Protocol #7014: Glutamatergic Modulation of Disordered Alcohol Use: A randomized, controlled trial

NCT02539511

September 5th, 2017

II. RESEARCH STRATEGY.

Overview: Alterations in glutamate neurotransmission are an important target of pharmacotherapy for alcohol dependence.[1-4] Our investigations with ketamine, a potent glutamate modulator, in drug dependent individuals suggest that it may exert unique therapeutic effects on dependence-related vulnerabilities.[47,48] This project will evaluate the effect of a single sub-anesthetic 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. The R21 mechanism is appropriate for this project because we aim to evaluate a highly innovative but moderate-risk intervention in a manner that has the potential to make important contributions.

Significance: *The role of glutamate in alcohol dependence.* Alcohol dependence remains a significant public health problem[5] for which novel pharmacotherapy strategies are needed.[6] As the field continues to elucidate the neural correlates of alcohol dependence, we have gained a greater understanding of alcohol-related neurobiological vulnerabilities that perpetuate problematic use, and that might be targeted by innovative medications development. One important target are alterations in glutamate neurotransmission, ranging from up-regulated glutamate receptors to prefrontal functional changes.[1-4] Alterations in glutamate signaling have been implicated in several problematic adaptations to alcohol and drug use, including withdrawal, increased stress sensitivity, neurotoxicity, and cue reactivity.[1-4,7,8] Perhaps best characterized are the changes in *N*-methyl-D-asparate receptors (NMDARs), the predominant class of glutamate receptors involved in plasticity, memory, and learning.[4] NMDARs have been found to be up-regulated with chronic alcohol exposure; and changes in NMDAR structure and functioning are thought to account for alcohol-associated neurotoxicity, prefrontal alterations, withdrawal, and stress sensitivity.[1-4,7,20] The impact of adaptations such as stress sensitivity on alcohol use is well recognized. In rodents, stress, especially when uncontrollable, increases alcohol self-administration, and stressors, including cues, promote reinstatement of alcohol use.[9,10] In humans, heightened cue and stress sensitivity demonstrably leads to cravings, alcohol use, and relapse.[11,12] Alcohol-induced stress sensitivity may thereby create a vicious circle of problematic and progressively uncontrollable alcohol use.[1-4,11] The chronic stress brought on by compulsive drinking may further evolve into prefrontal pathology resembling "learned helplessness": a glutamate-mediated adaptation typically associated with depression and prefrontal neural deficits,[13,14] but which in substance users might manifest as demoralization, craving and stress sensitivity, and impaired self-efficacy.[11,12,19] Thus, impaired motivation for changing drug use, as well as high sensitivity to stress or drug cues, may emerge from a cascade of adaptations in alcohol dependent individuals,[3] with the early disruptions in glutamate signaling evolving into prefrontal abnormalities similar in pathophysiology to those associated with stress-related or affective conditions.[15,16] Alcohol-related alterations in glutamate homeostasis have been observed to lead to prefrontal changes comparable to those observed with depressive and anxiety disorders;[3,14-19] impaired prefrontal regulation of midbrain structures, such as the nucleus accumbens and amygdala, is a well-described correlate of not only affective and anxiety disorders, but also addictive disorders.[3,14-19] Anterior cingulate cortex (ACC) alterations in particular have been implicated in stress sensitivity,[17,18] as well as in high reactivity to cues and an increased risk of relapse.[12,19]

Ketamine for Alcohol Dependence. Glutamate is therefore recognized as a promising target for alcohol treatment. Preclinical data suggest that NMDAR antagonists dampen withdrawal, reduce alcohol consumption, and address alcohol-related adaptations;[21-23] and in humans, mixed GABA agonists/NMDA antagonists such as topiramate and acamprosate have shown efficacy for some outcomes.[50,51,72] As a high-affinity, noncompetitive NMDAR antagonist,[24] ketamine hydrochloride is a possible, if unconventional, approach to effectively modulating this important class of receptors, as well as in addressing related prefrontal alterations. In a recent series of NIMH-funded trials, a single sub-anesthetic intravenous (IV) dose (0.5 mg/kg over 40 minutes) of ketamine had beneficial effects on suicidality[25], refractory unipolar depression[26] and bipolar depression[27] that persisted well beyond the acute perceptual and behavioral changes that accompany administration (in some cases, up to several weeks after a single dose).[26] The mechanisms thought to account for its unique anti-depressant may also be relevant to alcohol treatment. These effects include regulating ACC activity[29], which some evidence suggests might serve to reduce the risk of relapse[12,19]; and modulating default-mode connectivity and excitability[30], which have been shown to be altered in alcohol dependence.[28] Emerging data further suggest that ketamine, alongside the possibly therapeutic effects emerging directly from its NMDAR antagonism and modulation of glutamate neurotransmission, promotes increased prefrontal synaptic remodeling and neural plasticity through various mechanisms, including alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptor activation[31], increased mammalian target of rapamycin (mTOR) signaling[32], and mechanisms involving brain derived neurotrophic factor (BDNF) [33]. This unique effect on plasticity may address alcohol dependence, as it does depression,[32] by counteracting the synaptic deficits that develop with dependence,[1-4] and restoring healthy prefrontal functioning through neural remodeling.[31-33]

Ketamine: A Unique Modulator. These potent effects on prefrontal neural plasticity and connectivity/ activity are what primarily serve to distinguish ketamine from selective NMDAR antagonists with which it might be grouped, such as memantine, but which are ineffective for alcohol problems.[34] Other important distinctions include ketamine's high affinity for NMDA receptors and specific sub-receptor activity[35-37], as well as its mode

of administration (i.e., infused for discrete periods at sub-anesthetic doses).[25-28] These differences indicate the ways in which ketamine may be uniquely helpful. Indeed, preclinical data suggest that ketamine's downstream effect on plasticity, thought to primarily account for its anti-depressant efficacy, may also be crucial to its possible anti-addiction benefits. A recent rodent study found that ketamine-associated reductions in alcohol consumption were abolished with mTOR inhibition[38]; as mentioned, mTOR activation has been implicated in ketamine-related promotion of neural plasticity[32]. The effects of ketamine on prefrontal plasticity might thereby address alcohol-related neuroadaptations in humans as well, particularly those associated with glutamate-based prefrontal deficits such as impaired self-efficacy,[13,14] impulsivity,[39] and cue and stress sensitivity.[12,16-19,40]

The Effect of Ketamine on Dependence Deficits. The neuroadaptations related to problematic alcohol intake are shared with other drugs, such as cocaine, and may represent pathology common to most substance use disorders.[1-4,16,19] We therefore assessed the effect of ketamine on these dependence-related deficits,[47,48] specifically low motivation to quit and high reactivity to drug cues (see **Preliminary Data**). We found that sub-anesthetic ketamine, when compared to an active control (lorazepam), significantly increased motivation to stop drug use (*p<0.05)* in active cocaine users, and reduced cue-induced craving (*p<0.05*). These effects were measured 24 hours post-infusion, but the enhanced motivation in particular persisted for at least 72 hours. Additionally, participants who experienced a robust improvement in motivation following ketamine (with a score corresponding to the "maintenance" stage of change) remained abstinent from cocaine, by urine toxicology, during the 4-week follow-up, even in the absence of treatment. It remains to be determined whether these apparently beneficial effects of ketamine extend to alcohol. Previous work with ketamine indicates that it can be safely and tolerably administered to detoxified alcohol dependent individuals.[41,42,84] Further, ketamine has been found to facilitate abstinence initiation when administered intramuscularly (IM) in preliminary research.[43]

Ketamine with Psychotherapy. The primary purpose of this trial is to investigate the efficacy of a sub-anesthetic dose of ketamine (0.71 mg/kg IV over 52 minutes) on problematic alcohol use in 40 non-depressed alcohol dependent individuals receiving Motivational Enhancement Therapy (MET), an effective psychotherapy for alcohol dependence[44-46] that may serve to enhance and extend the benefits of ketamine in two ways. First, it provides a behavioral platform for harnessing the therapeutic potential of the above neurobiological effects. Second, we expect that MET might similarly synergize with ketamine's psychoactive properties. We recently showed that a subset of psychoactive effects, as ascertained by the Hood Mysticism Scale,[67] may mediate the robust effect of ketamine on motivation to quit:[48] a finding consistent with reports of spontaneous mystical experiences motivating alcoholics towards sobriety.[49] This profile distinguishes ketamine from agents with similar receptor activity but no psychoactive effects,[36,37] and suggests a psychological mechanism by which ketamine may enhance motivation to quit.[48] Thus, a psychotherapy aimed at optimizing this mechanism, as is the case with MET, may increase and sustain ketamine-induced motivational enhancement.[42,48] Further, our experience (see below) suggests that integrating a ketamine infusion into addiction psychotherapy is feasible.

Innovation: Though NMDAR antagonists have long held interest as potential treatments for alcohol use disorders, IV ketamine has not been investigated in non-depressed alcohol dependent individuals, ostensibly because of concerns about behavioral toxicity and abuse liability. These risks are important to address, but they should no longer be prohibitive, particularly in light of data from our group (see **Preliminary Data)** and others that under appropriate conditions ketamine can be administered without adverse effects, including psychotic symptoms, evidence of ketamine misuse, or behavioral disturbances.[25-28,41,42,47] The proposed study would therefore represent the first attempt to study the effect of IV sub-anesthetic ketamine on alcohol dependence, without depressive comorbidity, in a clinical setting. Another innovation pertains to combining ketamine with MET. Alongside the novelty of this pairing, the integration of pharmacotherapy with a therapeutic framework with which synergy is possible represents an innovative approach to addiction treatment.[51] Even if our hypotheses are not confirmed, this proposal stands to contribute to the field because glutamate modulation with such potent prefrontal effects has yet to be investigated in this manner and with this population.

Approach:

Preliminary Data: The effects of subanesthetic doses of ketamine in cocaine users. In a lorazepam-controlled double-blind trial,[47] we assessed the effect of ketamine (0.11 mg/kg bolus over 2 minutes followed by 0.30 mg/kg IV) on motivation to stop use and cue-induced craving in non-depressed cocaine dependent individuals (*n*=8*)*, as well as the effects of an additional ketamine dose on these outcomes (0.11 mg/kg 2-minute bolus followed by 0.60 mg/kg IV, over 50 min) Assessments occurred 24 hours after each infusion; the three counter-balanced infusions were separated by 48 hours. All infusions have been well tolerated, with no psychotic symptoms or behavioral disturbances reported. Ketamine (K1) increased reported motivation to stop use (University of Rhode Island Change Assessment) ($p<0.05$) (a), and reduced cue-induced craving by sum VAS scores ($p<0.05$) (b), compared to the active control lorazepam (LZP). These changes in motivation to quit and cue-induced craving were robust and comparable to a 60% change from preceding values. A correlation was also found between post-K1 motivation scores and sustained abstinence in follow-up. An additional ketamine dose (K2) led to further significant reductions in cue-induced craving. All acute effects of ketamine resolved within 15 minutes post-infusion, with increased blood pressure and time-limited dissociative phenomena being the most common effect. Participants rated LZP, K1, and K2 as low and comparable in drug-liking scores (c), and there was no evidence of ketamine misuse or drug-seeking in the 1 month follow-up

period. *Post-hoc* analyses indicated that participants rated the higher dose of ketamine (K2) as most helpful in regards to initiating cocaine abstinence or use reduction, but it was not associated with higher drug-liking scores. These promising preliminary data suggest that ketamine may have a beneficial effect on clinically relevant outcomes, and that it can be safely administered to drug dependent individuals.[47,48]

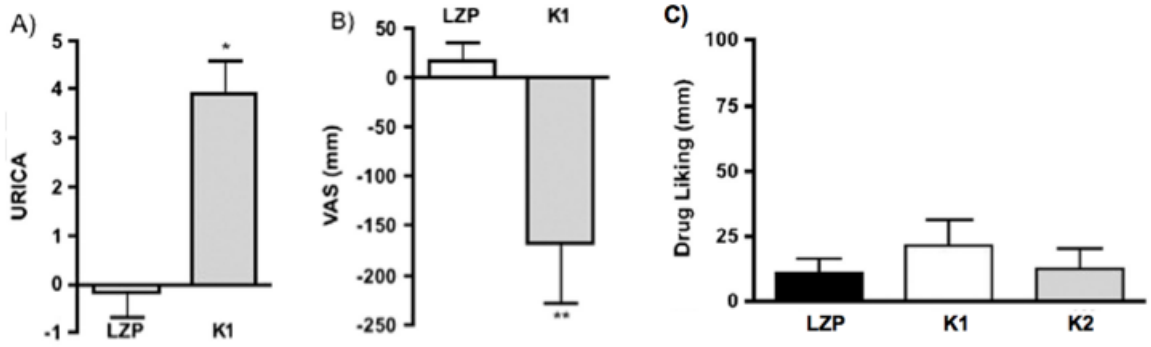

FIGURE 1. K1 vs LZP on A) Motivation to quit, B) Cue-induced Craving, and C) Drug-liking Scores; *p=0.012, **p=0.012

The Clinical Feasibility of Ketamine Combined with Psychotherapy. Expanding on the above data, we are conducting an ongoing trial for cocaine dependence that involves embedding a single ketamine infusion (vs. midazolam) in a mindfulness-based framework adapted to the individual setting. Our data thus far (n=26) suggest that this approach is feasible and well tolerated, with minimal adverse effects and a combined sample abstinence rate approaching 50%. Further, several of the patients with comorbid alcohol abuse or dependence (7 of 12 participants) maintained abstinence from alcohol by self-report. While we cannot yet determine whether ketamine is effective for substance problems because we remain blinded, our results so far suggest that psychoactive infusions can be feasibly combined with outpatient psychotherapy in clinical settings.

Study participants, recruitment, screening*:* We expect to enroll 50 participants recruited through word of mouth, advertising, and referral. 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)[53] and Dissociative Experiences Scale (DES),[54] and meet with a psychologist for a standardized diagnostic evaluation (MINI)[52] and with a psychiatrist for a medical and psychiatric evaluation. If still eligible, they undergo serum collection (CBC, thyroid panel, Chem 20 panel including liver function tests) and other diagnostic tests (ECG). Applicants are 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. Eligible participants are scheduled for another visit for informed consent and admission into the protocol.

Setting and Personnel*:* This project will be carried out at our Substance Treatment and Research Site (STARS), an established outpatient facility in which several clinical trials for substance use disorders are currently being conducted. Infusions will take place at the Biological Studies Unit (BSU) within the New York State Psychiatric Institute (NYSPI). A multidisciplinary team of physicians, psychiatrists, and therapists will be involved in various capacities, including assessments, monitoring, and psychotherapy.

TABLE 1.

	Procedures (by week)	1	2A	2B	2C	3	4	5
ACTIVITY	MET	X	X	X		X	X	X
	MD meet	X			X	X	X	X
	Abstinence		X					
	Infusion			X				
	Study End							X
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

Activities: *MET: once weekly motivational enhancement therapy; MD meet: weekly meeting with a physician for measures and safety checks; Abstinence: stop alcohol use for 24 hours; Infusion: randomized to ketamine or midazolam; Study end: end of study ratings*

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*

[a] *MD meet and MET occur on separate days each week, with most assessments occurring on the MD visit. TLFB occurs on both days.*

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

Study Procedures*:* 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 control. We expect to randomize at least 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) [55], and to ascertain craving (VAS), withdrawal (CIWA) [56], self-efficacy (Drug Taking Confidence Questionnaire and Alcohol Abstinence Self Efficacy Scale) [57,58], perceived stress (modified Perceived Stress Scale) [59], mindfulness (Five Facet Mindfulness Questionnaire) [60] and impulsivity (Barrett's Impulsivity Scale)[61]. Follow-up by telephone occurs at 1 month and 3 months after study completion, and is intended to assess drinking behavior

Motivational Enhancement Therapy (MET): MET is a psychotherapy found effective for various substance use disorders.[44-46] 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. Our therapists 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 will be taped and overseen by a senior therapist 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.

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,[25-28] 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.[42,62,63] 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.[64] 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.[65,47] 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)[66] and Hood Mysticism Scale (HMS) [67] 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.

Compensation: Participants will be given $10 for each 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. Compensation is therefore a maximum of $170.

Interviews: *Mini International Neuropsychiatric Interview (MINI):* A semi-structured diagnostic interview designed to assist researchers in making reliable DSM-IV psychiatric diagnoses[52]; *Clinician Administered Dissociative States Scale (CADSS):* A 23 item clinician administered instrument used to measure current dissociative symptoms[66]; *Dissociative Experiences Scale (DES):* A 28 item questionnaire for assessing the extent of daily dissociative experience, modified to be administered by a clinician[54]; *Brief Psychiatric Rating Scale (BPRS) for positive symptoms:* A 4 item subscale for assessing psychosis; *Hood Mysticism Scale (HMS):* a 32 item scale for assessing infusion-dependent mystical experience, modified to be administered by study staff; *Five Facet Mindfulness Questionnaire (FFMQ):* A 39 item instrument modified to be clinician administered that assess five mindfulness domains: observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity[60]; *Clinical Institute Withdrawal Assessment (CIWA):* a validated clinician-administered assessment to ascertain severity of withdrawal symptoms[56]; *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[57]; *Barratt Impulsiveness Scale (BIS):* a 30 item questionnaire used to assess impulsivity, modified to be administered by a clinician[61].

Self-Reports: *Drug-Taking Confidence Questionnaire (DCQ):* A validated assessment of self-efficacy[58]; *Alcohol Abstinence Self-Efficacy Scale:* a 40-item assessment that assesses confidence to stop using alcohol in various situations[57]; *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[59]; *VAS for alcohol craving (VAS-A):* A 10 cm long line from "not at all" to "extremely" to assess craving intensity and frequency.

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.[83]

Data Analysis:

Outcome measures and covariates: *Primary outcome measures:* The ***primary outcome*** will be self-reported abstinent days following the infusion. ***Secondary and exploratory outcome measures*** will be heavy drinking days post-infusion (defined as the number of days with >4 drinks consumed for men and >3 women)[68]; time to first heavy drinking day; drinks per drinking day (number of drinks per week divided by number of drinking days); treatment retention; and measures of craving, GGT, withdrawal, mindfulness, impulsivity, motivation, and self-efficacy. ***Covariates****:* Covariates include baseline levels of alcohol use, and baseline levels of secondary outcomes. An exploratory covariate is serum ketamine levels.

Overview of data analysis plan: *Sample:* The randomized trial will go on for 2 years. We expect at least 40 participants to be randomized and receive medications. The main analyses in this study will be on all infused patients in an intent-to-treat (ITT) sample. Patients 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. *Analytic Approach:* Weekly assessments of percentage heavy drinking days will be modeled as a function of time and treatment (ketamine vs. midazolam) with mixed effects models. PROC GENMOD in SAS[69] will be used to carry out analyses. *Significance Testing:* All tests will be two-sided and performed at significance level p = 0.05, except where noted. A primary outcome measure is specified in advance. *Preliminary analysis:* Before the primary analysis described in Hypotheses Testing is carried out, the data will be examined at all time points for outliers; distributions of continuous variables will be checked for normality; and transformations will be employed if necessary. The distribution of baseline demographic variables, and values will be examined in terms of means, standard deviations, and 95% confidence intervals.

Power analysis: Previous research suggests that a difference of 30% between active and control conditions in percent drinking days is clinically meaningful.[68,70-72] With an n of at least 20 in each group, we will be able to detect a difference of 30% between ketamine vs. midazolam, with a medium effect size = 0.80, and two-tailed alpha = 0.05. Even if it fails to detect this large and meaningful difference, this preliminary trial will allow us to demonstrate feasibility, detect large effects on various outcomes, and estimate effect sizes for future studies.

Testing the Primary Aim (ketamine promotes abstinence): Percentage drinking days at each time point will be modeled using longitudinal mixed effects models. Participants will be modeled as random factors, with a temporal within-subject autoregressive (AR) correlation structure. The estimate of percentage reduction over time will be tested by examining the time-by-treatment interaction. Tests of difference will be performed over all time points separately and a test for trend will also be performed.

Key Design Choices and Limitations *Ketamine Safety Concerns.* Ketamine administration carries certain risks, including increased blood pressure, perceptual changes, and abuse liability. However, the safety profile, pharmacokinetics, and range of tolerable sub-anesthetic doses of ketamine have been very well studied in diverse psychiatric populations, including alcohol dependent individuals.[42] It has excellent, reliable

bioavailability by the IV route, blood levels of active metabolites can be readily monitored, and due to its short half-life, its immediate cardiorespiratory effects tend to subside within fifteen minutes of stopping the infusion.[62,63] Over the course of the past several years during which we have administered infusions to over 40 drug-dependent participants, we have refined ketamine administration procedures and introduced several safeguards to ensure that its risks are minimized. Thus far, ketamine has been well tolerated, with the most common acute effect being dissociation and increased blood pressure (without symptoms), which resolve within 30 minutes of infusion termination. There were no instances of ketamine misuse, psychosis, or persistent dissociation over the course of study participation. We will institute the same precautions and procedures in the present study, and expect that infusions will be similarly well tolerated.

Infusion administration procedures. We have aimed to address various limitations pertaining to infusion procedures, including the possibility of adverse interactions and unknown ketamine dose efficacy. The risk of interactions between intoxicants and ketamine is addressed by asking that participants maintain abstinence for 24 hours prior to receiving the infusion and assessing sobriety prior to infusion initiation. The short half-lives of ketamine and midazolam (3 and 6 hours respectively) ensure that each study drug will be effectively cleared in case that participants resume drinking following discharge.[62-64] The effect of IV subanesthetic ketamine on alcohol seeking has not yet been studied, so it is unclear whether the proposed dose will be effective on this outcome, despite our promising preliminary findings. A related concern is that alcohol use disorders are associated with a reduced response to ketamine,[84] and that a therapeutic dose may need to be higher than in cocaine users. We have addressed these uncertainties by using the highest dose tolerated in our preliminary studies. Further, weekly assessments will elucidate the temporal course of ketamine's effects. Thus, even short-lived effects should be apparent. Future studies can determine the optimal dose and frequency.

Abstinence Initiation. There are risks associated with asking participants to maintain abstinence prior to receiving the infusion. One risk relates to the possibility that they will not do so, and will present to the BSU actively intoxicated. Obtaining BAC levels and performing a sobriety test prior to the infusion will identify intoxicated participants and defer the infusion until another day to prevent adverse interactions. Another risk relates to the precipitation of withdrawal phenomena. The current design expects that participants will experience some withdrawal, but that it will be mild enough (CIWA<11) to not constitute a risk. Despite screening procedures aimed at excluding individuals prone to severe withdrawal, some individuals may experience intolerable and/or severe withdrawal. Frequent administration of CIWA and close monitoring will ensure that these individuals will be identified quickly, discontinued, and provided appropriate management.

Primary Outcome: The question of which addiction treatment outcome provides the most clinically relevant indication of efficacy is a matter of some debate. We have designated percent heavy drinking days as the primary outcome because it is widely used, clinically relevant, sensitive to changes in problematic use, and found to correlate with degree of functionality.[68,70-72] Percent abstinent days, drinks per drinking day, and time to first heavy drinking will serve as secondary and exploratory outcomes to help clarify the temporal course and clinical relevance of ketamine efficacy. GGT and BAC will be obtained as biological markers of alcohol use. [83]

MET: A related problem is that the efficacy of the psychotherapy platform may disguise the efficacy of the medication. As an evidence-based intervention, MET provides treatment-seeking participants with feasible and effective care,[44] but its efficacy is considered relatively modest[85] and we do not expect it to obscure the efficacy of ketamine. Our assumption, moreover, is that MET may serve to heighten and extend the effects of ketamine on vulnerabilities that perpetuate problematic use, including low motivation to quit and impaired self-efficacy. If ketamine + MET leads to a significant effect on alcohol dependence, as compared to midazolam + MET, the hypothesis of synergy may be later investigated using the appropriate two by two study design.

Possible Intensification of Alcohol-Cue Conditioning: Research with other glutamatergic agents that promote plasticity, such as D-cycloserine (DCS), suggests that receiving the medication while still using drugs may serve to enhance conditioning to drug-cues (thereby *increasing* cue reactivity).[73,74] Efficacy in facilitating cue extinction may therefore require exposure to cues unpaired with acute drug effects,[75] as in our inpatient preliminary study. Thus, in this proposed outpatient study with active alcohol users, it is possible that ketamine (though modulating glutamate and promoting plasticity through different mechanisms than does DCS)[76] may have effects opposite to what is hypothesized. The pre-infusion 24-hour abstinent period and therapeutic setting makes this unlikely. Nonetheless, we will conduct an interim mid-point analysis to investigate this possibility, and will have precautions in place to identify, and exclude from further participation, individuals who experience clinical worsening. A ketamine-related intensification of cue reactivity or alcohol use in active users would provide important information about the role of glutamatergic modulation in alcohol dependence. As such, even if our primary hypothesis is contradicted, this study stands to contribute to the field.

Future directions: The proposed study aims to investigate the effect of a single sub-anesthetic dose of ketamine on problematic alcohol use in individuals with alcohol dependence. Given the innovative and moderate-risk nature of this investigation, it is well suited to the R21 mechanism. The aims of this project would help push the field forward by clarifying the effect of potent glutamatergic modulation on alcohol use in individuals engaged in MET, and on various vulnerabilities associated with prefrontal deficits. Thus, it can possibly pave the way for future trials aimed at better understanding the utility of this unconventional intervention in clinical settings, in tandem with ongoing research aimed at addressing the same question in depression treatment. Future studies might also focus on clarifying the mechanisms by which ketamine-induced glutamatergic modulation can improve prefrontal functioning and thus address alcohol dependence.