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

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Protocol version 4

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Ibudilast Withdrawal Protocol
Study Design

Specific Aims

Alcohol use disorder (AUD) is a prevalent and disabling psychiatric disorder with few, and only moderately efficacious, treatment options. Consequently, the identification of novel treatment targets and the development of rigorous laboratory paradigms to screen and optimize novel therapeutics represents a research priority. Ibudilast (IBUD) is a neuroimmune modulator that inhibits phosphodiesterase-4 and -10 and macrophage migration inhibitory factor. Recently in an AUD sample, IBUD was shown to decrease reactivity to a psychological stressor. Furthermore, IBUD was effective in blunting alcohol reward among participants with greater depressive symptoms, a hallmark symptom of protracted withdrawal. It is still unknown how neuroimmune modulation impacts brain processes that underlie alcohol reward processing. Recently, preclinical research in opiates has demonstrated that drug withdrawal is necessary for microglia activation and neuroinflammation in reward networks, suggesting that IBUD may be most effective among patients who experience withdrawal-related dysphoria. Therefore, this proposed study aims to examine withdrawal-related dysphoria as a moderator of IBUD efficacy in the natural environment measured using Daily Diary Assessment (DDA) approaches. To accomplish this aim, participants meeting criteria for AUD and balanced on the presence of withdrawal-related dysphoria will be enrolled in a double-blinded IBUD trial including consisting of two weeks randomized to medication, DDA assessment, and fMRI. The proposed research aims are:

Aim 1: Test whether IBUD reduces basal negative affect in abstinence and blunts alcohol-related negative reinforcement. It is hypothesized that IBUD will reduce basal levels of negative affect during alcohol abstinence, and in so doing will interfere with alcohol-induced blunting of negative affectivity as captured during naturalistic drinking episodes.

Aim 2: Test whether IBUD attenuates neural alcohol cue-reactivity. It is hypothesized that IBUD will reduce BOLD activation to alcohol cues in mesocorticolimbic reward circuitry.

Aim 3: Test whether withdrawal-related dysphoria moderates the effects of IBUD. It is hypothesized that IBUD will alleviate basal negative affect, interfere with alcohol-induced negative reinforcement and attenuate BOLD activation to alcohol cues only among participants who experience dysphoria in withdrawal.

Aim 4: Test whether neural activation to alcohol cues is predictive of drinking outcomes. It is hypothesized that individuals with higher mesocorticolimbic activation to alcohol cues will report more drinking in the week following the neuroimaging session.

Participants

Participants (N = 50) will be men and women ages 21 to 45 recruited in Los Angeles. Participants will be screened for inclusion and exclusion criteria by online and telephone screens which will also assess for withdrawal-related dysphoria. Eligible participants will then complete an in-person behavioral screen where they will complete self-report assessments of demographics, psychological state/history, and alcohol and drug use. A Masters level clinician will complete a structured diagnostic interview (SCID) and assess for physiological withdrawal (CIWA).

Inclusion Criteria

(1) Age between 21 and 45

(2) Meet DSM-5 criteria for current Moderate-to-Severe AUD
(3) Current Heavy Drinking (> 14 drinks per week for men; > 7 drinks per week for women), as indicated by self-reported drinking for the 30 days prior to screening
(4) Have reliable internet access

Exclusion Criteria

(1) Currently receiving or seeking treatment for AUD*
(2) Past year DSM-5 diagnosis of any substance use disorder other than alcohol or nicotine
(3) A lifetime diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder
(4) Current use of drugs, other than marijuana, verified by a urine toxicology screen*
(5) Pregnant, nursing, or refusal to use reliable birth control (if female)*
(6) A medical condition that may interfere with safe participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension, diabetes, or AST, ALT, or GGT ≥ 3 times upper normal limit)
(7) Self-reported recent (i.e. past 30 day) use of medications that are contraindicated with ibudilast*
(8) Non-removable ferromagnetic objects in body
(9) Claustrophobia
(10) Serious head injury or prolonged period of unconsciousness (>30 minutes)

* Participants who meet these criteria at any point during the course of the study (i.e. after randomization) will be withdrawn from the study for safety purposes.

Stratification

To test the role of withdrawal-related dysphoria, participants will be balanced on their yes/no response to the item “I drink because when I stop, I feel bad (I am nervous, irritable, and I sleep poorly)" taken from the Reasons for Heavy Drinking Questionnaire (RHDQ).

Medication Administration

Study medication and matched placebo will be provided by Medicinova Inc. and dispensed by the UCLA Health Pharmacy Investigational Drug Section who will also maintain the blind. After establishing eligibility, participants will be provided with their first medication dosage in a blister-pack. IBUD will be provided in 10 mg capsules and participants will be titrated as follows: 20 mg BID during days 1-2, 50 mg BID during days 3-14, or matched placebo. All capsules will contain a riboflavin (50 mg) tracer to verify compliance. EMA assessment will begin on Medication Day 1 and will continue through Day 15 (one day post medication termination).

Measures

Behavioral Screen Measures

1. Breathalyzer
2. Urine toxicology screen and pregnancy test (if female)
3. The Structured Clinical Interview for DSM-5 (SCID)
4. Drink Years Assessment (DYA)
5. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar).

6. A 30-day alcohol, cigarette, and marijuana timeline follow-back (TLFB)
7. Reasons for Heavy Drinking Questionnaire (RHDQ)
8. Reward-Relief Drinking Scale (RRDS)
9. The Alcohol Dependency Scale (ADS)
10. The Alcohol Use Disorders Identification Test (AUDIT)
11. Family Tree Questionnaire (FTQ)
12. Fagerstrom Test for Nicotine Dependence (FTND)
13. Beck Depression Inventory-II (BDI-II)
14. Pain Catastrophizing Scale (PCS)
15. Graded Chronic Pain Scale (GCPS)
16. RTC Ladder
17. Snaith-Hamilton Pleasure Scale (SHAPS)
18. Penn Alcohol Craving Scale (PACS)
19. Obsessive Compulsive Drinking Scale (OCDS)
20. Concomitant Medications Assessment
21. Center for Cognitive Neuroscience MRI Safety Screening Form

Physical Exam Measures

1. Breathalyzer
2. Urine toxicology screen and pregnancy test (if female)
3. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar).
4. Timeline follow-back (TLFB)
5. Concomitant Medications Assessment

Baseline Visit Measures

1. Breathalyzer
2. Urine toxicology screen and pregnancy test (if female)
3. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar).
4. Timeline follow-back (TLFB)
5. Beck Depression Inventory-II (BDI-II)
6. Graded Chronic Pain Scale (GCPS)
7. Snaith-Hamilton Pleasure Scale (SHAPS)
8. Penn Alcohol Craving Scale (PACS)
9. Obsessive Compulsive Drinking Scale (OCDS)
10. Side Effects Checklist (SAFTEE)
11. Open Ended Side Effects Interview
12. Concomitant Medications Assessment

Midpoint Measures

1. Breathalyzer
2. Urine toxicology screen and pregnancy test (if female)
3. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar).
4. Timeline follow-back (TLFB)
5. Beck Depression Inventory-II (BDI-II)

6. Graded Chronic Pain Scale (GCPS)
7. Snaith-Hamilton Pleasure Scale (SHAPS)
8. Penn Alcohol Craving Scale (PACS)
9. Obsessive Compulsive Drinking Scale (OCDS)
10. Side Effects Checklist (SAFTEE)
11. Open Ended Side Effects Interview
12. Concomitant Medications Assessment
13. Center for Cognitive Neuroscience MRI Safety Screening Form

Midpoint Functional Brain Imaging

After the midpoint measures (above) are collected, participants will complete a brain functional magnetic resonance imaging (fMRI) scan. 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.

Participants will be asked to have a normal night's sleep the night before the scan, have no more than one alcoholic drink, and abstain from drinking coffee within 2 hours prior to the scan. Breath alcohol concentration must be zero and for female participants the pregnancy test must be negative immediately prior to the scanning session. Prior to scanning, subjects will practice the task in front of a computer monitor with headphones and a button response box using the same stimulus delivery software as for fMRI scanning. The subjects will practice until it can be ascertained that they understand the task.

During the imaging session we will utilize several structural and functional scans. The structural protocol will consist of a high-resolution, matched-bandwidth (MBW) scan and a structural magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan. The functional scan will include a fMRI alcohol-cue reactivity paradigm previously reported to elicit blood oxygen level dependent (BOLD) response in mesocorticolimbic regions (Schacht et al., 2011).

The visual alcohol cue reactivity paradigm is a well-validated, with strong reliability and within-participant stability (1). The alcohol cues task consists of viewing alcohol and neutral cues, developed based on work by Schacht and colleagues (2011). There are five types of visual cues: alcoholic beverages, non-alcoholic (neutral) beverages, blurred alcoholic beverages, blurred non-alcoholic beverages, and a fixation cross. Stimuli are presented in six 120-s epochs (total scan duration: 12 minutes), with each epoch consisting of four 24-s blocks (one block of alcohol cues, one block of neutral cues, one block of blurred images, and one block of fixation). During each 24-s block, 5 individual pictures will be displayed for ~4.8 seconds each. Alcohol blocks will be specific to beverage type (beer, wine, or liquor), with two blocks of each beverage type. Each block will be followed by a 6-s washout period, which allows the hemodynamic response from the previous block to decline.

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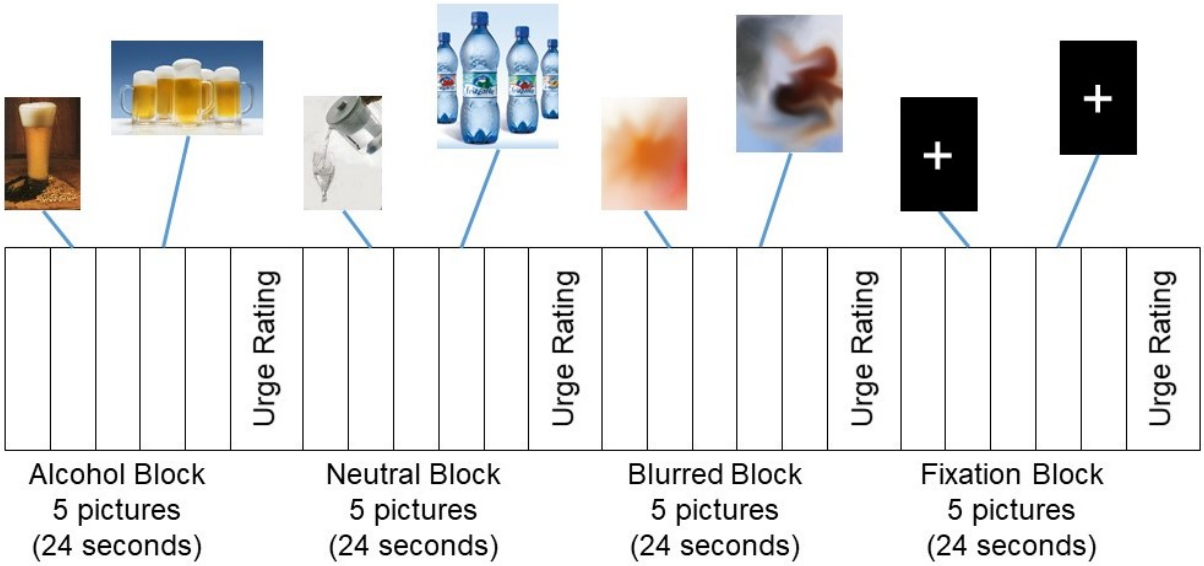
Prior to scanning, participants will be shown how to provide ratings of their cravings using an optically isolated universal serial bus (USB) interface, which consists of a four-button (1= low to 4= high) response box. Subjects will provide ratings of their craving immediately following each cue block.

Example Epoch of Alcohol Cue Reactivity Paradigm



Final Measures

1. Breathalyzer
2. Urine toxicology screen, ETG test, and pregnancy test (if female)
3. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar).
4. Timeline follow-back (TLFB)
5. Beck Depression Inventory-II (BDI-II)
6. Graded Chronic Pain Scale (GCPS)
7. Snaith-Hamilton Pleasure Scale (SHAPS)
8. Penn Alcohol Craving Scale (PACS)
9. Obsessive Compulsive Drinking Scale (OCDS)
10. Side Effects Checklist (SAFTEE)
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DDA Measures

- See attached IBUD DDA Codebook

Study Design and Flow Chart