Title: Alpha-1 Blockade for Alcohol Use Disorder (AUD) (DOXY)

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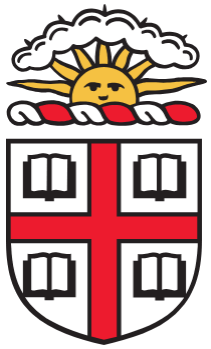

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Statistical Analysis Plan (SAP)

Focus: Selection a Priori of Moderators of Doxazosin Response in Alcohol Use Disorder

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Statistical Analysis Plan (SAP)

1. Study Design Overview

This trial evaluates the efficacy of the α_1-adrenergic receptor antagonist doxazosin versus placebo in reducing alcohol consumption and craving in individuals with Alcohol Use Disorder (AUD). The study comprises two distinct operational phases:

- **Naturalistic Phase:** A 12-week outpatient double-blind, randomized controlled trial (titration, 8-week active maintenance at target dose, and tapering) followed by a 4-week post-treatment follow-up period (Weeks 13–16).
- **Laboratory Phase**: A secondary mechanistic study testing the effect of doxazosin versus placebo on acute alcohol craving (Alcohol Craving Questionnaire; ACQ) during a combined pharmacologic stress (yohimbine) and cue-reactivity paradigm.

2. Preliminary Data Analysis and Data Integrity

Distributional Assumptions and Randomization Validation

Prior to primary hypothesis testing, all continuous primary and secondary outcomes (Drinks Per Week [DPW], Percentage of Heavy Drinking Days [HDD], Obsessive Compulsive Drinking Scale [OCDS], and ACQ) will be evaluated for distributional characteristics, normality, and severe skewness. Appropriate mathematical transformations (e.g., logarithmic or square-root) or generalized linear mixed-effects frameworks (e.g., negative binomial for count outcomes) will be applied as necessary.

Randomization balance across treatment arms (doxazosin vs. placebo) will be evaluated using chi-square (χ^2) tests for categorical variables and independent-sample t-tests for continuous baseline clinical measures (e.g., baseline blood pressure, cortisol, HAM-A). In accordance with CONSORT guidelines, any baseline imbalance identified will be treated as a candidate covariate. To preserve statistical power, key prognostic variables—including baseline drinking severity, biological sex, and age—will be pre-specified as fixed baseline covariates *a priori* regardless of statistical significance.

Attrition and Medication Adherence

Differential attrition between study arms will be evaluated using χ^2 tests. Descriptive statistics and between-group significance tests for objective adherence markers (pill counts and BP reduction) will be reported. To examine the effect of maximum tolerated dose and adherence, a secondary condition-by-adherence interaction (Tx × Adherence) on Week 12 DPW and HDD will be evaluated.

3. Naturalistic Phase Analysis Plan

Primary Outcomes and Model Specification

Primary analyses will follow the Intention-to-Treat (ITT) principle, including all randomized participants under a Missing at Random (MAR) assumption via Full Information Maximum Likelihood (FIML) estimation within Linear Mixed-Effects Models (LMM).

The primary model evaluates between-group differences in individual intercepts (mean levels during active maintenance, Weeks 5–11) and slopes (rate of change over time) for alcohol consumption outcomes (DPW and HDD). The longitudinal model is specified as:

$$Y_{it} = \beta_0 + \beta_1(\text{Tx}_i) + \beta_2(\text{Time}_t) + \beta_3(\text{Tx}_i \times \text{Time}_t) + \mathbf{\Gamma X}_i + u_{0i} + u_{1i}(\text{Time}_t) + \epsilon_{it}$$

Where:

Y_{it}: Outcome score (DPW or HDD) for subject i at week t.

Tx_i: Binary treatment indicator 1= doxazosin, 0 = placebo.

Time_t: Continuous week of assessment.

$\text{Tx}_i \times \text{Time}_t$: Interaction term evaluating treatment effect on slope trajectories over time.

ΓX_i: Vector of fixed baseline covariates, including baseline outcome value.

u_{0i}, u_{1i}: Subject-specific random intercepts and slopes.

In addition to ITT analyses, a secondary per-protocol analysis will be conducted on participants completing the full 12-week within-treatment period to evaluate treatment efficacy under optimal adherence conditions.

Discontinuous Post-Treatment Change Model (Weeks 1–16)

To model drinking trajectories across both active treatment (Weeks 1–12) and post-medication discontinuation (Weeks 13–16), a piecewise linear growth model will be implemented. Two distinct time components will be parameterized: $\text{Time}_{\text{active}}$ (coding weekly trajectory during active treatment) and $\text{Time}_{\text{post}}$ (coded 0 during active treatment, and $1,2,3,4$ across follow-up weeks 13–16). The interaction term $\text{Tx} \times \text{Time}_{\text{post}}$ directly tests whether the rate of change in alcohol consumption differs significantly between groups following medication discontinuation.

Secondary Naturalistic Outcomes (Craving)

Weekly alcohol craving outcomes—total OCDS score as well as the OCDS Obsession and Compulsion subscales—will be evaluated using the same LMM framework as described above, controlling for baseline OCDS subscale values.

4. Laboratory Phase Analysis Plan (Stress & Cue-Reactivity)

Laboratory aims evaluate the effect of doxazosin versus placebo on acute alcohol craving (ACQ) during a combined pharmacologic stress (yohimbine or placebo) and alcohol cue exposure paradigm[1]. The assessment schedule (baseline, minute 45, minute 90, and minute 135) aligns with the time-to-peak concentration ($T_{\max} < 1$ hour) of yohimbine. A repeated-measures LMM will analyze ACQ scores across the laboratory session:

$$\text{ACQ}_{it} = \beta_0 + \beta_1(\text{Tx}_i) + \beta_2(\text{Time}_t) + \beta_3(\text{Tx}_i \times \text{Time}_t) + \beta_4\left(\text{ACQ}_{\text{baseline},i}\right) + \Gamma \text{X}_i + u_{0i} + \epsilon_{it}$$

Where Time_t represents categorical laboratory assessment intervals (baseline, 45 min, 90 min, 135 min). The primary hypothesis tests the $\text{Tx} \times \text{Time}_t$ interaction to evaluate whether doxazosin attenuates peak craving at $T_{\max}$-aligned intervals (minutes 45 and 90) relative to placebo during active noradrenergic effect: coded as 1 = yohimbine; 0 = placebo.

5. Pre-Specified A Priori Moderation Analyses

Moderator Model Specification

To prevent post-hoc bias and identify responder phenotypes, five candidate moderator domains (three primary and two exploratory) were selected *a priori* based on noradrenergic neurobiology and stress-induced drinking mechanisms. Moderation will be evaluated by incorporating candidate moderators into the primary longitudinal mixed models:

$$\begin{aligned} Y_{it} = \beta_0 + \beta_1(\text{Tx}_i) + \beta_2(\text{Mod}_i) + \beta_3(\text{Tx}_i \times \text{Mod}_i) + \beta_4(\text{Time}_t) + \beta_5(\text{Tx}_i \times \text{Time}_t) + \beta_6(\text{Mod}_i \times \text{Time}_t) \\ + \beta_7(\text{Tx}_i \times \text{Mod}_i \times \text{Time}_t) + \Gamma \text{X}_i + u_{0i} + u_{1i}(\text{Time}_t) + \epsilon_{it} \end{aligned}$$

Where:

Mod_i: Pre-specified baseline moderator (entered as standardized continuous z-scores or binary genetic carrier indicators).

$\text{Tx}_i \times \text{Mod}_i$: Primary interaction term evaluating moderation of overall treatment intercept.

$\text{Tx}_i \times \text{Mod}_i \times \text{Time}_t$: Three-way interaction evaluating moderation of treatment slope over time.

Continuous moderators will be standardized (z-scores) prior to creating interaction terms. Significant continuous interaction terms ($p < .05$) will be probed using the Johnson-Neyman technique to calculate exact clinical region-of-significance thresholds. Multiple comparisons across candidate moderator tests will be controlled using the Benjamini-Hochberg False Discovery Rate ($q < .05$) procedure.

Summary of Candidate Moderators and Operationalizations

Family History Density of AUD (FHDA): Measured via the Family Tree Questionnaire (FTQ) weighted density score among first-degree relatives. Modeled continuously (z-score) in LMMs and dichotomized (≥ 0.50 median split) for visualization[2].

Baseline Physiological Sympathetic Tone: Measured via pretreatment standing Systolic and Diastolic Blood Pressure (SBP/DBP, mmHg). Modeled continuously (z-score), with clinical cutoffs ($> 130/80$ mmHg) evaluated during probing[3].

Alcohol Withdrawal Severity: Measured via the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) at baseline. Modeled continuously (z-score), with clinically significant withdrawal (CIWA-Ar ≥ 5) evaluated as a subgroup cutoff[4].

Stress Sensitivity & Trauma: Measured via the PCL-5 Hyperarousal subscale, Hamilton Anxiety Rating Scale (HAM-A), Perceived Stress Scale (PSS), and Stress Craving Visual Analog Scales (VAS). Modeled as continuous z-scores [5, 6].

Noradrenergic Polymorphisms: Targeted candidate gene variants governing pre-synaptic synthesis (*DBH* rs1611115) and post-synaptic expression (*ADRA1D* rs2236554). Coded under dominant genetic models: *DBH* ($0 =$ CC, $1 =$ CT/TT) and *ADRA1D* ($0 =$ AA, $1 =$ AT/TT)[7, 8].

6. Safety and Tolerability Analyses

Safety endpoints, including weekly incidence and severity of reported adverse events (e.g., headache, vertigo, edema, nausea, somnolence, anxiety, abdominal pain, palpitations), will be compared between treatment groups across the 12-week intervention and at the 16-week follow-up using Fisher's exact tests and generalized linear mixed models for binary outcomes.

7. Safety and Tolerability

To monitor safety and tolerability during the entire course of the study, we will examine between-group differences (doxazosin, placebo) in weekly reports of side effects (headache, vertigo, edema, nausea, somnolence, anxiety, abdominal pain, palpitations) during the 12-week study period and at the follow up visit (week 16).

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