NCT number: NCT02461927

1. Title
Ketamine for the Rapid Treatment of Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD)

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3. Objectives
We propose a novel use of ketamine for the treatment of comorbid major depressive disorder (MDD) and alcohol use disorder (AUD) in veterans and civilians. Although MDD and AUD are two of the top 4 leading sources of disease burden among all medical diseases, the efficacy of current pharmacotherapy is only modest. In recent years, the rapid-acting antidepressant ketamine has shown efficacy and safety for the treatment of depression. Since up to 40% of all depressed patients have AUD in their lifetime, it would be important to test ketamine in treating comorbid MDD and AUD—instead of targeting only MDD. Since most AUD patients have been excluded in clinical trials testing antidepressants, little is known about proper pharmacotherapy for patients with comorbid AUD and MDD. Thus, there is a critical need to develop effective pharmacotherapy for comorbid AUD and MDD. Also, ketamine has been suggested for potential treatment of AUD itself (Krystal, Petrakis, Krupitsky, et al., 2003; Krystal, Petrakis, Mason, Trevisan, & D'Souza, 2003).

Based on these scientific data, we recently tested a single intravenous (IV) infusion of ketamine in veterans with comorbid MDD and alcohol dependence. Our pilot data in a crossover trial shows that a single dose of IV ketamine at 0.5 mg/kg IV infusion is safe and effective in reducing both depression and alcohol craving. Recently, several research groups have shown that repeated ketamine infusions (up to 6 infusions) are even more effective than single ketamine infusion (Murrough, et al., 2013; Rasmussen, et al., 2013; Shiroma, et al., 2014).

To further (a) increase treatment efficacy for AUD and (b) minimize abuse potential of ketamine in patients with MDD and AUD, we have tested naltrexone plus ketamine treatment for safety and efficacy in our recent pilot study (GY0004). This pilot study showed that combination therapy of naltrexone and ketamine was safe and effective in reducing depression and alcohol consumption.

In order to expand our preliminary work, we propose an 8-week, randomized, double-blind, placebo-controlled, between-subjects trial in which repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) plus naltrexone will be evaluated for safety and efficacy. First, prior to the double-blind trial, we will conduct an open-label trial that will include 5 veterans with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) with a follow-up of 4 weeks. Second, after reviewing the safety and efficacy of repeated ketamine treatment from the open-label trial, we will conduct an 8-week, randomized, double-blind, placebo-controlled trial that will include 60 veterans and civilians with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) plus naltrexone with a follow-up of 4 weeks and a 4-month follow up. This is the first study examining the therapeutic potential of repeated ketamine for the treatment of comorbid MDD and AUD. We will compare 3 groups (ketamine plus naltrexone, ketamine alone, and placebo) for treating MDD and AUD as follows.

3 groups	
1	IV Ketamine (0.5 mg/kg) + IM Naltrexone (380 mg) (n=20)
2	IV Ketamine (0.5 mg/kg) + IM Placebo (n=20)
3	IV Placebo (midazolam 0.045 mg/kg) + IM Placebo (n=20)

4. Hypothesis
We predict that IV ketamine will significantly reduce the symptoms of MDD and AUD compared with active placebo (midazolam) in veterans and civilians with MDD and AUD.

Specific Aim #1: To evaluate if serial IV ketamine is superior to placebo in reducing depression. We hypothesize that serial IV ketamine is superior to placebo in reducing depression.

Specific Aim #2: To evaluate if serial IV ketamine is superior to placebo in reducing alcohol consumption. We hypothesize that serial IV ketamine is superior to placebo in reducing alcohol consumption.

Exploratory Aims:
Specific Aim #3: To evaluate if serial IV ketamine is superior to placebo in reducing alcohol craving. We hypothesize that serial IV ketamine is superior to placebo in reducing alcohol craving.

Specific Aim #4: To evaluate if serial IV ketamine is superior to placebo in reducing suicidal ideation. We hypothesize that serial IV ketamine is superior to placebo in reducing suicidal ideation.

Specific Aim #5: To evaluate the safety and tolerability of serial IV ketamine in patients with comorbid MDD and AUD. We hypothesize that serial IV ketamine is safe and well tolerated in this population.

Specific Aim #6: To evaluate whether naltrexone plus ketamine is superior to ketamine alone in reducing abuse potential of ketamine. We hypothesize that naltrexone plus ketamine is superior to ketamine alone in reducing abuse potential of ketamine as measured by the Drug Abuse Potential Scale.

5. Background

1) MDD and AUD are serious mental illnesses and frequently co-occur
MDD and alcohol use disorder AUD are two of the top 4 leading sources of disease burden among all medical diseases in the Americas as reported by the World Health Organization (World Health Organization, 2008). They are both relatively common, with lifetime prevalence rates of 13.2% and 30.1%, respectively, in the adult U.S. population (Hasin, Goodwin, Stinson, & Grant, 2005; Hasin, Stinson, Ogburn, & Grant, 2007). These two disorders frequently co-occur (Kessler, et al., 1997; Regier, et al., 1990). According to the National Longitudinal Alcohol Epidemiologic Survey in the United States, 40% of patients with MDD have comorbid AUD in their lifetime (Grant & Harford, 1995). The prevalence rates of MDD and AUD are even higher in some groups, such as veterans. The National Vietnam Veterans Readjustment Study reported that both prevalence rates of MDD and AUD are higher in theater veterans than in civilians (Jordan, et al., 1991).

In recent years, there has been widespread public concern about depression, suicide, and alcohol abuse among military personnel and veterans. A 2012 report by the Institute of Medicine acknowledged the seriousness of alcohol use problems in the U.S. military by noting that binge drinking by active duty service members increased from 35% in 1998 to 47% in 2008 (Institute of Medicine, 2012). Another report by IOM described that military personnel and veterans usually have more than one health problem, including AUD and MDD (Institute of Medicine, 2013). In addition, suicides in the U.S. military surged to a record high of 349 in 2012 (Burns, 2013). Veterans frequently have co-occurring alcohol problems and depression (Stecker, Fortney, Owen, McGovern, & Williams, 2010; Thomas, et al., 2010). In combat veterans, depression significantly increases alcohol misuse (Heltemes, Clouser, MacGregor, Norman, & Galarneau, 2014) with two studies showing veterans with concurrent depression were 2.1 to 4.2 times more likely to misuse alcohol (Heltemes, et al., 2014; Jakupcak, et al., 2010).

Previous studies have reported that individuals with comorbid MDD and AUD have more severe health conditions than those with MDD alone. In a general population sample, individuals with comorbid depression and AUD had more serious episodes of depression and suicidal behaviors than those with MDD alone (Grant, Hasin, & Dawson, 1996). In a prospective study of young adults (Briere, Rohde, Seeley, Klein, & Lewinsohn, 2014), comorbid MDD and AUD doubled the risk of alcohol dependence compared with AUD only. In this

study, the comorbidity also increased life dissatisfaction and lowered global level of functioning. In another study using a clinical sample comparing patients with single and dual disorders, dually diagnosed patients with MDD and AUD had higher suicidality, impulsivity, functional impairment, and lower self-esteem (Cornelius, et al., 1995). In addition to these indicators of more severe pathology and symptoms, dual diagnosis of MDD and AUD has also been associated with poorer treatment outcomes (Rounsaville, Dolinsky, Babor, & Meyer, 1987) presumably because each disorder increases the risk and severity of the other disorder in a bidirectional way over time (Briere, et al., 2014).

Using administrative data from the Veterans Health Administration (VHA), we recently identified 58,173 veterans who had a diagnosis of comorbid MDD and AUD nationally during a 12-month period (October 1, 2011 - September 30, 2012). Based on the VHA data, we have reported that dually diagnosed veterans with MDD and AUD, relative to veterans with MDD alone, had a greater number of comorbid health conditions, such as liver disease, drug use disorders, and bipolar disorder as well as greater likelihood of homelessness and higher health service utilization (Yoon, et al., 2014). Since there have been reports that (1) the prevalence of comorbid major depressive episodes and substance use disorders has increased significantly from the 1990s to the 2000s (Compton, Thomas, Stinson, & Grant, 2007) and (2) MDD is projected to be the number one cause of burden of disease in the 2030s worldwide (World Health Organization, 2008), future demand for services for veterans with comorbid MDD and AUD will likely grow. In addition, more veterans are already presenting to VA facilities for the treatment of this comorbidity (Milliken, Auchterlonie, & Hoge, 2007). Given the severe pathology and morbidity associated with comorbid MDD and AUD, it is important to develop effective treatments for dually diagnosed veterans with MDD and AUD.

2) Ketamine for the Rapid Treatment of MDD and AUD

Despite the enormous suffering, morbidity, and mortality in patients with MDD and AUD, the efficacy of current pharmacotherapy is only modest. Remission rates following current antidepressants are low (only 30%). Also, current antidepressants require a delay of weeks or months before the onset of antidepressant effect. Four medications approved for AUD do not treat depression or suicidality. Since most AUD patients are excluded in clinical trials for testing antidepressants, little is known about proper pharmacotherapy for patients with comorbid AUD and MDD. Thus, there is a critical need to develop effective pharmacotherapy for comorbid AUD and MDD.

Recently, a single intravenous infusion of ketamine, an NMDA receptor antagonist, has shown a rapid treatment effect on depression and suicidality (0.5 mg/kg IV infusion over 40 minutes). This rapid-acting antidepressant effect of IV ketamine was replicated by other ketamine studies, including our data. A meta-analysis including 8 double-blind, randomized controlled trials showed that effect size was large (standardized mean difference = 0.90), indicating the efficacy of ketamine in the rapid treatment of depression (McGirr, et al., 2014). Recently, several research groups have shown that repeated ketamine infusions (up to 6 infusions) are even more effective than single ketamine infusion (Murrough, et al., 2013; Rasmussen, et al., 2013; Shiroma, et al., 2014) for the treatment of depression. Currently, ketamine is an FDA approved medication for human use as an anesthetic. Many researchers have reported that ketamine has the potential to revolutionize clinical treatment of depression (Krystal, Sanacora, & Duman, 2013). However, all of these ketamine studies excluded patients with AUD.

Emerging evidence indicates that ketamine has the potential to treat AUD (Krystal, Petrakis, Krupitsky, et al., 2003; Krystal, Petrakis, Mason, et al., 2003) as other similar glutamatergic medications have been shown to reduce craving for alcohol (Hölter, Danysz, & Spanagel, 1996; Krupitsky, et al., 2007). The NMDA receptor antagonist ketamine could be an effective treatment by stabilizing glutamatergic system, suppressing alcohol withdrawal, and decreasing the development of alcohol tolerance. Chronic alcohol drinking upregulates NMDA receptor function, which can cause alcohol tolerance and withdrawal. NMDA receptor antagonist ketamine dose-dependently reduced alcohol self-administration in rats. This anti-alcohol effect of ketamine was mediated by the activation of mTOR. In a human lab studies, detoxified alcohol-dependent patients had less side effects to ketamine compared with healthy subjects. Additionally, ketamine was more effective for treating depression in patients with a family history of AUD. Several lines of evidence suggest that both AUD and MDD share many similar neurobiological features, such as disruption of glutamate neurotransmission and impaired

astroglial cell function. Based on these scientific data, we recently tested a single intravenous infusion of ketamine in patients with comorbid MDD and alcohol dependence. Our pilot data shows that a single dose of IV ketamine at 0.5 mg/kg IV infusion is safe and effective in reducing both depression as measured by the Hamilton Depression Rating Scale and alcohol craving as measured by the Alcohol Urges Questionnaire.

The primary goal of this proposal is to test repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) for comorbid AUD and MDD. First, prior to the double-blind trial, we will conduct an open-label trial that will include 5 veterans with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) with a follow-up of 4 weeks. Second, after reviewing the safety and efficacy of repeated ketamine treatment from the open-label trial, we will conduct an 8-week, randomized, double-blind, placebo-controlled trial that will include 60 veterans and civilians with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) with a follow-up of 4 months. Midazolam will be used as an active placebo (instead of regular placebo saline), as suggested by VA grant reviewers, to enhance blinding in placebo-treated subjects. Midazolam has been safely used as an active placebo in other ketamine studies (Afridi, Giffin, Kaube, & Goadsby, 2013; Galvez, et al., 2017). In our study, we will use a smaller dose of midazolam (0.045 mg/kg), as compared to Galvez's study that used 4.5 mg of midazolam. Also, to further enhance safety, (1) we will limit a maximum dosage of midazolam at 4.0 mg (4 mg of midazolam is equivalent to only 8 mg of diazepam) and (2) midazolam will be administered over 40 minute (a much longer duration) than other studies.

To further (a) increase treatment efficacy for AUD and (b) minimize abuse potential of ketamine in patients with MDD and AUD, we have tested naltrexone plus ketamine treatment for safety and efficacy in our recent pilot study (GY0004). This pilot study showed that combination therapy of naltrexone and ketamine was safe and effective in reducing depression and alcohol consumption.

Thus, we will compare 3 groups (ketamine plus naltrexone, ketamine alone, and placebo) for treating MDD and AUD as follows.

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3	IV Placebo (midazolam 0.045 mg/kg) + IM Placebo (n=20)

6. Significance

There is a critical need to develop new drugs to treat MDD and AUD. In recent years, ketamine has shown a large effect size for the treatment of depression. Since up to 40% of all depressed patients have AUD in their lifetime, it would be important to test ketamine in treating patients with comorbid MDD and AUD—instead of targeting only MDD. Also, ketamine has been suggested for potential treatment of AUD (Krystal, Petrakis, Krupitsky, et al., 2003; Krystal, Petrakis, Mason, et al., 2003). The proposed research will yield important information on ketamine for the treatment of comorbid MDD and AUD. This study has the potential to improve the treatment of comorbid MDD and AUD.

7. Subjects

A total of 110 depressed and recently-detoxified alcohol dependent subjects between the ages of 21-65 will be recruited with the goal of reaching 60 people who enroll *and* complete all study procedures. Subjects will be accepted into the protocol after an opportunity to review and provide voluntary written informed consent and completion of a comprehensive medical and psychiatric history, physical examination, mental status examination, and routine laboratory assessments. Patients will be recruited in outpatient settings. Participants will be enrolled if they meet the following criteria.

Inclusion Criteria:

1. Male or female veterans and civilians, 21-65 years old

2. Current major depressive disorder without psychotic features by DSM-5 (antidepressant regimens can be allowed and changed during the trial)
3. Montgomery–Åsberg Depression Rating Scale (MADRS) ≥ 20
4. A minimum of 4 of 11 current alcohol use disorder symptoms by DSM-5
5. Heavy drinking at least 4 times in the past month ('heavy drinking' defined as ≥ 5 standard drinks per day for men and ≥ 4 standard drinks per day for women)
6. Able to provide written informed consent

Exclusion Criteria:

1. Current substance use disorder by DSM-5 in the past 3 months (except alcohol, tobacco, or cannabis)
2. Current or past history of psychotic features or psychotic disorder
3. Current dementia
4. Current uncontrolled hypertension (systolic BP > 170 mm Hg or diastolic BP > 100 mm Hg)
5. Unstable medical condition or allergy to ketamine, midazolam, naltrexone, or lorazepam---clinically determined by a physician
6. Imminent suicidal or homicidal risk
7. Pregnant or nursing women, positive pregnancy test, or inadequate birth control methods in women of childbearing potential
8. Positive opioid or illicit drug screen test (except marijuana)
9. Opioid use within 10 days prior to study medication (injectable naltrexone) or risks for opioid use during the study
10. Liver enzymes that are three times higher than the upper limit of normal
11. Current use of benzodiazepine
12. Acute narrow-angle glaucoma
13. Severe sleep apnea---clinically determined by a physician

8. Privacy

All research records will be kept as confidential as possible. Only a code number will identify research records. The master list linking names to code numbers will be kept separately from the research data. In case of a medical emergency, the medication group blinding can be broken by the principal investigator or a designated covering staff member, in order to supply information required for emergency medical care of research subjects. If a subject shows clinical deterioration (worsening of MDD or AUD symptoms), Dr. Yoon will determine whether: 1) the subject can remain in the study, or 2) a higher level of care (e.g. referral back to a treating psychiatrist or referral to emergency or inpatient care) is needed.

10. Recruitment

Subjects will be recruited in traditional ways through flyers, posters, and research boards at the VA Connecticut Healthcare System. In addition, we will also be using online posting through Trialfacts in order to recruit individuals that traditional methods are not able to reach. Subjects will be identified via their response to advertisements and/or internal recruiting through the research clinics and mental health clinics. Subjects will be asked to call us (West Haven VA Alcohol Research Center) at the number provided on the flyers if they are interested in participating in the research study. In addition, subjects will be identified via internal recruiting through the research clinics and mental health clinics. Our research staff will review CPRS records only to identify potential participants and alert treatment providers in the VA Clinics regarding veterans who may meet criteria for our study. In this case, our research staff will make initial contact with potential subjects in person or by letter prior to initiating any telephone contact, unless there is written documentation from the patient's clinician that the subject is willing to be contacted by telephone about the study. Additionally, under a HIPAA waiver, IRB-approved letters of invitation can be mailed to prospective participants with a past diagnosis of AUD or Major Depressive Disorder (or episode) who otherwise might meet eligibility criteria. When an invitation letter is mailed out and there is no response from potential participant, study staff may contact the potential participant by telephone. However, no more than three attempts will be made, no more than one call a day, unless instructed otherwise by potential participant. There will be a "do not contact" log maintained by site staff for participants who decline to be contacted.

Subjects will be briefly screened over the phone for eligibility, and, if the subject seems suitable, he or she will present for an in-person evaluation that will be preceded by the consent process. All information obtained for the purposes of recruiting subjects, completing questionnaires, and processing data are confidential. Designated research staff will be responsible for recruiting potential subjects.

- All data will be obtained exclusively for research purposes and will be at no cost to the patients. They will be paid a nominal but fair amount of money for their time and participation, up to *$520* (i.e., enough money to fairly compensate and encourage follow-up without being coercive or encouraging risk taking). The payment schedule is as follows: $40 baseline assessments ($40; visit 1)
- $80 for infusion days ($80 x 4 = $320; visit 3, 4, 5, 6)
- $20 weekly visits ($20 x 3 = $60; visit 7, 8, 9)
- $50 for final 2 visits ($50 x 2 = $100; visit 10, 4-month F/U)

Payment will be made through electronic funds transfer (EFT). Participants will need to provide us with your banking information by completing a special payment form. Alternatively, if participants do not have a bank account, a check will be mailed to them instead. This check(s) will be mailed to the address they provide us with. Alternatively, patients may choose to receive gift certificates issued to them for use at the VCS canteen (retail store) or VCS cafeteria here at the VACHS. Study payments are subject to withholding for outstanding federal debts (i.e., defaulted student loans, interstate child support, back taxes etc) without notification.

11. Research Design

The primary goal of this proposal is to test repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) plus naltrexone for comorbid AUD and MDD. First, prior to the double-blind trial, we will conduct an open-label trial that will include 5 veterans with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) with a follow-up of 4 months. This open-label trial will allow us to examine the safety and tolerability of the ketamine treatment in this population.

Second, after reviewing the safety and efficacy of repeated ketamine treatment from the open-label trial, we will conduct an 8-week, randomized, double-blind, placebo-controlled trial that will include 60 veterans and civilians with comorbid MDD and AUD to test safety and efficacy of repeated ketamine treatment (0.5 mg/kg; once a week for 4 weeks; a total of 4 ketamine infusions) plus naltrexone with a follow-up of 4 weeks and a 4-month follow up. All patients will receive usual standard care during this trial. This study will be conducted at the West Haven VA.

12. Procedures

Table 1. Procedures involved from screening visit to visit 10

Visit	**1** Screening	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**4-mo F/U**
Day	-30-0	-9-1	0+	7+	14+	21+	28+	35+	42+	49+	120+
IM naltrexone or placebo		X					X				
Ketamine or Midazolam			X	X	X	X					
Informed Consent	X										
Inclusion/Exclusion	X										
Demographics	X										
SCID	X										
FHAM	X										

Psychiatric Eval	X										
Physical Exam	X										
EKG	X										
EtG, Liver Profile, GGT	X					X				X	X
CBC, Chemistry 7	X					X					
Urine Tox/Preg	X		X	X	X	X	X				
Urinalysis	X										
BP, Pulse, Weight	X		X	X	X	X	X	X	X	X	X
MADRS, QIDS-SR, HAM-A	X		X	X	X	X	X	X	X	X	X
C-SSRS	X		X	X	X	X	X	X	X	X	X
YCS, OCDS	X		X	X	X	X	X	X	X	X	X
BPRS, CADSS, VAS			X	X	X	X					
Concomitant Meds	X		X	X	X	X	X	X	X	X	X
TLFB	X		X	X	X	X	X	X	X	X	X
CIWA-Ar	X		X	X	X	X	X	X	X	X	X
Breathalyzer	X		X	X	X	X	X	X	X	X	X
Adverse Event			X	X	X	X	X	X	X	X	
DAPS			X	X	X	X	X	X	X	X	X
CGI			X	X	X	X	X	X	X	X	
Q-LES-Q			X			X				X	X
Genotyping			X								

A three day window is recommended for scheduling and completion of the weekly study visits; thus, subjects may be seen within 6-9 days of their last weekly visit. All evaluations and consent can be conducted in-person or by telephone (including video call, such as VVC). However, subjects need to come and meet with study staff to receive ketamine (or midazolam) and IM naltrexone (or placebo). The initial physical exam can be replaced by other physician's or clinician's CPRS notes documented in the past 3 months. However, a research physician can still conduct a physical exam if needed to examine any medical issues. Subjects are encouraged to come within 9 days from the designated date. **a.** Day -30-0 refers to the period between signing consent and completion of screening. As such Visit 1 refers to one or multiple screening visits. **b.** Informed consent will be obtained prior to any study procedure. **c.** psychotherapies will be allowed during the study. **d**. IM injections will be given by an unblinded nurse who is not involved in ratings or evaluations, due to the distinctive appearance of naltrexone suspension. **Abbreviations**: Structured Clinical Interview (SCID), Family History Assessment Module (FHAM), Columbia-Suicide Severity Rating Scale (C-SSRS), Montgomery- Åsberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR), Hamilton Anxiety Rating Scale (HAM-A), Time Line Follow Back (TLFB), Clinical Global Impression (CGI), Brief Psychiatric Rating Scale (BPRS), Clinician-Administered Dissociative States Scale (CADSS), Visual Analog Scale (VAS) of Mood States, Obsessive Compulsive Drinking Scale (OCDS), Quality of life enjoyment and satisfaction survey (Q-LES-Q), Electrocardiogram (EKG), Complete Blood Count (CBC), Ethyl glucuronide (EtG), Yale Craving Scale (YCS), Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar), Drug Abuse Potential Scale (DAPS)

Initial Telephone Screening

Subject eligibility will first be assessed via telephone screening. If medical record is available, medical record can be reviewed as well. However, medical record review is not required. Telephone screening will occur by experienced research personnel adept with this process. If the subject seems to be a likely candidate for inclusion in this protocol, he or she will be invited to a screening visit for study eligibility.

Screening Visit

At the screening visit, our research team will explain the overall study plan to potential subjects and go over the consent form. Subjects will have an initial screening evaluation that will include psychiatric history, medical history, mental status examination, physical examination, and laboratory assessment. Other detailed

procedures are described in Table 1. If the examination and test results are acceptable and the subject meets the inclusion/exclusion criteria, the subject will be invited to the baseline visit. Our research team may provide transportation by arranging a car service for any visits if needed.

Two Injectable Naltrexone Visits
Subject will receive injectable naltrexone or placebo twice, (1) first at visit 2 (between the screening visit and the first ketamine infusion session [1-9 days prior to the first ketamine infusion preferred]) and (2) second at visit 7.

Four infusion sessions (Day #0, 7, 14, 21)
T-60: Intravenous lines started
Vital signs (sitting/standing blood pressure, sitting/standing pulse, respiratory rate, oxygen saturation),
Urine Tox/Preg
YCS, MADRS, QIDS-SR, VAS, HAM-A, BPRS, CADSS*
T0: INFUSION BEGINS (approximately 40 minutes in duration) (ketamine or placebo midazolam)
T+60: Vital signs, YCS, MADRS, QIDS-SR, VAS, HAM-A, BPRS, CADSS, DAPS
T+240: Vital signs, YCS, MADRS, QIDS-SR, VAS, HAM-A, BPRS, CADSS

-If breathalyzer is positive for alcohol, ketamine (or placebo) infusion session will be cancelled and rescheduled.
-Vital signs will be continuously monitored during the 40-minute infusion. Vital signs will be also monitored at -60, 0, +60, +90, +120, +150, +180, +240.
- Dosage of midazolam will be 0.045 mg/kg (maximum dosage of midazolam = 4.0 mg).
-*Items that could not change within a session, *e.g.* sleep, appetite, will be rated only at T-60 and at follow-up sessions.
-After the subject receives study medication at the WHVA, he or she will receive lunch and be medically cleared before leaving.
-If necessary, intravenous lorazepam (ativan) at 1 mg will be available to reduce the behavioral effects of ketamine. This will be determined by a research physician.
-If necessary, intravenous flumazenil will be available to reduce the sedative effects of midazolam. This will be determined by a research physician.
-Subjects are not permitted to drive to and from the VA on ketamine treatment days, and subjects must make their own arrangements for a ride. However, if subjects cannot make their own arrangements for a ride, our research team may provide their transportation by arranging a car service on four ketamine/midazolam infusion days.

Four follow-up sessions (Day #28, 35, 42, 49)
A total of 4 weekly follow-up sessions will be performed on Day #28, 35, 42, and 49. All evaluations can be conducted in-person or by telephone (including video call, such as VVC).

4-month follow-up sessions (Day #120): The 4-month follow-up session will occur at day 120. After the study, participants will be provided with psychiatric and/or substance abuse treatment referrals to continue treatment at their discretion. All evaluations can be conducted in-person or by telephone (including video call, such as VVC).

13. Measures
Clinical Assessments
The proposed measures were successfully employed in previous ketamine studies where the rationale for their implementation was discussed in great detail (J. H. Krystal, et al., 1994).

Assessments and Ratings
1) Medical Assessments: Physical examination (including vital sign determination) and clinical laboratories (discussed in greater detail previously) will be completed at the first visit. Urine toxicology screen and breathalyzer will be performed on the morning of each infusion day, and the results will be determined before

proceeding with the infusions. The subject will not receive ketamine on the day if urine toxicology results are positive for any illicit drugs (except marijuana) or if his/her breathalyzer is positive for alcohol. A pregnancy test will also be administered to all reproductive age females enrolled in the study prior to participation.

2) Psychiatric Assessments: Ratings are performed by trained research assistants at the WHVA whose performance is evaluated routinely in inter-rater reliability sessions. Administration of clinical measures is supervised by the primary investigator. Each of the psychiatric assessment instruments is briefly described below.

1. Montgomery- Åsberg Depression Rating Scale (MADRS): The MADRS is a standardized instrument to ascertain depressed mood and neurovegetative signs and symptoms of a major depressive episode.
2. Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR): The QIDS-SR is a patient-rated depression instrument.
3. Hamilton Anxiety Rating Scale (HAM-A): The HAM-A is a standardized instrument to evaluate anxiety severity.
4. Clinical Global Impressions Scale (CGI): The CGI is a widely-used instrument which assesses overall severity of illness on a 1 to 7 point scale with 1 indicating “normal, not at all ill” and 7 indicating “among the most extremely ill patients.” It also assesses global improvement on a 1-to-7 point scale with 1 indicating “very much improved,” 4 indicating “no change” and 7 indicating “very much worse.”
5. Brief Psychotic Rating Scale (BPRS): The BPRS is a standardized instrument that contains scales assessing psychotic symptoms including positive and negative symptoms, activation and emotional distress.
6. Clinician-Administered Dissociative States Scale (CADSS): The CADSS has self and interviewer-administered items including 5 subscales, generated a priori, evaluating dissociation including altered environmental perception, time perception, spatial/body perception, derealization and memory impairment.
7. Visual Analog Scale (VAS) of Mood States: The VAS includes scales for anxiety, drowsiness, high irritability, anger and sadness. The scales are 100 mm lines marked by subjects at a point corresponding to the apparent intensity of the feeling state (0 = none, to 100 = most ever).
8. Time Line Follow Back (TLFB): The TLFB is a standardized measure utilized for collecting information on daily alcohol use as well as other substance use
9. Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS has both lifetime/recent and since last visit versions. The “Lifetime/Recent” version gathers information on lifetime history of suicidality and recent suicidal ideation/self-injurious behavior. The “Since Last Visit” version of the C-SSRS asks about any suicidal thoughts or behaviors the subject has exhibited since the last time administered the C-SSRS.
10. Obsessive Compulsive Drinking Scale (OCDS): The OCDS is a self-report measure of craving which consists of two subscales that measure obsessions and compulsions associated with craving for alcohol.
11. Quality of life enjoyment and satisfaction survey (Q-LES-Q): The Q-LES-Q is a self-report measure of quality of life.
12. Yale Craving Scale (YCS): The YCS will measure acute alcohol cravings.
13. Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar): The CIWA-Ar is a reliable and valid 10-item assessment for monitoring alcohol withdrawal symptoms.
14. Drug Abuse Potential Scale (DAPS): The DAPS will be used to assess abuse liability of study drugs.

3) *Termination Criteria:* If a subject develops active suicidal and/or homicidal plan during the protocol, he or she will be terminated from the study, and, based on a risk assessment performed by a licensed psychiatrist, will be observed in the most appropriate milieu, *e.g.* psychiatric emergency room and/or inpatient psychiatric unit, until the suicidality and/or homicidality resolves. All data on such subjects will be carried forward in an intention-to-treat analysis (see “Data Analysis” below for additional details).

14. Power Analysis

A power analysis was performed using the comparison of means from two independent samples. The published randomized placebo-controlled trials of 0.5mg/kg ketamine administered to treatment-resistant

depressed subjects with unipolar depression (Berman, et al., 2000; John H Krystal, et al., 1994; Valentine, et al., 2011; Zarate, et al., 2006) and bipolar depression (Diazgranados, et al., 2010) were used for this calculation. These studies all had moderate-to-large effect sizes. At 72 hours post-infusion, we calculated a minimum sample size of 18 subjects (at an α=0.05 and β=0.8) for a minimal detectable difference of 6 Hamilton Depression Rating Scale points considering a 6 point standard deviation.

15. Data Analysis

Study data will be collected and managed using REDCap electronic data capture tools hosted at VA CT Healthcare System. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources

All continuous outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary.

1) Specific Aim 1 (MDD): Our primary analysis will be to compare the proportions of subjects with clinical response, measured by the MADRS between the ketamine and midazolam groups at the end-of-treatment time point (Day 21, visit 6, T+240 minutes) using chi-square tests. All primary analyses will be intent-to-treat. For missing data, we will perform sensitivity analyses where response status is determined based on multiple imputations of the outcome to check the robustness of the results. As a secondary analysis we will use generalized linear mixed models for repeated binary data with medication condition as a between-subject factor, assessment time-point as a within-subject factor, logit link and subject as a clustering factor. This analysis will include all available data on an individual across assessment time points, does not require data imputation and will provide a test of the group and time main effects and the group by time interaction. In the primary analysis we expect to see significantly higher response rate in the ketamine group compared to the midazolam group. In the secondary analysis we expect both significant group effect and significant group by time effect.

2) Specific Aim 2 (AUD): Our primary analysis will be to compare the proportions of subjects with complete abstinence, measured by the TLFB between the ketamine and midazolam groups during the 4-week treatment (Day 28) using the same approach as outlined for specific aim 1. In the primary analysis we expect to see significantly higher abstinence rate in the ketamine group compared to the midazolam group. In the secondary analysis we expect both significant group effect and significant group by time effect.

3) Exploratory Aim 3: Alcohol craving, measured by the YCS, will be compared between medication conditions using linear mixed models with treatment (ketamine vs. midazolam) as a between-subject factor, time point as a within-subject factor and subject as a clustering factor. The best-fitting variance-covariance structure will be selected based on Schwartz' Bayesian Information criterion. A significant treatment main effect and possibly a treatment by time interaction, where alcohol craving is reduced during ketamine vs. midazolam, will be supportive of our hypothesis.

4) Exploratory Aim 4: Suicidal ideation, measured by the C-SSRS Suicidal Ideation category scores, will be compared between medication conditions using the same approach as outlined for exploratory aim 3. A significant treatment main effect and possibly a treatment by time interaction, where suicidal ideation is reduced during ketamine vs. midazolam, will be supportive of our hypothesis.

5) Exploratory Aim 5: Safety measures (adverse events profile) will be compared between medication conditions using Fisher's exact tests (ketamine vs. midazolam).

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