Withdrawal-Related Dysphoria as a Moderator of Ibudilast for Alcohol Use Disorder

NCT #: NCT03489850

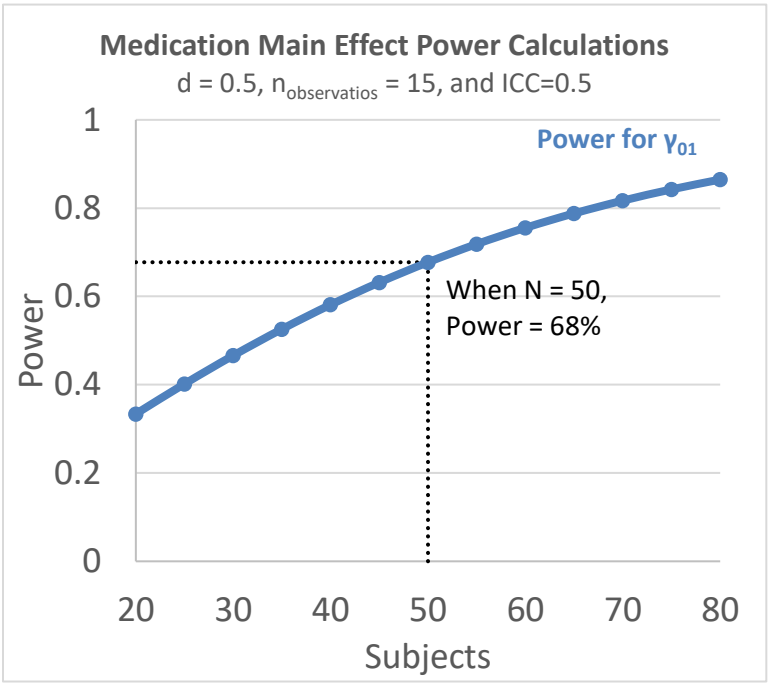
Statistics and Data Analysis Plan

Version 3

May 10, 2018

Ibudilast and Withdrawal-Related Dysphoria: Statistics and Data Analysis

Power Analysis



Given the exploratory nature of this proposed study, power analyses were conducted to determine statistical power to detect a medium effect size (Cohen's d = 0.5) for the main effect of medication. Power calculations were conducted using the method described in Scherbaum & Ferreter (2009) which was developed for the multilevel modeling framework necessitated in this study where DDA observations are nested within subjects [1]. Specifically, power was calculated based on (1) γ01 = 0.5 which represents a medium effect size for the main effect of medication, (2) 15 daily observations per subject, and (3) an ICC = 0.5, which is in line with a previous study from our laboratory which assessed mood and craving outcomes in a substance using sample. Based on these calculations (see Figure), the canonical 80% power is achieved at N = 70. However, pilot funding for this project unfortunately does not permit us to enroll more than 50 subjects. Given this maximal feasible N of 50, power was still adequate at 68%.

Interim Analysis

No interim analysis is planned.

Data analysis plan

Random Assignment Checks: To confirm the efficacy of random assignment and to check for medication group equivalence across demographics, drinking history, mood, alcohol use disorder severity and other relevant baseline measures we will perform t-tests on continuous items and $\chi 2$ tests of categorical items. Variables on which the two groups are unequal at pretest will be covariates in subsequent analyses. Medication groups will be stratified on the primary hypothesized mediator, withdrawal-related dysphoria to ensure equal representation.

Aim 1: IBUD effects on basal negative affect and alcohol negative reinforcement

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To test the effects of IBUD on basal negative affect in alcohol abstinence a series of multilevel models will be conducted on daily reports of negative mood collected with DDA. For this sample, only data collected at target IBUD dose (day 3 and beyond) and outside of the context of an alcohol drinking occasion will be used. Multilevel modeling will be employed to account for the nested nature of the data where observations are nested within subjects. In particular, we will analyze the effects of Medication, a two-level between-subjects factor, on self-reported negative affect taken from the POMS. Covariates will be: BDI-II score (a between-subjects variable), and any unbalanced demographic factors identified in the Preliminary analyses outlined above. All analyses will be conducted in **R** version 3.3.0 [2]. Multilevel models will be estimated using the **lme** function in the **multilevel** package [3]. This approach is consistent with our previous work in pharmacotherapy studies [4], [5].

IBUD effects on alcohol-related negative reinforcement will be tested through examining self-reported effects of alcohol in the context of a naturalistic drinking event. In this DDA study participants are trained to report when they drank alcohol the previous day and how the alcohol affected their mood and craving. In this study negative reinforcement will be operationalized by reductions in self-reported negative affect after consumption of alcohol. Based on the reported magnitude and duration of drinking we will estimate participants breath alcohol concentrations (BrAC's). To analyze alcohol's effects on negative affect, a series of multilevel models will test the effects of Medication (a 2-level between subjects factor), Alcohol (a binary within-subjects factor capturing mood "before," or "while" drinking), and the Medication × Alcohol interaction on the dependent variable, negative affect from the POMS. A significant Medication × Alcohol interaction will be interpreted in terms of IBUD affecting alcohol's negatively reinforcing effects.

Aim 2: IBUD effects on neural alcohol cue-reactivity
IBUD's effects on neural alcohol cue-reactivity will be analyzed using FSL's FEAT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). The following preprocessing steps will be used: 1) FSL'S MCLFIRT will be used for motion correction; 2) FSL's BET will be used for non-brain tissue and skull removal; 3) Data will be spatially smoothed using a Gaussian kernel of FWHM 8mm; 4) Data will be mean-based intensity normalized; and 5) Data will undergo highpass temporal filtering. Explanatory variables will be created by convolving the stimulus timing files with a double gamma hemodynamic response function. Contrast maps will be created by contrasting alcohol and neutral beverage cues. After transforming the masks into standard MNI space, higher-level analysis will be carried out and Z-statistic images will be thresholded using GRF-theory-based maximum height thresholding with a significance of one-tailed $p<0.05$. Hierarchical linear modeling (HLM) will be used to test for a medication effect. Cue type will be denoted by dummy-coded variables representing contrasts between alcohol and neutral beverage cues. The second level predictor will be medication condition (IBUD vs. placebo). The main approach is to test, at the whole-brain significance level, the effects of medication condition on BOLD activation generated during the alcohol cue reactivity paradigm.

Aim 3: Moderating Effects of Withdrawal-Related Dysphoria

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To test whether the presence of withdrawal-related dysphoria (WRD) predicts a greater response to IBUD, a series of multilevel models will be conducted building on the models analyzed in Aim 1. Specifically, in these models we will test the moderating effects of WRD, a binary between-subjects factor on IBUD effects through the inclusion of the Medication × WRD interaction. A significant interaction between Medication × WRD, or Medication × WRD × Alcohol will be interpreted as evidence that the presence of withdrawal related dysphoria is an important predictor of the clinically relevant effects of IBUD.

Aim 4: Neural Cue Reactivity as a Predictor of Future Drinking
To test whether neural alcohol cue reactivity can predict drinking in the week following neuroimaging, we will conduct a correlational analysis. We will calculate the number of drinks per drinking day for the 7 days following the Day 8 mid-point neuroimaging visit from the DDA data. We will also derive the maximum percent signal change from the whole brain fMRI analyses using Featquery (part of FSL's FEAT). This signal will be derived from the alcohol versus control cue contrast. For Primary Aim 2a, we will compute correlations between the number of drinks per drinking day and the whole brain percent signal change values using SAS Statistical Software.

Exploratory Aims:
Additional models analogous to those outlined for Aim 1 and Aim 3 will be conducted on the following outcomes: Positive Mood (POMS) and Craving (AUQ) assessed in daily diary reports, Withdrawal-Related Dysphoria (RHDQ) during alcohol abstinence, and Stimulation and Sedation (B-BAES).

Citations

[1] Charles A. Scherbaum and Jennifer M. Ferreter, "Estimating Statistical Power and Required Sample Sizes for Organizational Research Using Multilevel Modeling," *Organ. Res. Methods*, vol. 12, no. 2, pp. 347–367, Apr. 2009.
[2] R Development Core Team, *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2008.
[3] P. Bliese, *multilevel: Multilevel Functions*. 2013.
[4] L. A. Ray, S. Bujarski, P. F. Chin, and K. Miotto, "Pharmacogenetics of Naltrexone in Asian Americans: A Randomized Placebo-Controlled Laboratory Study," *Neuropsychopharmacology*, vol. 37, no. 2, pp. 445–455, Jan. 2012.
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[6] R. Miranda *et al.*, "Biobehavioral mechanisms of topiramate's effects on alcohol use: an investigation pairing laboratory and ecological momentary assessments," *Addict. Biol.*, p. n/a-n/a, Nov. 2014.