New York State Psychiatric Institute

Institutional Review Board

September 5, 2017

To: Dr. Elias Dakwar

From: Dr. Edward Nunes, Chairman, IRB

Subject: **APPROVAL NOTICE**: **CONTINUATION APPROVAL**
EXPEDITED PER 45CFR46.110(b)(1)(f)(8)(c)

Your protocol **#7014** entitled: **GLUTAMATERGIC MODULATION OF DISORDERED ALCOHOL USE: A RANDOMIZED CONTROLLED TRIAL** ACAR/PSF version date 8/30/17 and consent forms (version) have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **SEPTEMBER 8, 2017 TO SEPTEMBER 7, 2018.**

Consent requirements:

X Not applicable: (RECRUITMENT COMPLETED. DATA BEING ANALYZED)

☐ 45CFR46.116(d) waiver or alteration of consent for the telephone screen.

☐ Signature by the person(s) obtaining consent is required to document the consent process.

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐ Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

CC: RFMH (AA023010-01A1)
CU Grants & Contracts (DA029647-04)
CUMC-IRB (no number assigned)

EN/ls

Signed copy on file at IRB

Protocol Title:
Glutamatergic Modulation of Disordered Alcohol Use: A Randomized, Controlled Trial

Version Date:
09/05/2017

Protocol Number:
7014

First Approval:
09/19/2014

Expiration Date:
09/07/2017

Contact Principal Investigator:
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Co-Investigator(s):
Frances Levin, MD

Research Chief:
Herbert Kleber, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Substance Use

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.

There will be no unaffiliated personnel involved in this study.

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Study procedures have been well tolerated. There have been no adverse events. The most common effects from the infusion are transient psychoactive effects (subsiding by 15 minutes post-infusion) and sedation (resolving by 1 hr post-infusion). Participants have engaged with the psychotherapy appropriately and a majority has reduced alcohol use substantially.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
09/31/2018

Overall Progress

Approved sample size
50
Total number of participants enrolled to date
44
Number of participants who have completed the study to date
40
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
alcohol dependent individuals
Total number of participants enrolled from this population to date
44
Gender, Racial and Ethnic Breakdown

Race	Ethnicity	Female	Male
White	Hispanic	2	1
	Non-Hispanic	14	14
African American	Hispanic	1	0
	Non-Hispanic	4	2
Other	Hispanic	0	2
	Non-Hispanic	2	2
	Total	23	21

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
18
Did the investigator withdraw participants from the study?
Yes
Circumstances of withdrawal:
1 participant stopped drinking during screening, and maintained abstinence after consent. Another participant decided she did not want to change her drinking. Both participants were not randomized and continued with MET, as per protocol.
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults
✓ Adults over 50
✓ Substance Users

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study
2

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract application is a pending review or a funding decision
Source of Funding
Federal
Institute/Agency
NIAAA
Grant Name
R21
Grant Number
AA023010-01A1
Select one of the following

Single Site
Business Office
RFMH
Does the grant/contract involve a subcontract?
No

Funding Source #2

Is the PI of the grant/contract the same as the PI of the IRB protocol?
No
Who is the PI of the grant/contract?
Levin, Frances, MD
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
NIDA
Grant Name
K24
Grant Number
DA029647-04
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Alcohol dependence is associated with many changes in the brain, including alterations in the functioning of molecules involved in neural communication (neurotransmitters). Glutamate is the most abundant excitatory neurotransmitter in the brain, and various lines of evidence indicate that

various problems associated with drug dependence involve alterations in the transmission of glutamate. Modulation of glutamate is therefore an important medication strategy for alcohol dependence. Our investigations with ketamine, a potent glutamate modulator, in drug dependent individuals suggest that it may exert unique and helpful effects on problems associated with addiction, such as impaired motivation to quit, high sensitivity to stress, and reactivity to drug-related cues. This project will evaluate the effect of a single dose of ketamine on alcohol use in treatment seeking, non-depressed, alcohol dependent individuals who complete a 5-week outpatient double-blind, randomized, controlled study. Participants will engage in Motivational Enhancement Therapy (MET), an evidence-based therapy aimed at shoring up motivation to effect positive changes.

Background, Significance and Rationale

Background, Significance and Rationale

Modulation of *N*-methyl-D-aspartate (NMDA) receptor activity is recognized as an important treatment strategy for alcohol use disorders. As a high-affinity NMDA antagonist with potent modulatory and down-stream effects, ketamine is a promising, if unconventional, candidate for uniquely targeting the NMDA alterations and related deficits associated with alcohol dependence.

In a recent study aimed at testing the anti-addiction benefits of ketamine, we investigated its effects (24 h post-infusion) on dependence-related deficits that implicate glutamate-based neuroadaptations, specifically low motivation to quit and high cue reactivity. A single infusion significantly increased motivation to stop cocaine in active cocaine users (as assessed by the U. Rhode Island Change Assessment), as well as reduced cue-induced craving (by Visual Analogue Scale), when compared to the active control (lorazepam). The substantial effect of ketamine on motivation to quit extended to at least 72 h post-infusion, and predicted abstinence during follow-up.

It is possible that ketamine may effectively address the problematic use of alcohol or other drugs, especially in the context of a treatment aimed at enhancing and sustaining ketamine-induced benefits (e.g., increased motivation to quit). To this end, we have feasibly integrated a single ketamine infusion into an ongoing treatment for cocaine dependence. In the present trial, we propose to investigate the effect of a single sub-anesthetic dose of ketamine on problematic alcohol use in non-depressed alcohol dependent individuals receiving Motivational Enhancement Therapy (MET), an evidence-based treatment aimed at promoting motivation for changing problematic behaviors. We predict that ketamine will significantly reduce percentage of heavy drinking days (>4 drinks for men, >3 for women) as compared to the active control (midazolam). Other aims pertain to 1) abstinence following ketamine, and 2) effects of ketamine on deficits that implicate prefrontal dysfunction or NMDA hypersensitivity, such as craving and low self-efficacy.

Specific Aims and Hypotheses

Specific Aims and Hypotheses

Primary Aim: Test the hypothesis that ketamine will significantly reduce percentage of heavy drinking days (number of heavy drinking days divided by post-infusion study days) compared to the control.

Secondary Aim 1: Test the hypothesis that ketamine, as compared to the control, will increase percentage of abstinence days (defined as number of abstinent days divided by post-infusion study days).

Secondary Aim 2: Test the hypothesis that ketamine, as compared to the control, will significantly improve adaptations linked to disruptions in glutamate, including low mindfulness and self-efficacy, impulsivity, withdrawal phenomena, and perceived stress sensitivity.

Description of Subject Population

Sample #1

Specify subject population
Alcohol Dependent Adults
Number of completers required to accomplish study aims
40
Projected number of subjects who will be enrolled to obtain required number of completers
55
Age range of subject population
21-60

Gender, Racial and Ethnic Breakdown

The study described in the present application seeks to include women and minorities; the study does not exclude any potential participants on the basis of race and gender. Based on previous studies conducted with treatment-seeking alcohol dependent individuals, the sample is expected to include approximately 60% White, 35% African American, 20% Hispanic, 5% other racial groups. Approximately 35% will be women. This profile is representative of the areas from which our research facility draws participants in New York City and the greater metropolitan area.

Description of subject population
Applicants will be considered eligible if they meet baseline use criteria (e.g., at least 4 heavy drinking days per week), are medically healthy, have alcohol dependence, are interested in reducing or stopping use, and are between 21 and 60. Exclusion criteria include severe physiological dependence on alcohol or certain other substances, a history of abuse of or adverse reaction to ketamine or benzodiazepines, a history of psychotic or dissociative symptoms, a first-degree family history of psychosis, obesity (BMI > 35), or cardiovascular/pulmonary disease, and pregnancy, lactation, or active attempts to become pregnant.

Recruitment Procedures

Describe settings where recruitment will occur

Adult male and non-pregnant female patients will be recruited in the New York City metropolitan area. This project will be carried out at the research clinic of the Biological Studies Unit (BSU) within the New York State Psychiatric Institute (NYSPI), where several studies for substance use disorders are currently being conducted. Infusions will take place at a dedicated site within the BSU.

How and by whom will subjects be approached and/or recruited?
At the first contact, a standardized telephone interview is conducted. Those who preliminarily meet entry criteria are scheduled for a first screening visit, during which they give informed consent, provide a urine sample for toxicology and urinalysis, complete the Hamilton Depression Scale (HAM-D) and Dissociative Experiences Scale (DES).
How will the study be advertised/publicized?
We expect to randomize 40 participants recruited through word of mouth, advertising, and referral.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02539511

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
No

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Alcoohl Dependent Adults
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criterion	Method of Ascertainment
Active alcohol dependence. In the case of the use of other drugs, alcohol is designated as the primary drug. At least four heavy drinking day over the past 7 days (>4 drinks a day for males, >3 drinks for females) OR minimum weekly use of 35 drinks for males and 28 for females	MINI, Psychiatric Interview, self-report, utox

2. Physically healthy	Laboratory tests (urinalysis, blood chemistry, 12-lead ECG in normal limits), physical examination, self-reported medical history
3. No adverse reactions to study medications	Subjects will be asked about previous exposure to ketamine and midazolam
4.21-69 years of age	Self-reported age, verification with legal identification
5. Capacity to consent and comply with study procedures, including sufficient proficiency in English	A short written test about study procedures, MINI, psychiatric interview
6. Seeking to reduce or stop alcohol use	Psychiatric Interview, self-report

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criterion	**Method of Ascertainment**
1. Meets DSM IV criteria for current major depression, bipolar disorder, schizophrenia, any psychotic illness, including substance induced psychosis, and current substance-induced mood disorder with HAMD score > 12.	Psychiatric Interview, MINI, HAMD
2. Physiological dependence on another substance, such as opiods or benzodiazepines, excluding caffeine, nicotine, and cannabis	MINI, Psychiatric Interview
3. Delirium, Dementia, Amnesia, Cognitive Disorders, or Dissociative disorders. Significant dissociative symptoms (DES>30)	MINI, Psychiatric Interview
4. Current suicide risk or a history of suicide attempt within the past year	MINI, Psychiatric Interview
5. Inability to safely initiate 24 hours of abstinence from alcohol, as evidenced by CIWA > 10 during screening; **repeated inability to initiate abstinence during the trial without**	Psychiatric Interview, CIWA

incurring significant withdrawal (CIWA > 10); history of severe withdrawal phenomena over the past 6 months (e.g., withdrawal-related seizure); or self-reported inability to maintain abstinence for 24 hours without substantial distress.		
5. Pregnant or interested in becoming pregnant during the study period	Blood and urine pregnancy testing, self-report	
6. Any of the following cardiac conditions: angina, clinically significant arrhythmia, or mitral valve prolapse	Laboratory tests (12-lead ECG in normal limits), physical examination, self-reported medical history	
7. Unstable physical disorders which might make participation hazardous such as end-stage AIDS, hypertension (**blood pressure elevated at >140/90)**, WBC < 3.5, active hepatitis or other liver disease with elevated transaminase levels (< 2-3 X upper limit of normal will be considered acceptable if PT/PTT is normal), renal failure (creat > 2, BUN >40), epilepsy, or untreated diabetes	Physiological tests (urinalysis, blood chemistry, 12-lead ECG), physical examination, self-reported medical history	
8. Previous history of ketamine or benzodiazepine misuse or abuse, and a history of an adverse reaction/experience with prior exposure to ketamine or benzodiazepine	Physical examination, self-reported medical history	
9. Recent history of significant violence (past 2 years)	MINI, Psychiatric Interview	
10. First degree relative with a psychotic disorder (bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis NOS)	MINI, Psychiatric Interview	

11. BMI > 35	Physical examination
12. On psychotropic or other medications whose effect could be disrupted by participation in the study	Psychiatric interview, self-reported medical history

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
Yes
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Participants will be provided a consent form (which also doubles as the primary study consent form) that outlines the screening procedures for the present protocol. Participants will be provided an opportunity to ask any questions. If they express understanding about what screening involves, they will be asked to document consent, and screening procedures will proceed appropriately.
Describe Study Consent Procedures
Participants will have consented for screening, as above, and have completed screening . Eligible participants will then be provided the consent form for the present protocol, and after reading it and discussing it with the PI (E.D.), will undergo a brief quiz to ensure understanding.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
Yes
Is breach of confidentiality the main study risk?
Yes
Describe the study component(s) for which waiver of documentation is requested
We request a waiver of documentation of consent for the phone screen only (due to verbal consent only, not written documentation of consent). The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Dakwar, Elias, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Overview: Consenting participants meeting study criteria will be entered into the study and begin MET. In week 2, they will achieve abstinence for 24 hours, and be randomized (1:1) to receive either ketamine or active control (midazolam). We expect to randomize 40 participants.

Clinic Visits (5 weeks) Participants will present twice weekly to clinic for engagement in MET and to meet with a psychiatrist, except for week 2, when they will meet with staff on 3 occasions. Assessments are intended to investigate patterns of alcohol and other drug use by interview (Timeline Follow Back), and to ascertain craving (VAS), withdrawal (CIWA), self-efficacy (Drug Taking Confidence Questionnaire and Alcohol Abstinence Self Efficacy Scale), perceived stress (modified Perceived Stress Scale), mindfulness (Five Facet Mindfulness Questionnaire) and impulsivity (Barrett's Impulsivity Scale). Follow-up by telephone occurs at 1 month and 3 months after study completion, and is intended to assess drinking behavior. **Vital signs are obtained after measures are completed, and prior to the MET session and/or meeting with a psychiatrist. Participants who have consecutive BP readings of >160/110 between visits as they begin to taper or discontinue alcohol will be removed from the trial and provided referrals to other providers. All participants meet with the PI or Co-I at every visit. The PI or Co-I is available at all times to meet with participants, and no participant undergoes procedures, including screening and therapy, without one of them being present or available on the floor.**

Motivational Enhancement Therapy (MET): MET is a psychotherapy found effective for various substance use disorders. The approach is patient-centered, with the therapist utilizing a variety of strategies to promote motivation and self-directed change by guiding the exploration and resolution of ambivalence. MET consists of an initial session, during which goals are explored and motivational statements elicited, and 2 to 4 subsequent sessions to achieve these goals. In this trial, a standard 5-week MET platform will be

provided, with an additional session after the infusion (6 sessions total). The short length of MET is appropriate for evaluating the efficacy of a single infusion, while still providing an effective treatment to participants. MET will be provided by individuals who will have been trained in MET and the therapy procedures in this protocol will be nearly identical to what we have used in previous trials. Sessions may be taped if participants provide consent, and will be overseen and supervised by Dr. Dakwar to ensure fidelity.

Abstinence Initiation: In week 1, participants will decide with their therapists on a day in week 2 in which they will initiate abstinence. They will also present to the clinic on that day for a session of MET and to receive assessments (CIWA, BAL, TLFB). Participants would have been screened prior to consent to ensure that the risks of alcohol cessation will be minimized (e.g., no history of severe withdrawal, no history of withdrawal-related seizures, self-reported ability to undergo alcohol cessation >24 hours). On the following day, 24 hours after abstinence initiation, they will return to the clinic, and be reassessed for intoxication and withdrawal. **Participants who present intoxicated or in moderate withdrawal will be offered an opportunity to return at a different day within a week for a reassessment.**

Infusion Procedures: Assuming sobriety (BAC=0) and less than moderate withdrawal symptoms (CIWA < 11), participants will be randomized to receive a single infusion of ketamine or midazolam. The infusion will take place at the BSU within the Division on Substance Abuse, during Week 2. So as to minimize risk, infusions will be given in a highly monitored setting. Further, our preliminary studies, as well as studies with depression, have suggested that a single dose of ketamine has efficacy. Thus, for the purposes of this study, a single infusion (0.11 mg/kg over 2 min bolus followed by 0.6 mg/kg over 50 minutes) may suffice to affect the outcome measures without exposing subjects to the added risk of multiple infusions. Patients will have not used alcohol in 24 hours to address the risk of adverse interactions with study medications. They will also be instructed to not eat since midnight prior to the infusion so as to reduce the risk of nausea and aspiration. Participants will be informed throughout the study that they may possibly receive any of a number of substances at each infusion, including amantadine, buspirone, d-cycloserine, ketamine, lorazepam, memantine, saline, or any combination of these. This IRB-approved procedure is consistent with blinding procedures at our institution and is intended to disguise what drug is specifically given so as to minimize expectancy effects (e.g., anticipating a certain set of psychoactive effects) and address the possibility of participants identifying which drug has been given.

Active control (midazolam 0.025 mg/kg in saline infused over 52 minutes) or ketamine hydrochloride (0.11 mg/kg followed by 0.60 mg/kg in saline over 50 minutes) will be prepared and packaged for slow-drip infusion by the pharmacy at NYSPI, and administered between 10 am and 12 pm on day 2. This dose of ketamine was selected on the basis of published reports suggesting that it was well-tolerated. It was also the highest dose tolerated by participants in our preliminary studies, and may have added efficacy over the lower dose. Midazolam was chosen as the active control because it produces mild psychoactive effects, further obscuring the distinction between conditions so as to ensure blinding, and because of its short half-life. Further, though midazolam might acutely reduce alcohol craving or withdrawal, it has no known persistent (> 8 hrs) effect on alcohol dependence. Blood pressure, heart rate, and blood oxygen saturation will be continuously monitored. Infusions will take place in the presence of an ACLS and BLS certified psychiatrist, who will be responsible for decisions pertaining to the discontinuation of the infusion in the case of an adverse event. The psychiatrist will remain available for up to three hours after the infusion is terminated and will provide a brief psychiatric evaluation and field sobriety test prior to discharge from the facility. After the infusion, a lunch will be provided to participants while they wait for medication effects to

fully subside and for assessments to be completed. The participant will also meet with a therapist for a session of MET prior to discharge.

Prior experience with sub-anesthetic ketamine administration in research and clinical settings suggest that preparation and relaxation exercises reduce or prevent the anxiety that might develop during administration. In our preliminary study, we found relaxation and mindfulness-based exercises to be helpful when administered before and during the infusion if needed. These relaxation exercises will also be employed here. A Clinician Administered Dissociative States Scale (CADSS) and Hood Mysticism Scale (HMS) will be administered at the conclusion of the infusion by the research assistant. Participants will also complete various assessments pertaining to drug effect. Ketamine and norketamine (an active metabolite) levels will be obtained at 30 minutes into the infusion and at 70 minutes (18 minutes after the infusion is terminated), the results of which will remain unavailable to all staff for each participant until all assessments are complete.

Blinding: Various other safeguards, in addition to making metabolite levels unavailable, will be placed to ensure that blinding is maintained. Staff who will be carrying out most of the assessments in this study will not participate in infusion procedures because of the possibility, given the expected psychoactive effects, that they will recognize which patients are randomized to ketamine. A blinded nurse will also collect serum for testing.

Follow-up: Follow-up will occur by phone at 1 and 3 months after study completion, and will aim at assessing alcohol use patterns since discharge from the clinical trial.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Participants who experience two or more consecutive blood pressure readings of 160/110 between visits over the course of study participation will be removed from the trial and referred to appropriate treatment. Participants who complain of new symptoms consistent with cardiovascular instability (chest pain, new onset dyspnea on exertion) will also be removed and provided appropriate referrals. Participants who experience a clinical worsening while involved in the study (e.g., development of psychiatric symptomatology, worsening drug use) will be removed from the study, provided with acute psychiatric care if needed, and provided appropriate referrals. This will be ascertained by the close psychiatric and medical monitoring that participants receive throughout study participation.

Participants who decide to discontinue will have their reasons for doing so documented, if these are available, and every effort will be made to ensure that their data are complete, including follow-up data for drop-outs.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Blood will be collected during the screening process, during the study, and at the end of the study. Blood drawing will be conducted by personnel with the requisite training to carry these procedures out at minimal risk to participants. Urine will also be collected during screening to detect other drug use. Data will be coded with numbers assigned to each participant, and this data will be stored in password-protected computers.

Two vials of blood will be drawn during the screening process amounting to 10 cc (¾ tbsp). During the study, blood will be drawn during infusions for ketamine and norketamine levels. These samples will require about 10 cc (1 tbsp).

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Interviews: Mini International Neuropsychiatric Interview (MINI): A semi-structured diagnostic interview designed to assist researchers in making reliable DSM-IV psychiatric diagnoses (45 min); Clinician Administered Dissociative States Scale (CADSS): A 23 item clinician administered instrument used to measure current dissociative symptoms (5 min); Dissociative Experiences Scale (DES): A 28 item questionnaire for assessing the extent of daily dissociative experience, modified to be administered by a clinician (5 min); Brief Psychiatric Rating Scale (BPRS) for positive symptoms: A 4 item subscale for assessing psychosis (1 min); Hood Mysticism Scale (HMS): a 32 item scale for assessing infusion-dependent mystical experience, modified to be administered by study staff (5 min); Five Facet Mindfulness Questionnaire (FFMQ): A 39 item instrument modified to be clinician administered that assesses five mindfulness domains: observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity (5 min); Clinical Institute Withdrawal Assessment (CIWA): a validated clinician-administered assessment to ascertain severity of withdrawal symptoms (5 min); Timeline Follow-Back (TLFB): a retrospective method of quantifying daily consumption of alcohol and other drugs, assisted by the maintenance of a weekly use diary (5 min); Barratt Impulsiveness Scale (BIS): a 30 item questionnaire used to assess impulsivity, modified to be administered by a clinician (5 min).

Self-Reports: Drug-Taking Confidence Questionnaire (DCQ): A validated assessment of self-efficacy; Alcohol Abstinence Self-Efficacy Scale: a 40-item assessment that assesses confidence to stop using alcohol in various situations (5 min); Perceived Stress Scale (PSS): A 9 item scale that measures levels of subjective

stress, modified from a monthly assessment to one that evaluates stress between visits (5 min); VAS for alcohol craving (VAS-A): A 10 cm long line from "not at all" to "extremely" to assess craving intensity and frequency (1 min).

Physiological Measures: Breath alcohol concentration (BAC) will be assessed using the Alcohawk® ABI Digital Alcohol Breath Tester. This is a professional grade unit that meets the strict requirements for testing issued by the Food and Drug Administration (FDA) and the Department of Transportation (DOT). Gamma-glutamayl-transferase (GGT) is a liver enzyme that is a widely accepted and validated laboratory measure of drinking. Plasma GGT can therefore provide an additional biological marker of drinking reduction.

TABLE 1.

Assessments (by week)		1	2A	2B	2C	3	4	5
ASSESSMENT	AASE/DCQ	X			X		X	
	VAS-A	X		X		X	X	X
	FFMQ	X			X		X	
	BAC/GGT			X			X	
	BPRS(+)			X				
	CADSS&HMS			X				
	(Nor)Ket			X				
	PSS	X			X	X	X	X
	CIWA	X		X	X	X	X	X
	BIS	X			X		X	
	DES					X		
	TLFB	X	X	X	X	X	X	X

Assessments: *AASE: Alcohol Abstinence Self Efficacy Scale; DCQ: Drug Taking Confidence Questionnaire; (Nor)Ket: Ketamine and norketamine levels; BIS: Barratt Impulsiveness Scale; PSS: Perceived Stress Scale; VAS-A: Visual Analogue Scale for alcohol craving. FFMQ: Five Facet Mindfulness Questionnaire; CADSS: Clinician Administered Dissociative Symptoms Scale; HMS: Hood Mysticism Scale; DES: Dissociative Experiences Scale; BAC: breath alcohol concentration by breathalyzer; GGT: serum levels of gamma-glutamyl-transferase; BPRS (+): Brief Psychiatric Rating Scale for positive symptoms; CIWA: clinical institute withdrawal assessment; TLFB: Timeline Follow-back*

Week 2 visits (A,B, and C) occur consecutively, 3 days in a row

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study

✓ Drug

Select the number of drugs used in this study

2

Drug #1

Name of the drug
Ketamine Hydrochloride
Manufacturer and other information
The pharmacy at PI will be supplying the drug.
Approval Status
IND is approved
IND#
110,464
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Dakwar, Elias, MD

Drug #2

Name of the drug
Midazolam
Manufacturer and other information
The pharmacy at PI will be supplying the drug.
Approval Status
IND is approved
IND#
110,464
Who holds the IND/IND sponsor?
IND is held by PI/CU Investigator
Dakwar, Elias, MD

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
The screening process should take about a week, after which eligible participants will be consented and provided MET, an effective psychotherapy for alcohol use disorders. Ineligible participants will be referred to appropriate treatment. Thus, the maximum duration of delay to treatment is about a week.
Maximum duration of delay to standard care or treatment of known efficacy
MET is an evidence-based, standard treatment for alcohol use disorders that is provided to all consenting participants after they complete the screening process. The maximum delay to standard treatment is therefore about a week.
Treatment to be provided at the end of the study
All participants will be referred to appropriate evidence-based treatment for substance use disorders, including 12-step groups, further psychotherapy, addiction psychiatry, or outpatient rehabilitation, depending on the individual's needs and preferences.

Clinical Treatment Alternatives

Clinical treatment alternatives
Participants will be provided MET, an effective and standard approach to alcohol dependence. Other alternative include inpatient or outpatient rehabilitation; pharmacotherapy (such as topiramate, naltrexone, disulfiram, or acamprosate); 12-step groups; and other types of psychotherapy. Ineligible participants will be provided referrals to these services, as will study completers and those who opt to discontinue study participation in favor of other treatment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Potential Risks:

Ketamine administration: A major risk of participating in this research project ensues from receiving ketamine hydrochloride. Ketamine is currently approved by the FDA as an anesthetic at doses significantly higher than the sub-anesthetic doses used in this study (2-3 mg/kg). Sub-anesthetic doses have been used in psychiatric research for nearly two decades in a variety of studies, including research exploring the glutamatergic system, studies employing a pharmacological model of schizophrenia, and more recently, clinical trials investigating the effect of ketamine on depression. The intravenous dose used in this study (0.71 mg/kg over 50 minutes) has been well studied in laboratory settings, and is comparable to the dose used in clinical trials for the treatment of depression. There has been no report of persistent problems or significant adverse effects, including hallucinations or other psychotic derangements, initiation of ketamine misuse, or behavioral disturbances. The short half-life of ketamine (2 to 3 hours) also ensures that the risk of interactions with alcohol will be minimized by the time that participants leave the facility post-infusion. Yet there remain various significant risks that are important to address, as well as various side effects that must be noted.

The following side effects are limited to the period of time during which ketamine is actively administered; due to ketamine's short half-life, they generally subside completely within 15 minutes of terminating the infusion. Ketamine infusions at the proposed dose can result in nausea, modest increases in blood pressure and heart rate, sedation, nystagmus, dissociative symptoms (depersonalization, derealization), anxiety, euphoria, perceptual changes (telescoping vision), behavioral alterations (including psychomotor retardation, slurred speech, and reduced hand-eye coordination), and diaphoresis. Transient ketamine-induced psychotic symptoms have been reported as well, though these are rare. Though the above effects generally subside shortly after the infusion is terminated, they can be greatly distressing to certain participants and may cause lingering anxiety. In clinical practice, anesthesiologists have found that providing relaxation exercises while administering ketamine ameliorates the subjective distress that may accompany it. Mindfulness-based relaxation will be provided by a sitter for the duration of the infusion, and may reduce any subjective distress that ensues from the infusion. In addition to excluding patients who are likely to be medically or psychiatrically compromised by these acute effects, patients will be instructed to not eat since midnight preceding the infusion so as to minimize the risk of nausea and vomiting. In order to

ensure that adverse interactions do not occur between alcohol and study medications, participants will have ceased alcohol use for the 24 hours prior to the infusion. They will undergo assessments, including blood alcohol concentration (BAC) testing, a field sobriety test, and a CIWA evaluation, on that day to test for sobriety (BAC=0; no signs of intoxication by the sobriety test) and to ensure that participants are not experiencing moderate to severe withdrawal phenomena (CIWA < 11).

Patients will be further instructed that they may request to stop the infusion at any time. Medical surveillance will ensure that any problematic changes in vital signs will be addressed.

Ketamine can also have cardiovascular effects due to its sympathomimetic properties. These effects include modest tachycardia and systolic blood pressure elevation. They tend to emerge in the latter half of the infusion session; on average, the heart rate elevation is by 15 bpm, and the blood pressure elevation is by 20 mmHg. In our experience to date with this dose of ketamine, we have found that these effects did not lead to any difficulties, were well tolerated, and subsided within 10 minutes of infusion discontinuation.

Ketamine is also associated with some abuse liability. In the community, ketamine is generally insufflated, ingested, or injected intramuscularly, and is used in combination with other substances such as marijuana, alcohol, gamma-hydroxy-butyrate (GHB) and 3,4-methylenedioxymethamphetamine (ecstasy). There is a risk, therefore, that participants may seek out ketamine after becoming exposed to it, and develop problematic patterns of ketamine use during or after the study. This risk may be compounded by the fact that it is given in this study to individuals who may have an increased vulnerability to developing substance use problems in light of their problematic alcohol use. While this important risk cannot be removed entirely, various safeguards can be implemented to ensure that it is minimized, including:

1) using a blinding procedure and giving participants the impression that they may receive any of a number of medications during each infusion; this will protect participants from identifying ketamine following the infusion and seeking it out, even though our preliminary data indicate that cocaine users rated ketamine as a substance they would likely not seek out and did not in fact initiate ketamine misuse in the follow-up period in both laboratory and clinical settings. In order to protect informed consent, the side effects and risks of all possible medications, and particularly ketamine and midazolam, will be clearly conveyed

2) excluding participants with a history of ketamine misuse or abuse.

3) carefully monitoring drug use to ensure that any emergent patterns of misuse or abuse of ketamine, or any other substance, is properly addressed in a timely manner. Futhermore, ketamine is administered in this study in a way that is unrepresentative of how it is commonly used in the community (slow-drip IV infusion). In addition, this slow, sustained method of administration is unlikely to lead to the acute powerful effects generally associated with heightened reinforcing effects and abuse liability. See "Adequacy of protection against risks."

As mentioned above, ketamine may also precipitate psychosis in certain individuals. Recent evidence suggests that glutamate dysfunction is implicated in schizophrenia, and that NMDA antagonists can mimic the symptoms of schizophrenia. Therefore, individuals who have a diathesis towards psychosis may be at greater vulnerability to developing a psychotic disorder after receiving NMDA antagonists. This risk is

addressed in the proposed study by 1) excluding individuals with a personal history of psychotic symptoms, 2) excluding individuals with a first-degree family history of psychosis, and 3) closely monitoring patients for the emergence of psychotic symptoms.

Sedation following the administration constitutes another risk. Clinical and research experience suggest that mild sedation may persist for up to 8 hours following the infusion. Participants will be instructed to not drive following the infusion and to refrain from operating heavy machinery until the following day. They will also undergo a field sobriety test prior to discharge from the facility.
Ketamine may interact adversely with opioids, sedatives, and alcohol. In order to minimize the risk of adverse interactions, participants will have initiated abstinence for at least 24 hours prior to the infusion, and will have remained in the facility for several hours post-infusion so that the acute effects of ketamine will have subsided by the time that they are discharged. A field sobriety test is also performed to ensure participants are not experiencing persistent psychoactive effects prior to discharge.

Ketamine poses a risk to pregnancy; women who are pregnant or expecting to be pregnant will be excluded. Ketamine may interact with psychotropics and other medications. During screening, the medication regimens of all participants will be rigorously investigated for medications that may lead to adverse interactions with ketamine, such as sedatives, opioids (including propoxyphene), tricyclic antidepressants, MAO inhibitors, and SNRIs such as duloxetine. Participants on medications whose effect may be disrupted by participation in the study will be excluded.

Midazolam infusion: A major risk of participating in this research ensues from receiving midazolam. Midazolam is a benzodiazepine that is FDA approved for the treatment of anxiety. Midazolam will be used in the study as an active placebo. The dose to be used in this study will be within the range of normal use, and is not normally associated with significant adverse events. The short half-life of midazolam (3 to 6 hours) ensures that risk of adverse interactions with alcohol will be minimal. Yet there are important risks that need to be addressed in order to ensure the safety of participants.

The notable side effects of midazolam include sedation, euphoria, and respiratory depression. A small minority of individuals may also have an adverse reaction characterized by loss of behavioral control called "paradoxical disinhibition." Individuals with a history of any allergic or adverse reaction to midazolam will be excluded. Furthermore, patients with medical complications that may make participation hazardous, such as obstructive sleep apnea, obesity, or a propensity for respiratory depression, will be excluded as well.

Sedation following the administration constitutes another risk. Clinical experience suggest that sedation may persist for up to 6 hours following the infusion. Participants will be informed of this risk at that time and encouraged to abstain from operating heavy machinery or engaging in any activities that sedation may make hazardous. A field sobriety test will be performed prior to discharge from the facility on the infusion day.

Midazolam also possesses some abuse liability. There is a risk, therefore, that participants may seek out midazolam after becoming exposed to it, and develop problematic patterns of midazolam use during or after the study. This risk may be compounded by the fact that it is given in this study to individuals who may have an increased vulnerability to developing substance use problems in light of their dependence on alcohol. While this important risk cannot be removed entirely, various safeguards can be implemented to ensure that it is minimized, including:

1) exercising a blinding procedure and giving participants the impression that they may receive any of a number of medications during each infusion, while ensuring that the side effects and risks for each possible medication are clearly conveyed; this may prevent patients from identifying midazolam and subsequently seeking it out.

2) excluding participants with a history of midazolam misuse or abuse.

3) carefully monitoring drug use to ensure that any emergent patterns of misuse or abuse of midazolam, or any other substance, is properly addressed in a timely manner.

Futhermore, midazolam is administered in this study in a way that is unrepresentative of how it is commonly used in the community (slow-drip IV infusion). In addition, this slow, sustained method of administration is unlikely to lead to the acute powerful effects generally associated with heightened abuse liability. See "Adequacy of protection against risks."

Midazolam may interact adversely with opioids, sedatives, and alcohol. In order to minimize the risk of adverse interactions, infusion procedures will be preceded by a 24-hour abstinent period. Participants who present intoxicated on the infusion day (by BAC and field sobriety test) will be scheduled for another attempt on the following week.

Midazolam poses a risk to pregnancy; women who are pregnant or expecting to be pregnant will be excluded.

Midazolam may interact with psychotropics and other medications. During screening, the medication regimens of all participants will be rigorously investigated for possible problematic interactions with midazolam, such as sedatives, opioids (including propoxyphene), and atypical antipsychotics (such as clozapine and olanzapine). Participants on medications whose effect may be disrupted by participation in the study will be excluded.

Pregnant and lactating women are especially at risk as the medications used can be harmful to a fetus or newborn child as well as the mother herself.

Abstinence Initiation: Another risk of research participation is related to abstinence initiation for a 24 hour period prior to the infusion. This abstinence period is intended to facilitate safe administration of medications in order to prevent adverse interactions with alcohol. It also serves to designate the date at which efforts at alcohol reduction or abstinence can begin in earnest (e.g., a “quit date”). The risk is that withdrawal phenomena might emerge during that 24-hour period that threaten participant safety. During screening, various measures and inclusion/exclusion criteria are intended to identify and exclude from enrollment individuals susceptible to developing problematic withdrawal phenomena. Furthermore, individuals are assessed with the CIWA on the day of infusion; those experiencing CIWA > 10 will be discharged from the study and provided appropriate medical management and/or referrals.

Structured interviews, rating scales, questionnaires: These should not pose any medical or physical risk. The major disadvantage is the time required to complete them, and possible discomfort at sharing the sensitive, personal information sought through them. Judging by our past experience with these measures, these are acceptable to most participants in our trials. Nonetheless, some participants may still object to how tiresome and time-consuming some of these assessments can be. All participants are informed that they may refuse to answer any questions, and that they may ask to stop at any time. Should participants become upset, uncomfortable, or exceedingly stressed while completing the interviews or assessments, assistance will be made available to them.

Blood drawing and intravenous placement: Blood drawing may cause slight and momentary discomfort at the puncture site, sometimes resulting in a small bruise. Intravenous placement can be associated with infection, clotting, pain, or bruising. Blood drawing and intravenous placement will be conducted by personnel with the requisite training to carry these procedures out at minimal risk to participants.

Blinding Procedure: Participants will be informed that they may receive any of a number of NMDA antagonists, any of a number of psychotropics, and/or saline at the infusion, even though they will only be receiving ketamine or midazolam, with saline. The ability to provide informed consent will be protected because patients will receive adequate information about the medications they may possibly receive, and particularly about ketamine and midazolam. However, participants may get frustrated at not knowing all the details of this study. We will do our best to reassure them that such blinding procedures have been designed to not add additional risk, and that they may refuse to participate or remove themselves from the study at any time.
Describe procedures for minimizing risks

Protection Against Risks

Screening:
The exclusion criteria are drafted to minimize the medical psychiatric risks to the participants.
To minimize the risk associated with the study, participants receive a thorough psychiatric and medical evaluation during the screening process. Close attention is paid to any evidence of a personal or family history of psychosis, as well as a history of ketamine or midazolam misuse or abuse; the most severe risks in this study are that participants will develop persistent psychosis after receiving ketamine, or that they will develop problematic patterns of use of midazolam or ketamine after being exposed to them. The above exclusion criteria ensure that participants with heightened vulnerability to these risks are excluded.

In order to minimize risk associated with the medications used, pregnancy, lactation, or failure to practice a reliable birth control method are exclusionary, and patients are instructed to inform their psychiatrist immediately if they suspect they may be pregnant. Urine HCG is done monthly during the trial.

Participants with a history of an adverse reaction to any of the study medications are also excluded.

The screening process is also designed to detect chronic, unstable, and/or problematic medical or psychiatric conditions that may study participation hazardous. In addition, participants are asked about their medication history, and patients on medications whose effect may be disrupted by participation are excluded. The

screening evaluations include 1) complete physical examination, including assessment of blood pressure and heart rate, 2) serologic and biological analyses, including electrolytes, blood counts, pseudocholinsterase level, urinalysis, liver function tests (noting if there is an elevation > 3 X normal),, thyroid tests, urine toxicology, and urine pregnancy tests, and 3) an electrocardiogram (with consultation from a cardiologist, Dr. Angelo Biviano). This evaluation, with a concurrent medical history, is designed to detect any medical or other conditions that may make participation hazardous.

Infusion Administration Protections
We have provided over 60 infusions to cocaine and polysubstance users, as well as pathological gamblers, and have developed a safety protocol to minimize any associated risks, in addition to the screening procedures described above. These protections are incorporated into infusion procedures, as well as into follow-up assessments.

During the infusion, heart rate, blood oxygen saturation, and blood pressure will be continuously monitored. Greater than a 35% increase in baseline heart rate or blood pressure will lead to termination of the infusion or procedure. It is expected that blood pressure and heart rate should normalize within 15 minutes of terminating the infusion or procedure. Blood oxygen saturation lower than 90% will also result in the infusion being terminated. An ACLS and BLS certified staff psychiatrist will be available during all procedures and infusions. After the infusion, a psychiatric evaluation, including the administration of a BPRS, investigates for an adverse psychiatric reaction to the infusion.

Participants will not be under the influence of alcohol, as well as other intoxicants, as assessed by BAC and a field sobriety test. This is to prevent adverse interactions between the study medications and other drugs, including alcohol. The approximately 24-hour pre-infusion abstinent period protects against interactions between alcohol, other intoxicants, and the study medications. Individuals who present in an acutely intoxicated state on the day of infusion will be provided another opportunity the following week to maintain abstinence before the infusion. Individuals who are unable to maintain abstinence on the second opportunity will be removed from the trail and provided referrals. The post-infusion period is modified accordingly (e.g., the infusion day is followed by a 7-week post-infusion period, whether the infusion occurs on the first or second opportunity).

Participants will also be expected to not eat on the morning of to the infusions. These measures are intended to minimize the risk of nausea, vomiting, and aspiration during the infusion. Participants can elect to discontinue the infusion at any time. Nausea and vomiting, should it occur, will be treated supportively.

During infusions, participants may develop subjective distress at the psychoactive effects of ketamine or midazolam. Pre-infusion relaxation exercises have been found to reduce such distress in the setting of ketamine administration, and mindfulness-based relaxation exercises, drawn from the MBRP manual, will be provided before and during the infusion by a sitter. Psychological preparation has also been found helpful in such settings, and participants will be provided with information regarding what may occur at various points in the protocol: during the consent process, and prior to the infusion. These measures will minimize the risk of participants developing distress during the infusion. Additionally, participants may elect to discontinue the infusion at any time.

In order to address the potential cardiovascular effects of ketamine, vital signs (blood pressure and heart

rate) will be monitored every five minutes beginning five minutes before the infusion begins, and will be monitored after the infusion until baseline vital signs are restored. If the HR increases > [220-participant's age]*, and if systolic blood pressure increases by > 60 mm or diastolic blood pressure increases by > 40 mm during the ketamine infusion **relative to the blood pressure obtained during screening at baseline**, the infusion will be permanently discontinued. The blood pressure will be monitored and if there is no decrease after 5 minutes, then nitroglycerin or clonidine will be administered. If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER.

Persistent psychological effects may occur after receiving ketamine; rare but severe risks include persistent psychosis and dissociation. Participants will be monitored for 2 hours after receiving the infusion, and will be administered a BPRS, positive symptom subscale. They will also meet with a psychiatrist for medical and psychiatric clearance before discharge from the hospital. In addition, they will meet thrice a week with research staff for monitoring. Participants who develop psychosis will be removed from the study, and provided with the necessary level of care. Participants who develop persistent, clinically significant dissociative symptoms will also be removed from the study and provided with the necessary level of care. Participants will also educated, as mentioned above, on the potential persistent psychiatric risks of medication administration so that they can report problematic symptoms as soon as they emerge, without having to wait for an appointment. MDs are available 24 hours/day, 7 days/week for emergencies.

Prior to discharge from the facility on the day of infusion, participants will be monitored closely and provided various assessments, including a psychiatric evaluation and field sobriety test. These assessments are intended to identify persistent medication-related psychoactive effects, such as sedation or altered sensorium. Participants will remain in the facility under close psychiatric monitoring until they can pass the field sobriety test.

Patients will be encouraged to contact the clinic should any problems arise. Patients will also be informed of the abuse liability of some of the substances that they believe they may receive by infusion; they will be encouraged to report any drug-liking effects from the infusion, or any desire to seek out similar effects. Our previous results suggest that these effects are not desired by participants, and that they do not go on to seek ketamine or benzodiazepines.

Participants who experience a clinical worsening while involved in the study (e.g., development of psychiatry symptomatology, worsening drug use) will be removed from the study, provided with acute psychiatric care if needed, and provided appropriate referrals.

Protections related to Abstinence-Precipitated Withdrawal:
In addition to the screening procedures mentioned above that are intended to identify individuals susceptible to problematic withdrawal during pre-infusion abstinence initiation, participants will be assessed for withdrawal on the day of the infusion (using CIWA). Individuals with problematic levels of withdrawal (CIWA > 10) will be discharged from the study and provided appropriate medical management and/or referrals. **Participants who experience two or more consecutive blood pressure readings of 160/110 between visits over the course of study participation will be removed from the trial and referred to appropriate treatment. Participants who complain of new symptoms consistent with cardiovascular instability (chest pain, new onset dyspnea on exertion) will also be removed and provided appropriate referrals.**

Protections related to Pregnant Women and New Mothers

In order to safeguard against risks towards pregnant women, evaluation will be conducted on whether the risk of treatment is acceptable for women of childbearing potential. Staff will discuss with participants the risks associated with participation and the importance of adequate birth control practice. In addition, staff will evaluate whether the participant is willing and reliable to practice effective birth control during the study. Urine pregnancy testing will be conducted at baseline evaluation and on a weekly basis throughout the course of the study. Staff will periodically discuss with patients to review importance of not becoming pregnant, and adequacy of birth control practices (all of which will be documented). As the testing methods used have limitations, participants will be encouraged to inform the research staff if they believe they have become pregnant so that the safety of the participant can be ensured. As the risk towards pregnant women outweighs the benefits of participating in this study, if a participant becomes pregnant during the course of the study, they will be discontinued from their participation.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Protection of Confidentiality:
A certificate of confidentiality will be acquired for the study to offer added protection for the privacy of participants against forced disclosure by subpoena or court order. This certificate will allow investigators and others with access to research records to refuse to disclose information that could identify subjects in any civil, criminal, administrative, or legislative proceeding at the Federal, State, or Municipal level. The certificate of confidentiality is granted for studies that collect information that, if disclosed, could damage the participant's financial standing, reputation, employability, or insurability.
We use coded records (e.g., initials and numbers), and store signed consent forms in a locked file cabinet. Only coded records will be entered into the computer and the security of the electronic data is ensured at the level of the server, the user, and the database. Upon entry to the study, the participant is informed that it would be preferable if s/he divulges the contact information of someone s/he knows and trusts, and who knows of his or her participation in the study. This is used to aid in the case of emergency. Providing this information is not required for participation in the study. If s/he agrees to this, the participant will inform the designated individual that s/he may be contacted by study staff. Only after the participant has informed the designated individual about possible calls will the contact information be provided and the consent form addendum be signed. In the event that the study staff need to contact the participant's physician, a HIPPA form will be presented to the patient to authorize contact between the research psychiatrist and the participant's physician.
Will the study be conducted under a certificate of confidentiality?
Yes, we will apply for the Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Potential benefits of the proposed research to participants:

There are only a few effective pharmacotherapy treatments for alcohol dependence. This study may lead to greater understanding of how alcohol dependence might be treated using novel pharmacotherapy strategies. All participants will also receive a form of psychotherapy found effective for substance use problems. In light of the innovative aspects of this research proposal, we believe that we have put in place necessary and sufficient safeguards to protect the safety of participants, and detect early potential risks. We further believe that the risks of participation have been made manageable and reasonable, and outweigh the risks of alcohol use itself. Should our hypotheses concerning the use of ketamine be substantiated, we may also provide substantial therapeutic benefit to patients.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Compensation: Participants will be given $10 at eacg screening visit and appointment day to defray the costs of travel and to compensate for time, as well as $25 for screening itself. Participants will also be compensated $25 for the infusion day, which is longer than a typical visit, to be received on the infusion day. Compensation is therefore a maximum of $170.

References

References
References are available upon request.

Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload evidence of FDA IND approval(s)
Upload copy(ies) of the HIPAA form
HIPAA_7014_091715.pdf
Upload any additional documents that may be related to this study

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7014 **Principal Investigator:** Elias Dakwar, MD

Name of Study: Glutamatergic Modulation of Disordered Alcohol Use: A Randomized, Controlled Trial

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☑ Researchers and their staff at the following organizations involved with this Research:
Substance Use Research Center, New York State Psychiatric Institute

☑ The Sponsor of the Research,
NIAAA
and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Elias Dakwar, MD, 1051 Riverside Drive, Unit 66, New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**