STUDY PROTOCOL

RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROL STUDY OF A SINGLE VERSUS REPEATED INTRAVENOUS SUB-ANESTHETIC KETAMINE TREATMENT IN REFRACTORY DEPRESSION

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BACKGROUND

Prevalence and Impact of Treatment-Resistant Depression

Treatment-resistant depression (TRD) has been broadly defined as a major depressive disorder that fails to remit despite an adequate course of antidepressant medication treatment (Fava 2003). Among patients with major depressive disorder (MDD), those with TRD have greater risk of suicide (Papakostas et al. 2003), earlier relapse if remission is achieved (Fekadu et al. 2009) and incur the highest direct and indirect medical costs compared to treatment responders (Russell et al. 2004). Considering various definitions of TRD, the estimated prevalence ranges from 10% to 60% of all depressed patients (Fava 2003) (Rush et al. 2006).

A case-control study from the Veterans Health Administration and the National Death Index estimated that among depressed veterans who committed suicide between 2003-2006, 11.6% had TRD compared to 6.4% among controls (Pfeiffer et al. 2013). In the same study, the risk of suicide was 73% higher among veterans with MDD compared to veterans with other diagnosis (Pfeiffer et al. 2013). Considering that the prevalence of MDD in the VA Healthcare System (VAHCS) is almost twice as high as in the general United States population (12% vs.7%) (Blow FC, Owen RE, Valenstein M, Austin K, Khanjua K, McCarthy JF.), and the high rates of hospitalization, suicide, and comorbidity among depressed VA patients (Blow FC, Owen RE, Valenstein M, Austin K, Khanjua K, McCarthy JF.); (Valenstein et al. 2009), **the prevalence of veterans with TRD should be at least similar if not higher than more broadly representative depressed populations in the community**. The prevalence and severity of depression, including TRD, within veterans suggests a need for wide dissemination of maximally effective treatments for depression throughout the VA system. Unfortunately, some of the most effective treatments for depression, such as ECT, are not well distributed across VA medical centers (Pfeiffer et al. 2011). A recent report by the HSR&D's Evidence-based Synthesis Program found a lack of evidence to support favoring psychotherapy over antidepressant medication for mid-life adults with TRD (Trivedi et al. 2009).Thus, **there is a pressing need to investigate new interventions in the treatment of TRD.**

To enhance drug development efforts for depression, study of interventions that are radically different from current agents are now being utilized. The cutting-edge discovery of ketamine's rapid and efficacious effect in TRD opens new avenues to examine the potential role of glutamatergic agents. However, a single ketamine infusion appears insufficient to maintain response as the duration of antidepressant effects appeared to be approximately 1 week in some patients. To improve antidepressant efficacy, the use of repeated intravenous (IV) ketamine infusions is beginning to be explored. Rasmussen et al. (Rasmussen et al. 2013) had a response rate of 80% using up to four infusions. Murrough et al. (Murrough et al. 2013b) reported a response of 71% at the end of six infusions. In our pilot study among veterans with TRD (Shiroma et al. 2014), 92% responded after completion of six infusions, and 45% maintained response for at least 4 weeks after the last infusion. The strategy of multiple infusions to increase efficacy and sustain antidepressant effects has not yet been systematically evaluated in an RCT.

SPECIFIC AIMS

The overall objective of this proposal is to determine the efficacy of a single vs. multiple sub-anesthetic IV ketamine infusions for patients with TRD. We plan to conduct a randomized controlled trial (RCT) comparing a single ketamine infusion preceded by 5 midazolam infusions vs. six ketamine infusions. Midazolam, a $GABA_A$ agonist without action on NMDA receptors, will serve as an active placebo. We plan to test our central hypothesis by pursuing the following specific aims:

Primary Aim 1: To determine the efficacy of a single versus six IV ketamine infusions among patients with TRD over a 12-day treatment phase. H1: Patients who complete six ketamine infusions will have greater reduction of depression severity than those who received a single ketamine infusion (preceded by 5 midazolam infusions).

Aim 2: To determine the durability of antidepressant effect after completion of a single versus six ketamine infusions. H2: Patients treated with six ketamine infusions will sustain antidepressant effect for longer period than those who received a single ketamine infusion (preceded by 5 midazolam infusions) over a 6-month follow-up period.

Exploratory Aim 3: To assess the time course of change in depressive symptoms among patients who received six IV ketamine infusions over a 12-days treatment.

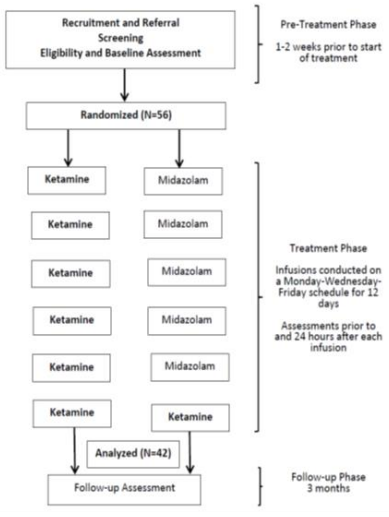
Exploratory Aim 4: To study predictors of treatment response that focus on functional brain imaging (resting state and task functional MRI) , intracellular mediators of antidepressant effects and cognitive function.

RESEARCH DESIGN AND METHODS

Design Overview

The proposed study is a one-center, interventional, efficacy study designed to determine antidepressant outcomes (response, remission and relapse) of serial ketamine infusions compared to a single ketamine infusion among patients with TRD (*Figure 1*). Given our pilot findings, we have hypothesized that six infusions will be superior to a single infusion of ketamine in both decreasing severity of depressive symptoms and maintaining response. Participants will be male and female patients (18 to 75 years old) of any era or military background who suffer from TRD. Potential participants will be recruited from Mental Health clinics in the MVAHCS and screened for eligibility using a two stage process (phone/chart review, followed by interview). Those who meet eligibility criteria will complete baseline assessments 1-2 weeks prior to starting treatment. We estimate that 56 participants will be randomly assigned to one of two parallel treatment conditions: 1) a single ketamine infusion preceded by five midazolam infusions or 2) six ketamine infusions. Midazolam, a short-acting benzodiazepine and anesthetic agent, may serve as a control

Figure 1: Study Design



condition given pharmacokinetic characteristics similar to those of ketamine, fast onset of action, and short elimination half-life (Kanto 1985). Midazolam would also mimic ketamine in terms of the time course of dissociative and nonspecific behavioral effects (e.g., sedation, disorientation). In fact, the use of IV midazolam at 0.045 mg/kg was recently used as active placebo to enhance masking intention (Murrough et al. 2013a). Each intervention will be administered over a 12-day infusion-phase on a Monday-Wednesday-Friday schedule followed by 6-month follow-up. We estimate that out of 56 patients, 42 will complete treatment phase and will be considered for primary analysis. Independent evaluation of depressive symptom severity and potential covariates of antidepressant effect will be ascertained at baseline, at several time points during infusion period, and at follow-up.

Subject Recruitment and Selection

Participants will be recruited from patients receiving mental health treatment in the MVAHCS and in the community. Referrals will occur from clinicians and clinics, and responses from posted fliers and study pamphlets. Potential participants will be provided with information about the study and screened through medical records, chart review, and by telephone to determine whether they meet basic inclusion/exclusion criteria. Those who qualify will be scheduled for a more rigorous assessment (*see further details below*).

Eligibility Criteria. The following eligibility criteria that identify a broad array of participants with TRD.

Inclusion Criteria:

1. Male or female patients aged 18 to 75 years.
2. Have a telephone in their home and able to hear telephone conversations.
3. Must meet current DSM-IV criteria for MDD, single or recurrent, without psychotic features confirmed by depression subset of the Structured Clinical Interview-Clinical Trial for DSM-IV (SCID) (Lobbestael, Leurgans & Arntz 2011).
4. Have score ≥32 on the Inventory of Depressive Symptomatology—Clinician Rated (IDS-C_{30}) (Rush et al. 1996) for severity of major depressive episode (MDE) at screening.
5. Current major depressive episode resistant to treatment defined as failure to achieve improvement from at least 2 antidepressant trials of different pharmacological classes. Systematic evaluation of previous antidepressant trials will be assessed by the Antidepressant Treatment History Form (ATHF) (Sackeim 2001).
6. If applicable, current antidepressant dosages including augmenting agents and/or frequency and duration of psychotherapy sessions must remain stable for at least 6 weeks prior to beginning of the study.

Exclusion Criteria:

1. Inability to speak English.
2. Inability or unwillingness to provide written informed consent.
3. Moderate/severe cognitive impairment by Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh 1975) scores ≤27.
4. Current or lifetime DSM-V criteria for post-traumatic stress disorder (PTSD), acute stress disorder, psychosis-related disorder, bipolar disorder I or II disorder, substance-induced mood disorder, any mood disorder due to a general medical condition or any Axis I disorder other than MDD as the primary presenting problem.

5. History of moderate or severe traumatic brain injury, Parkinson's disease, dementia of any type, multiple sclerosis, seizures or other CNS related disorders.
6. History of comorbid substance disorder within 6 months of assessment plus positive urine toxicology screen test during baseline assessments.
7. Clinically unstable medical illness that could compromise the patient's ability to tolerate or likely interfere with the study procedures (e.g., history of or current myocardial ischemia or arrhythmias, congestive heart failure, severe pulmonary, renal, or hepatic disease, uncontrolled hypertension).
8. Current or within less than 14 days use of barbiturates or monoamine oxidase inhibitors (MAOi).
9. For women: pregnancy (confirmed by lab test), initiation of female hormonal treatments within 3 months of screening, or inability/ unwillingness to use a medically accepted contraceptive method during the study.
10. Imminent risk of suicidal/homicidal ideation and/or behavior with intent and/or plan.

Pre-Screening. In order to reduce subject burden, we will obtain a waiver of HIPAA authorization to allow potential subjects to be pre-screened by chart review and in person or by telephone prior to scheduling an Eligibility and Baseline Assessment visit. Potential participants will be provided with information about the study and asked a series of questions to determine if they meet basic inclusion/exclusion criteria (e.g., indicators of current MDD). They will be informed that the treatment involves multiple infusions of sedatives at subanesthetic doses. Those interested will be scheduled for an Eligibility and Baseline Assessment.

Informed Consent Procedures
Before Eligibility and Baseline Assessment, voluntary informed consent will be obtained in accordance with local IRB approvals. At the consent session, all assessments, and information on treatment will be explained. Subject comprehension of information will be assessed by the Modified Dysken Screening Tool, an instrument commonly used at MVAHCS to determine decision-making capacity of a potential research subject to provide informed consent to participate in research. Willingness to participate in assessments and random assignment to 1 of 2 treatments will be confirmed and information about confidentiality and study payments will be provided.

Assessment Procedures. Assessments will take place in two contexts:1) at baseline and throughout treatment and follow-up, and 2) during each infusion. Baseline and outcome assessments will take place in the initial contact with the participant and over the phone, while infusion assessments will take place as part of the infusion procedures. These assessments are summarized in Table 1 and Table 2, respectively. Clinical interviews will be conducted by trained independent evaluators (IEs) who are blind to participant treatment condition. Subject compensation will also be provided to increase participant retention and reduce missed assessments (*see further details below*).

Eligibility and Baseline Assessment. The Eligibility and Baseline Assessment will be accomplished during 1-2 visits over a 7-14 day period prior to starting treatment. It will take a total of 4 hours. TRD will be defined by the ATHF (Sackeim 2001) based on information from patient's report, and from past treatment providers, pharmacies, and medical records. IEs will

administer the Inventory of Depressive Symptomatology-Clinician Version (IDS-C_{30}) (Rush et al. 1996) to determine the severity of current depressive episode. The Structured Clinical Interview-Clinical Trial version for DSM-IV (SCID-CT) (Lobbestael, Leurgans & Arntz 2011) will confirm the diagnosis of MDD and the absence of exclusionary diagnoses. Lack of moderate/severe cognitive impairment will be ascertained with an MMSE (Folstein, Folstein & McHugh 1975) score ≥ 28. Imminent risk of suicide/homicide ideation and/or plan will be assessed by interview. The Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version – Since Last Visit will be added to complement suicide exclusion criterion (affirmative response to questions 3, 4, 5 or 6). Perceived effectiveness with treatment received (CEQ) will also be assessed.

Evaluation of exclusionary criteria involving unstable medical illnesses will be based on medical record review by Principal Investigator in consultation with study anesthesiologist, Dr. Wels. A urine pregnancy and drug screen will be obtained to ensure no one is pregnant and to document possible illicit substance use. Research staff will also assess clinical impression of illness severity (CGI) (Guy 1976) and quality of life (WHOQOL-BREF) (Skevington et al. 2004). In addition, patients will provide information from at least two competent adults that will serve as alternative emergency contact during the study (see Appendix 1). In this same line of thought, a hand-out describing steps to follow in case of decompensation including VA contact information will be provided prior to study onset (Appendix 2).

Treatment Assessment. The research staff will ascertain for measures of depressive symptoms severity, potential covariates of antidepressant effect, and side effects at Eligibility and Baseline Assessment beginning and at Day 2, 4, 6, 9, 11, and 13 during infusion phase. We will assess levels of anxiety (BAI) and pain intensity (NSR for pain) as covariates because 1) anxiety might negatively impact antidepressant response (Steffens, McQuoid 2005); 2) the analgesic effect of ketamine used in this study may indirectly result in improvement of depressive symptoms. To reduce subject burden, and decrease missing data, repeated measures (MADRS, BAI, C-SSRS,and NSR for pain) will be conducted via telephone interviews 24-hours post infusion on the repeated measure. Prior studies suggested that peak of antidepressant effects to ketamine occur 24 hours after administration (Zarate et al. 2006a) (Mathew et al. 2010). The MADRS for interviews conducted by telephone is comparable to interviews conducted by face-to-face administration (Kobak et al. 2008); as self-reported tools, the BAI and NRS can be reliably used in a similar way. Psychotogenic effects will be measured with the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+) (Overall 1962) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization; dissociative effects and manic symptoms will be measured with the Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al. 1998) and Young Mania Rating Scale (YMRS) (Young et al. 1978), respectively. Additionally, the patients were regularly questioned during the infusions about any dysphoric emotions or altered sensory experiences. We anticipate the telephone treatment assessments will take no more than 20 minutes on the phone.

Follow-up Assessment. Following completion of treatment (Week 3), participants will attend Post-Treatment Assessment at weekly intervals for the first 4 weeks, at 2-week intervals for the next 8 weeks, and at 4-week intervals for the remaining 12 weeks. Psychiatric medication changes will be discouraged during follow-up. In the case that the patient relapses (‹50% of baseline MADRS score at that follow-up visit), follow-up will continue as scheduled with

subsequent mental care being managed by her clinician to change or add medications if needed. Each visit will take about 2 hours. Similar to the baseline assessment session, follow-up assessments will involve interview guide for depressive symptom severity (MADRS), suicide assessment (C-SSRS), clinical impression of illness severity and improvement (CGI), as well as self-reported measures of pain intensity (NRS for pain), level of anxiety (BAI), and quality of life (WHOQOL-BREF).

Secondary Outcomes.

Neuroimaging: The neural networks involved in ketamine treatment need to be elucidated yet. For this purpose, a multi-modal imaging technique will be obtained within one week prior to the first infusion and again within one week following the final infusion for a sub-sample of 15 participants. This portion of the study will remain optional and clearly expressed in the informed consent. Additional monetary compensation will be provided for participation. Patients will be scanned using 3Tscanner located at the University of Minnesota Center for Resonance Research (CMRR-Project #10097). We will obtain a 5 min high-resolution T1-weighted anatomical image, and a 6 min multi-band resting-state scan comprising 180 contiguous echo planar imaging (EPI) whole-brain functional volumes (TR = 2000ms; TE = 30ms; flip angle = 90; 34 contiguous AC-PC aligned axial slices; matrix = 64×64; FOV = 22cm; acquisition voxel size = 3.4×3.4×4mm). A 14-min functional MR (fMRI) with same parameters as above will be conducted while participants engage in an Emotional Stroop task, where they will be asked to evaluate words appearing below happy or sad faces, as 'positive' or 'negative'. This task is designed to have 4 different runs, each lasting for 3.5 min and containing 16 words (8 positive-8 negative) recurring as congruent (e.g. positive word-happy face) and incongruent (negative word- happy face). Once neuroimaging is completed, information about active vs placebo arm for those 15 patients will be disclosed from the research pharmacist to study co-investigator at the CMRR (Dr. Lim). Patients will be identified by an alphanumeric code different from that used at the VA. In this sense, we will assure blinding to investigators and assessors involved in conducting the clinical trial at VA site.

Peripheral biomarkers: The pathophysiology of antidepressant-resistant depression is characterized by dysregulated neural network activity, hypothalamic-pituitary-adrenal axis dysfunction, elevated levels of pro-inflammatory cytokines and kynurenines, with consequent alterations in neurotransmitter signaling (particularly glutamate) and central metabolic disruption. We plan to examine a platform of biomarkers of treatment response that focus on major metabolites; white blood cell stimulated protein kinase B (Akt), mTOR, and glycogen synthase kinase 3 (GSK3) signaling (intracellular mediators of antidepressant response) and an exploratory ketamine response gene expression signature (transcriptomic bioinformatics approach). For this purpose, 20cc blood will be drawn for Peripheral Blood Mononuclear Cell (PBMC) isolation prior to the first infusion and 2 hours after the fifth infusion. 10cc blood will be drawn into a serum tube for serum and buffy coat prior to the first infusion and 2 hours after the final infusion. Another 20cc of blood only for Peripheral Blood Mononuclear Cell (PBMC) isolation will be drawn by venipuncture as described above at each subsequent follow-up visit after infusions are completed. All tubes will be labeled with a study identifier, collection date, and time of draw. Analyses will be conducted by Dr. Susannah Tye at Mayo Clinic. Buffy coat and serum samples will be flash frozen and stored at -80C. Serum will be stored as 1ml aliquots at −80°C. Metabolomics analysis will be performed on serum samples and differential pre- versus post-ketamine mRNA and protein levels will be quantified from buffy coat samples.

Bioinformatics pathway analysis will be used to identify key differences in molecular responses to ketamine. These assays will be used to better understand the physiologic mechanisms of ketamine response/non-response.

The 20cc heparinized tube of whole blood will be mixed with an equivalent amount of phosphate buffered saline (PBS). This mixture will be slowly overlaid onto Ficoll, the mononuclear layer recovered, and cells washed with PBS. PBMCs will be isolated from whole blood and viably frozen. PBMCs will be cultured and stimulated with insulin and intracellular Akt, mTOR, and GSK3 gene and protein levels will be quantified following 0, 5, 15, and 30 minutes of stimulation. This signaling pathway is implicated in mediating the antidepressant response to ketamine. Western blot and rt-PCR techniques will be used to quantify protein and gene expression respectively. This assay will be used to identify potential key deficits in this signaling pathway that may serve as future biomarker screen of ketamine response/non-response. Outcomes of each assay will be correlated with patient response profile. All tissue will be destroyed upon completion of the study.

Cognitive functions: There are concerns of potential cognitive risks of longer-term ketamine treatments. While studies suggest that low-dose ketamine administered over short periods to patients with unipolar and bipolar depression does not cause cognitive deficits, in contrast to studies of high-dose, long-term administration in frequent ketamine abusers, further evidence are needed. On the other hand, slow processing speed at baseline appears to predict respond to repeated ketamine treatments in TRD. For this purpose, we will assess cognitive function at baseline, within a week after completed infusions, and during subsequent follow-up visits using computerized cognitive tasks (www.cogstate.com). Cognitive subtests will include measures of multiple domains such as processing speed, working memory, executive function, and associative learning. All tests will be based on playing card formats, with little reliance on or assessment of verbal abilities. The battery requires 15 to 20 minutes to be completed. This battery was developed for repeat testing with extensive results concerning practice effects.

Quantitative electroencephalography (QEEG): Recent literature indicates that QEEG power in the theta and alpha frequency band may identify individuals more likely to respond to TCAs and SSRIs within one week of starting an antidepressant medication. This has led to the development of QEEG parameter, the Antidepressant Treatment Response (ATR) index, which has been shown to significantly predict remission of depression symptoms at 7 weeks following initiation of multifarious SSRIs (Cook 2013; Caudill 2014; Hunter 2011). Similarly, reduction in QEEG theta cordance measured during ketamine infusions was shown to correlate with increased positive emotions in healthy volunteers (Horacek 2010). As such, we propose to evaluate frontal quantitative electroencephalogram recordings as a predictive factor of ketamine response. For this purpose, we plan to QEEG to be conducted before (t-15), during (t+25 min) and after (t+145 min) the first study drug infusion. Electroencephalogram data will be collected in a laptop computer connected to a 4-channel EEG amplifier unit. Self-prepping electrodes will be placed at 4 sites on the forehead and 2 on earlobes. Each EEG data will be recorded while subjects rest during two 6-minute segments with eyes closed, separated by a 2-minute eyes-open segment (total time of 15 minutes).

Emotion Processing: A modified emotional Stroop task (EST) will be used to evaluate emotion processing. Subjects will be asked to evaluate words appearing below happy or sad faces, as 'positive' or 'negative'. This task is designed to have 4 different runs, each lasting for 3.5 min and containing 16 words (8 positive-8 negative) recurring as congruent (e.g. positive word-happy face) and incongruent (e.g. negative word-happy face). The task will be administered at baseline and then then at post-infusion visits on week 5, 10, 14, 20 and 28

Rumination: Ruminative responding in major depressive disorder is defined as a recurrent, self-reflective, and uncontrollable focus on depressed mood and its causes and consequences. Higher levels of rumination have been found to predict both more severe depressive symptoms in depressed individuals and the onset of depressive symptomatology in non-depressed people. We will study rumination by using a recently developed task named the Internal Shift Task (IST) and the ruminative response scale (RRS). The RRS is a 22-item self-report measure and consists of items that describe responses to a depressed mood that are focused on the self-symptoms, or consequences of depressed mood. Participants are requested to indicate how often they engage in these responses using a four-point Likert scale ranging from 1 (almost never) to 4 (almost always). The estimated time to complete the RRS-NL is 8 minutes and will be administered at baseline.

The IST examines cognitive control held in working memory by updating of and mainly switching between internal mental representations. The task will be programmed using E-prime 2.0 software package and run on a laptop computer. The stimuli will be faces taken from the Karolinska Directed Emotional Faces. In the IST, faces will be presented at the center of the computer screen. Participants will complete an emotion (faces categorized as neutral or angry) and gender (faces categorized as male or female) tasks. There will be 12 blocks for both conditions with random 10 to 14 trials (or faces) with in each block. The participant's task will keep a silent mental count of the number of faces in each category, presented within a block of trials (e.g., participants have to update counters for male and female or neutral and happy faces in the gender and emotion condition, respectively). When a face is presented, participants will be asked to press the space bar as fast as possible (reaction time measure) to indicate that they have updated both internal counters. The next face will appear on the screen after a 200ms inter-trial interval. Participants have to report the number of faces of both categories (accuracy measure), using the number path of the keyboard, at the end of each block in a fixed order to encourage a consistent counting strategy (e.g., report counts for the neutral and then for the happy faces in the emotion condition; in the gender condition the order will be male–female). The estimated time to complete the IST is 15 minutes.

Impulsivity: The Barratt Impulsivity Scale (BIS-11) is a self-administered 30-item questionnaire designed to assess the personality/behavioral construct of impulsivity and takes 10 minutes to administer. The Go/No-Go task (GNG) measures impulse control by manipulating response prepotency by presenting a preliminary go or no-go cue before the actual go or no-go target is displayed. The Go/No-Go task presents 250 trials and requires 10 minutes to complete. The

Balloon Analogue Risk Tasks (BART) is a computer based measure to assess risk taking. In each of 30 trials, a cartoon image of a balloon appears. Participants click a button to increase the size of the balloon. Each time the balloon is pumped, the participant earns money. However, the balloon, if pumped excessively, will burst, and all the money for that trial is forfeited. The size at which the balloon will burst varies across trials and is not specified to participants. The average number of clicks represents a measure of propensity to accept risks. This task takes 10 minutes to complete. All three impulsivity tasks will be administered at baseline and then at post-infusion visits on week 5, 10, 14, 20 and 28

Assessment Schedules and Measures

Table 1 illustrates the schedule of assessments over the course of the study including measure of depression symptom severity, DSM-IV MDD and other diagnoses, secondary outcomes, and perception of treatment.

Table 1. General Assessment Schedule

Construct	Measure	Eligibility and Baseline Assessment	Repeated Treatment Assessments	Repeated Follow-Up Assessment
		1-2 weeks before start of treatment	Day 2 to 13	Weekly for 4 weeks, biweekly for 8 weeks and monthly for 3 months
Primary Outcome Measure				
Depressive Symptoms	MADRS		X	X
Interview Based Assessments				
Decision-making capacity	Modified Dysken Screening Tool	X		
TRD Diagnosis	ATHF	X		
MDD Diagnosis and rule-out other diagnosis	SCID-CT	X		
Severity of current MDE	(IDS-C_{30})	X		
Rule-out moderate/severe cognitive impairment	MMSE	X		
Side Effects and Secondary Outcome Measures				
Brain imaging		X	X	
Peripheral biomarker			X	X
Cognitive assessment		X		X
Emotion Stroop Task (EST)		X		X
Rumination (IST and RRS-NL)		X		X
QEEG		X	X*	
Impulsivity (BIS-11,GNG, Bart)		X		X
Side Effects (dissociative, psychotogenic, and manic symptoms)	CADDS, BPRS+, YMRS		X	
Suicide Risk	C-SSRS	X	X	X
Anxiety Symptoms	BAI		X	X

Pain Intensity	NRS		X	X
Recovery from study drug infusion	mAldrete		X	
Quality of Life	WHOQOL-BREF	X		X
Global Rating of Illness Severity and Improvement	CGI	X		X
Perceptions of Treatment Measure				
Perceptions of Treatment	CEQ	X		

*QEEG will be conducted before (t-15), during (t+25 min) and after (t+145 min) the first study drug infusion and then 25 minutes during infusion and at 145 min post-infusion.

Randomization Procedures

Our planned enrollment includes 28 patients in each treatment condition, for a total of 56 patients (*see Sample Size Determination below*). Participants will be randomly assigned to six ketamine infusions or single ketamine infusion preceded by 5 midazolam infusions. Randomization will be conducted using SAS PROC PLAN. Group assignments for each participant will be concealed in sequentially numbered, sealed, opaque envelopes will be provided to the study staff by the research pharmacist.

Treatment Conditions

Over the course of the study, infusions in both treatment conditions will be administered individually in a private room located in 3E Unit. Baseline assessments and post-infusions follow-up measures will occur at the Mental Health Outpatient. The procedures for both treatment conditions are similar and described as follows:

Procedures during infusion. Table 2 describes the schedule of assessments on the day of infusion. Patients will arrive in the morning or afternoon after fasting for 8 hours. An indwelling catheter will be placed in the non-dominant arm for medication administration. Digital pulse oxymetry, respiratory rate, pulse rate, and blood pressure will be recorded every 10 min for 1 hour beginning 10 min before infusion. Based on the dose, rate of infusion, and endpoint/purpose of the study, the infusions do not fall into the category of "moderate sedation" and therefore no cardiac monitoring will be required at our institution. Subjects will then receive IV infusion of either 0.5 mg/Kg of ketamine hydrochloride solution or midazolam 0.045 mg/kg over 40 minutes. Only study MDs (Dr. Shiroma, Dr. Wels or Dr. Albott) or study nurse (Debra Condon RN), will administer study medications, namely, programming infusion pumps and initiating intervention. The dose of ketamine will be calculated by ideal body weight based on sex, age, height, and body frame in the Metropolitan Life Insurance tables. Evaluation procedures include rating scales (MADRS, BAI, NRS, CADDS, BPRS+, YMRS, and CGI) will be obtained before infusion. Potential side effects related to ketamine (CADDS, YMRS, and BPRS+) will be measured again immediately upon completion of each infusion and during post-ketamine monitoring period. Guidelines established for clinically significant changes in vital signs and mental status during the ketamine infusions will be as follows: systolic blood pressure (BP) ›161 or ‹89, diastolic BP ›110; heart rate ‹40 or ›130 beats/min; respiratory rate ‹10 or ›30 per minute; pulse oxymetry ‹90%; severe hallucinations, confusion, delusions, irrational behavior, or agitation. Research personnel will record vital signs prior, during and after infusion. One of MDs or RN will be present throughout the infusion plus study anesthesiologist (Dr. Wels) will be available to be reached during infusions if necessary. Medications such as labetalol, ondansetron,

and flumenazil as well as a crash cart will be available to manage unanticipated side effects. The infusion will be discontinued if adverse events do not respond to interventions. After end of infusion, MD or RN will assure that patient's physical and mental status are stable and appropriate continue with monitoring of vital signs and completion of rating scales. All subjects will be monitored at least for 2 hours post infusion. Before leaving the infusion unit, subjects will be assessed by MD or RN to demonstrate that all clinically significant side effects are resolved by obtaining a score≥9 in the modified Aldrete scoring system (Aldrete 1995). Written instructions about rare but serious side effects and several measures to improve recovery at home will be provided at discharge. The standard operating procedure (SOP) in Appendix 3 include a detailed plan for administration of the study drug and monitoring of participants including a description of the qualifications of the personnel responsible for each of these tasks.

Table 2. Assessment Schedule on Infusion Day

	Measure		**Baseline (t_0)-60 min**	**t_0+40 min**	**t_0+100 min**	**t_0+160 min**	**t_0+24 hrs.**
Primary Outcome Measure							
Depressive Symptoms	MADRS		X				X
Secondary Outcome Measures							
Anxiety symptoms	BAI		X				X
Pain intensity	NRS		X				X
Suicide Risk	C-SSRS		X				X
Hemodynamic Measures							
BP,pulse,RR,$SatO_2$			X*	X	X	X	
Side Effects Measures							
Dissociative Symptoms	CADDS		X	X	X	X	
Psychotogenic Symptoms	BPRS+		X	X	X	X	
Manic Symptoms	YMRS		X	X	X	X	
Recovery from study drug infusion	mAldrete					X	

*Hemodynamic measures will be monitored every 10 minutes for one hour, beginning 10 minutes prior to the infusion.

Compensation for assessment sessions

Participants will be compensated for completing the assessment sessions throughout the study. Assessment sessions involve individual clinical interviews, self-report, and semi-structured questionnaires. Compensation for assessment sessions will be delivered according to the following schedule: $50 for Eligibility Screen and Baseline (1-2 weeks prior to starting treatment, approximately 4 hours), $25 for each Treatment Assessment (a total of 6 over 12 days, approximately 3 hours each), $50 when Treatment is complete, and $30 for each Follow-up Assessment (total of 11 over 6 months following end of treatment, approximately 2 hours each) for a total of $580. Participants who prematurely withdraw from study assessments will not be compensated for assessment sessions that have not yet taken place. For the brain imaging part of the study, an additional $50 will be given after each scan (total of $100).

Test of Blinding.

The success of blinding will be tested on a 5-point scale at the end of the infusion period using a 2 × 5 format (LaRosa, 1994). Subjects will be asked to rate the extent of certainty about their

treatment on the following scale: 1) strongly believe the treatment is active, 2) somewhat believe the treatment is active, 3) somewhat believe the treatment is placebo, 4) strongly believe the treatment is placebo and 5) do not know. In addition, subjects who initially answered 'do not know' will be re-asked to choose one treatment (in 2×2 format) providing validation of the 'do not know' data.

Table 3. Study Timeline

	Year 1				Year 2				Year 3				Year 4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Start-up																
Enrollment																
Interventions																
Outcome assessments																
Data entry/cleaning																
Statistical analysis																
Report writing																

Potential Problems & Alternative Strategies. 1) *Recruitment could be slower than anticipated.* Based on our pilot recruitment, and the fact that over 400 veterans meet criteria for TRD based on administrative data, we are very confident of our ability to meet recruitment goals. However, we have the option of expanding recruitment to outpatient satellite clinics (CBOCs) and non-VA community clinics if needed to increase enrollment rates. 2) Severe attrition and missing data. Based on our sample size calculation including conservative attrition rate of 30%, the study is adequately powered for our study aims. In our own sample, out of 14 subjects, only 2 dropped out, consisting with tolerability and safety from previous reports (Murrough et al. 2013b) (Rasmussen et al. 2013). If risk of dropping out due to assessment burden occurs, subjects will have the option of completing a minimum core assessment comprising primary outcome measures. A DSMB will be assembled to ensure safety. Missing data would be handled as described in Data Analysis. 3) Patients may be lost to follow-up. We would initiate outreach procedures such as letters and phone calls. If there is concern about suicide risk as an outpatient, established clinical procedures that includes safety check by police will be performed.

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