory)		

AUDIT	V1	sample description
Drinking Motives Questionnaire	V1, V8	sample description
Obsessive Compulsive Drinking Scale	V1, V2, V8	sample description
Form-90 (alcohol)	V2, V8	sample description and outcome
Positive and Negative Mood States	IVR, V8	sample description
Barrett Impulsivity Scale	V2, V8	sample description
Stroop	V2, V8	sample description
PROMIS Pain Impact	V2 – V8	sample description
PROMIS Sleep quality	V2 – V8	sample description
PROMIS Wake Disturbance	V2 – V8	sample description
PROMIS General Distress; Anxiety	V2 – V8	sample description
Important People Inventory	V2, V8	sample description and possible moderator
Craving Induction Preparation		
Script Preparation Form	V2	provide details for craving inductions
Medication Management / Safety Checks		
Adverse Events Checklist and Vital Signs	All	clinical data for medication management
PHQ-9 Suicide item (#9)	All Phone Calls	safety

Data Safety Monitor/Research Monitor

In accordance with DODI 3216.02, the research monitor, Joseph Reoux, MD, has the authority to stop this research protocol in progress, remove individual human subjects from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess his report. Dr. Reoux is responsible for promptly report his observations and findings to the IRB or other designated official. He may also have direct contact with study participants should it be necessary to evaluate their safety and to make recommendations for any needed care or actions.

Data Management

Jane Shofer, M.S., a biostatistician from the University of Washington, will analyze the study data. Because Ms. Shofer is not a VA employee, the study data will be temporarily transferred to her laptop for analysis. Ms. Shofer will have the study data for one year. After one year, Ms. Shofer will delete them from her laptop. All data transfers will be made using methods approved by the VA Privacy Office and Information Security Office.

The transferred data will not have any identifying information connected with them. They will be raw data numbers only identified by a study code number. Inadvertent disclosure of any of these data will not have any impact on participants, as a third party would not be able to discern what the data are. The study crosswalk, the bridge between the study code and participant's name, will be kept in the project folder in the VA secure network (\\R01PUGHSM03.R01.MED.VA.GOV\Research\Simpson\IVR_Studies\00623 (AA-PaN Study)\11 - Tracking & Databases) and will not be shared with Ms. Shofer.

Statistical Analysis Plan

Statistical analysis will focus on three primary outcomes and a secondary outcome (average drinks per drinking day). The three primary outcomes are Percent Drinking Days (PDD), Percent Heavy Drinking Days (PHDD), and craving scores from PACS. The Form-90 will be used to gather drinking data for the three months prior to receipt of study medication as well as the six-weeks of study medication. This information will be used to compute PDD, PHDD, and average drinks per drinking day. Heavy drinking is defined as five or more drinks or four or more drinks in a day for men and women, respectively.

Hypotheses will be tested using intent-to-treat (ITT) linear mixed effect analyses. Specifically, differences in outcome measures from pre-treatment through the study medication phase will be estimated using linear mixed effects regression of outcome (the dependent variable) on treatment by study visit interaction (the independent fixed effects). Study visit will be modeled as categorical (post- vs. pre-treatment). Study participant will be modeled as a random effect. Model results will be summarized with estimated marginal means at pre- and post-treatment for each treatment group, within-group mean change from pre-treatment and mean difference in change by group. The latter set of means will also be presented as standardized effect sizes calculated using the standard deviation of the outcome at baseline as the denominator. Hypothesis testing for the overall difference in change in outcome by treatment will be carried out using the likelihood ratio test for the significance of the study visit by treatment interaction term. All means will be accompanied by standard errors, and all mean differences will also be presented with 95% confidence intervals (CIs), which will be adjusted for the four sets of differences estimated corresponding to the four treatment groups using the single-step method.

Exploratory analyses will be carried out to separate the effect of the treatment from the effect of the pre-treatment levels of each outcome on the estimates of post-treatment change in outcomes by adding a pre-treatment outcome by visit interaction term to the model. Descriptive analyses will be carried out to summarize clinical outcomes at the last week of study. Lower risk drinking will be defined using NIAAA guidelines; for men this means exceeding neither 14 drinks per week nor 4 drinks per day and for women this means exceeding neither 7 drinks per week nor 3 drinks per day. The number of abstinent drinking days and the number of participants who are completely abstinent during the last week will also be computed. Additionally, both the raw mean PDDs and PHDDs will be computed for each week of study medication and plotted by group to illustrate changes over time in these outcomes. Type 1 error will be set at .05 for each outcome. Analyses will be carried out using R 3.6.2, and the packages lme4, emmeans and tidyverse.

Descriptive information pertaining to study visit attendance, medication adherence, participant safety, adverse events, and medication adjustments will be provided by medication treatment condition.