A naturalistic study of serial infusion of low-dose ketamine for treatment resistant depressive disorders in an academic psychiatric hospital: The UTHealth Ketamine Project

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Study protocol: A naturalistic study of serial infusion of low-dose ketamine for treatment resistant depressive disorders in an academic psychiatric hospital: The UTHealth Ketamine Project

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1. Specific aims

The glutamate N-methyl-D-aspartate (NMDA) receptor antagonist ketamine is an FDA approved general anesthetic with immediate calming effects (within 24 hours). Ketamine has proved to have great utility for emergency procedures and management of chronic pain syndromes. In psychiatry ketamine has been shown to induce a rapid antidepressant response in patients with Treatment Resistant Depression (TRD) following a 0.5 mg/kg dose administered intravenously over 40 minutes. These benefits were maintained for approximately 1 week post-infusion (Murrough et al., 2011). There is also a significant body of evidence for the mood-enhancing and anti-suicidal properties of ketamine in patients with bipolar and unipolar depression (Griffith et al. 2014). This promising area of research poses a variety of methodological challenges. The optimal dose of ketamine for therapeutic purposes is still unknown but previous studies have used doses of ketamine of up to 0.5 mg/kg (Kollmar et al., 2008; Messer et al., 2010; Murrough et al., 2011; Rasmussen et al., 2013; Stefanczyk-Sapieha et al., 2008; Zanicotti et al., 2012). Ketamine administration requires close anesthetic monitoring in most institutions. As a result, the administration of ketamine involves major costs that insurance companies and patients cannot afford (Rasmussen et al., 2013). Thus, much work is still needed to increase/maintain high response rates to ketamine and lower the costs associated with administration.

The *primary objective* of our study is to determine the effectiveness of serial infusions of intravenous (IV) ketamine in adults *with treatment resistant depression (TRD) - diagnosed with either Major Depressive Disorder or Bipolar Disorder* - at a slower infusion time than reported in previous studies. We expect that this approach alongside with the presence of a psychiatrist with Advanced Cardiac Life Support (ACLS) training will eliminate the need for continuing anesthetic monitoring during infusion, thus leading to a more cost-effective intervention. As part of this objective, we plan to recruit 30 individuals with Treatment Resistant Depression and conduct an open label, naturalistic study using slow infusions of ketamine over a time period of 40 minutes. **The duration of this study will be 12 weeks and will include twice weekly infusions over a period of 4 weeks and weekly infusions for the following 4 weeks of the study treatment period (8 weeks). There will also be a 4 week observational period post- treatment.**

Our *hypotheses* are that patients suffering from TRD receiving weekly slow IV infusions of ketamine (0.5 mg/kg) over 40 minutes will:

1. Report similar efficacy and better tolerability than those reported with conventional schemes of 3 infusions per week over a 12 day period.
2. Report less psychiatric side effects measured by changes in test scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), Quick Inventory of Depressive Symptomatology (QIDS) and Young Mania Rating Scale (YMRS) compared to those previously reported with conventional schemes of serial ketamine infusions.
3. Report an almost immediate effect based on the PANSS and Q-LES-Q scales which will be administered after the 40 min infusion period.
4. Report less suicidal ideation measured by changes in scores on the Scale for Suicide Ideations (SSI; Beck et al., 1979), and the Suicide Status Form (SSF; Conrad et al., 2009) scores compared to that previously reported with conventional schemes of serial ketamine infusions.
5. Report a better global outcome of treatment measured by a decrease in scores on in the Clinical Global Impression Scale (CGI; Guy, 1976) score compared to that previously reported with conventional schemes of serial ketamine infusions.
6. Experience less hemodynamic changes in blood pressure and heart rate compared to than those previously reported with conventional schemes of serial ketamine infusions.
7. Experience no cognitive impairment on the Brief Assessment of Cognition in Affective Disorders (BAC-A) following ketamine infusions. To our knowledge this hypothesis has not been previously assessed after an 8-week serial ketamine infusion treatment period.

Clinical relevance

Treatment Resistant Depression (TRD) is a major public health problem that constitutes a great burden for patients and mental health providers because of its prevalence, impact on people's quality of life and overall cost to the society (Nemeroff et al., 2007). Given the dearth of the research in the field of Ketamine treatment, more naturalistic follow-up studies focusing on ketamine's innovative antidepressant properties are warranted. Further, the findings of this study will provide health professionals with additional knowledge on the antidepressant properties of repeated ketamine IV infusions in both resistant Major Depressive Disorder (MDD) and Bipolar Disorder (BD). The current study will also help characterize responders from non- responders to ketamine, and will enable the assessment of the response and remission rates following ketamine intervention.

2.0 Research Strategy

A. Significance

Background and Rationale

Major psychiatric disorders such as major depressive disorder (MDD) and bipolar disorder (BD) are among the most disabling mental illnesses worldwide with a global social cost of $66.5 million and 16.8 million disability-adjusted life years (DALYs) respectively (Collins et al. 2011). MDD is a chronic and disabling mental illness (Kessler et al., 2005a, 2005b; Murray et al., 2012), associated with increased mortality and shortened lifespan (De Hert., et al. 2011; Ferrari et al., 2013; Whiteford et al., 2013). Likewise, BD is one of the most severe and lethal psychiatric disorders (Nock et al., 2009; Nordentoft et al., 2011). The lifetime prevalence of BD is approximately 4% in the United States (Merikangas et al., 2007) with depressive symptoms dominating the longitudinal course of the illness (Calabrese et al., 2008; Judd et al., 2002, 2003).

A growing body of evidence has revealed that most patients with MDD who receive evidence-based treatments do not achieve sustained remission with first-line antidepressants (McIntyre et al., 2014). Treatment resistant depression (TRD) is generally defined as a reduced clinical response to adequate doses and duration of antidepressants (Dodd et al., 2005; Fava, 2003; Hauptman et al., 2008; Rush et al., 2003). Similarly, treatment resistance in bipolar depression refers to the lack of response to adequate trials of monotherapy with lithium or lamotrigine or the combinations of these two mood stabilizers with anticonvulsants or antipsychotics (Lipsman et al., 2010) and non-remission despite receiving three adequate trials of first line medications with mood stabilizing properties (Malhi et al., 2012).

In spite of the advances in the treatment of depression (which includes new-generation antidepressants and multimodal treatment strategies (combining mood stabilizers, atypical antipsychotics, hormone supplementation, and psychosocial interventions), treatment resistant depression remains a significant problem in the clinical management of MDD and BD (Gaynes et al., 2009; Nelson et al., 2009; Spielmans et al., 2013; Warden et al., 2007; Zarate et al., 2013b, Prudic et al., 2013, Rabheru et al., 2012). Furthermore, the time lag in onset of therapeutic effect limits treatment response and adherence in bipolar depression (Calabrese et

al., 2006; Thase et al., 2006; Weisler et al., 2008). The additive effects of all these factors increase the overall risk for comorbidity and suicidality (Jick et al., 2004; Machado-Vieira et al., 2008).

The antidepressant properties of ketamine, an anesthetic agent with N-methyl-D-aspartic acid receptor (NMDAR) antagonist properties has been demonstrated in MDD, bipolar depression, and TRD (Abdallah et al. 2012; Diazgranados et al. 2010a; Kranaster et al. 2011; Kudoh et al. 2002; Murrough et al. 2013a,b; Okamoto et al. 2010; Zarate et al. 2012). Further, a recently published meta-analysis has confirmed the efficacy of intravenously administered ketamine in depressive disorders independently from the severity, refractoriness or specificity of the depressive disorder (Fond et al., 2014). However, there is some reluctance to use ketamine in the clinical practice due to the potential concerns of misuse (Morgan and Curran 2011) dosage, side effects, duration of efficacy, and impact on suicidal ideations.

The results of the largest study conducted thus far on the antidepressant effects of repeated ketamine infusions included twenty-four subjects with TRD who underwent a washout of antidepressant medication followed by a series of up to six intravenous (IV) infusions of ketamine (0.5 mg/kg) over 40 minutes administered open-label three times weekly over a 12- day period (Murrough et al., 2013b). The TRD patients meeting response criteria were monitored for depressive relapse for up to 83 days from the last infusion. The antidepressant effect of ketamine was evident very early in the course of treatment. Moreover, ketamine exerted a broad-spectrum effect on individual symptoms of depression, and rapid response to the first infusion was highly predictive of a sustained response to subsequent infusions (Murrough et al., 2013b). Although preliminary, ketamine's large and sustained effect size regarding its antidepressant properties seems to be carried over repetitive IV infusions. In particular, suicidal ideation (SI) rapidly decreases even among non-responders to repetitive ketamine IV infusions. Therefore, ketamine is suggested to exert a unique anti-SI effect even in the absence of a full antidepressant response (Murrough et al., 2013b). This finding is consistent with previous reports highlighting the potential anti-SI effects of single dose infusion of IV ketamine in depressed populations (Diaz-Granados et al., 2010b; Larkin and Beautrais, et al 2011; Price et al., 2009).

Recently, researchers at the Mayo Clinic have performed serial ketamine infusion but at a lower infusion rate (Rasmussen et al., 2013). Ten depressed patients were treated with twice weekly

infusions of ketamine 0.3 mg/kg administered over 100 min until either remission was achieved or four infusions were given. Patients were naturalistically followed weekly for four weeks after completion of the infusions and psychiatric side effects were assessed with the Young Mania Rating Scale (YMRS; Young et al., 1978) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorman, 1988) respectively. While a 50% remission rate was documented without any significant increase on BPRS or YMRS measures, only two patients maintained remission at the 4-week follow up session. Nonetheless, it seems that ketamine infusions at a lower rate than previously reported might produce similar efficacy, excellent tolerability, and thus may be more available for routine clinical care.

Ketamine infusions do not appear to have negative neurocognitive sequels. In a recent study, 15 patients with TRD underwent six IV infusions of 0.5 mg/Kg ketamine over 40 min, (three times a week during a 12-day period) followed by a 4-wk observational period. Following the last ketamine infusion the authors observed an improvement in visual memory and. working memory. These cognitive changes may have been due to the decrease in the severity of the depressive symptoms (Shiroma et al. 2014). Along the same line, Murrough et al. (2015) found no change in cognitive functioning 7 days post-ketamine treatment in individuals with treatment- resistant depression.

To the best of our knowledge, the only published study exploring the tolerability, safety, and efficacy of repeated-dose open-label IV ketamine (six infusions over 12 days) focused on 10 medication-free symptomatic patients with TRD who had previously shown a meaningful antidepressant response to a single ketamine dose (Aan het Rot, et al., 2010). Patients received a 40-min IV infusion of ketamine (0.5 mg/kg) in an inpatient setting with continuous vital-sign monitoring and repeated recording of adverse events such as psychotomimetic effects. In the event that patients showed a 50% reduction in MADRS scores on day 2, they received five additional infusions on an outpatient basis on days 3, 5, 8, 10, and 12. Follow-up visits were conducted twice weekly for 4 weeks or until relapse. Ketamine elicited minimal transient positive psychotic or dissociative symptoms. Side effects during and after each ketamine infusion although common were reportedly mild. The response criterion was met by nine patients after the first infusion as well as after the sixth infusion of ketamine. MADRS scores after the sixth ketamine infusion were reduced by 85%, and an 89% relapse rate was reported between weeks 3 and 4 after finishing repeated IV ketamine infusion.

To summarize, these findings confirm the feasibility of low concentration and slower infusion rate of repeated-dose IV ketamine infusions for the acute treatment of TRD in the clinical practice (Aan het Rot, et al., 2010; Murrough et al., 2013b; Rasmussen et al., 2013).

Thus, in the current study we want to naturalistically explore the antidepressant effects of serial slow IV infusions (40 minutes) of ketamine at a dose of 0.5 mg/kg, over a treatment period of 8 weeks in an academic psychiatric hospital. This is a minimal sedation treatment. This dosage is the highest used so far in the literature and was selected because of its reported benefits in a psychiatric population. The dosage will be calculated using the patient's weight in kilograms. For dosing purposes, 0.5-0.9 round up to the next dose and from .01-0.49, we will round down to the lower dose. The primary outcome measure of this study will be *remission* estimated based on the severity of depressive scores (MADRS). After the 8 weeks of treatment, there will be a four week observational period. During the observational period, participants will receive treatment as usual and will be contacted over the phone for follow-up questions regarding their overall health status, mood and clinical state using MADRS, YMRS and CGI. They will also complete a neurocognitive task at the end of the 4 week observational period.

B. Innovation

The approach taken in the current study is novel for two reasons: 1) we are testing a novel dosage and time of infusion for the administration of slow infusion, repeated IV ketamine targeting TRD; 2) this is the first naturalistic study of repeated ketamine IV infusion for MDD and BD in a psychiatric setting. Furthermore, this will constitute the largest study conducted to date testing the antidepressant effects of repeated ketamine infusions in a combined population of MDD and BD patients with TRD.

C. Approach

The current project will exploit the feasibility of recruitment associated with ongoing studies at the University of Texas, Center of Excellence on Mood Disorder, Department of Psychiatry and Behavioral Science in Houston aimed at identifying the neural correlates of BD. The clinical sample will include individuals from various ethnic/racial backgrounds, reflecting the local community in the greater Houston area. We will use slow infusions of ketamine over a time

period of 40 minutes. **We will conduct an open label, naturalistic study focusing on the antidepressant effects of ketamine twice a week for the first 4 weeks and then weekly injections up to week 8 in an academic psychiatric hospital (UTHealth Harris County Psychiatric Center - HCPC).** Thirty patients with clinically documented TRD will be screened for diagnosis with the depression and bipolar disorder subset of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996) at baseline to establish the presence of a major depressive episode.

The administration of ketamine and urine tests will be carried out at the UTHealth Harris County Psychiatric Center (HCPC) in Houston, Texas. Routine blood tests and clinical/cognitive assessment will be done at the UTHealth Harris County Psychiatric Center (HCPC). Study drug will be provided in identical syringes, containing clear solutions including 1 mL of ketamine, e.g. 100 mg/mL with 9 mL of normal saline. A syringe will be used to provide IV applications of solution (). An ACLS psychiatrist will monitor the patient at HCPC. The administration of ketamine will be initiated by the anesthesiologist. The anesthesiologist will be present during the ketamine administration (40 minutes) and post-procedure (until patient is awake and anesthesiologist deems patient is clinically stable. The infusions will be conducted in our hospital during the mornings in a room set specially for this study. During the infusion, patients will be asked constantly about -how they feel‖ and will receive constant attendance from a psychiatric nurse and the attending ACLS- trained psychiatrist. ECG and pulse oximetry monitoring will be maintained throughout the infusions to check for hemodynamic changes.

After completion of each 40 minute infusion, patients will rest for 2 hours under observation of the clinical nurse before being discharged to a responsible adult who will accompany the patient home. Based on Zarate et al.'s (2012)'s protocol infusions will be administered twice a week, every 3 days for the first 4 weeks of the treatment period.

Routine blood tests will be performed in fasted state before the first ketamine infusion, prior to infusions at week 4 and at week 8. These tests aim to test the participants' overall health state. Blood samples will also be used for genetic testing and to measure levels of inflammatory markers. Samples will be stored at [redacted]. As stated in the consent form, participants will not receive any medical results or genetic counseling by providing a sample. All participants will undergo urine drug tests before each ketamine infusion.

Clinical questionnaires (e.g. MADRS) will be administered at baseline, at weeks 4, 8, and Week 12. The PANSS and Q-LES-Q scale will be administered after each ketamine infusion is completed. During the course of infusions, patients will receive treatment-as-usual from their primary psychiatrists as would be the case in a traditional therapeutic setting. There will be no changes in medication regimen throughout the 8 week treatment period as well as the 4 week observational follow-up period. Participants will be provided with a contact card directing them to the nearest ER/physician in case of emergency. Participants will be contacted weekly during the 4 week observational period to review the patient's health status and administer clinical scales. Upon conclusion of the intervention patients will be offered the opportunity to come back for maintenance sessions. The frequency of these sessions will depend on the patient's wishes and the physician's clinical judgment. The maximum session frequency will be once every month for a maximum of 12 months.

Assessment

The protocol consists of two components: clinical and cognitive assessments.

Clinical assessment

This evaluation will obtain family history and demographic data. Copies of any recent medical evaluations (past medical history, physical exam, etc.) will be requested from treating clinicians and health care providers. We will perform a urine drug screening (UDS) to rule out recent undisclosed use illicit substances. Demographic information is obtained through a standardized form and covers: age, race, gender, education (information both on siblings and their parents), religion, and socioeconomic status. Participants will fill out mood questionnaires rating the severity of the clinical symptoms.

-MINI Interview: This is the standard psychiatric research evaluation for ascertainment of psychiatric diagnosis in the context of research studies (Sheeha et al., 2016)). It is a comprehensive structured interview for determining axis I diagnosis according to the DSM-V.

-Clinical Global Impression Scale (CGI): This is a clinical instrument to assess global changes in patients' status in clinical studies. We will use the CGI-BD, for use with BD patients (Guy et al., 1976).

-Montgomery-Åsberg Depression Rating Scale (MADRS): this scale rates depressive symptoms, and its psychometric properties are well-established (Montgomery et al. 1979).

-Young Mania Rating Scale (YMRS): This is a well-established clinical severity rating scale for manic symptoms that has adequate inter-rater reliability and internal consistency (Young et al., 1978).

- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q): this scale is patient-reported and measures the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning (Endicott et al., 1993).

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- The Positive and Negative Syndrome Scale (PANSS) includes 30- items and was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms. It is composed of four scales measuring positive and negative syndromes, their differential, and general severity of illness. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Kay, Stanley R.; Flszbein, Abraham; Opfer, Lewis A. Schizophrenia Bulletin, Vol 13(2), 1987, 261-276.This scale will be administered following each ketamine infusion to assess acute changes in mood.

Self-report questionnaires to assess mood and anxiety:

1. Adult (Brief Dissociative Experiences Scale [DES-B]—Modified): Frequency: After every injection, to monitor the dissociative side effects, Scale features: simple, easy to use, new DSM-5 self-rated scale
2. Severity Measure for Generalized Anxiety Disorder—Adult : Every 4 weeks, to measure the severiy of anxiety. Scale features: simple, easy to use, new DSM-5 self-rated scale
3. Snaith–Hamilton Pleasure Scale: every 4 weeks, to measure the level of anhedonia, Scale features: easy to use, used before in ketamine studies, self-rated scale

Cognitive assessment

The BAC-A is based on the Brief Assessment of Cognition in Schizophrenia (BAC-S). The BAC-S has been validated both linguistically and psychometrically in a number of psychiatric populations, including patients with schizophrenia and BD (Cuesta et al., 2011; Hill et al., 2013; Kuswanto, Sum, & Sim, 2013; Salgado et al., 2007; Segarra et al., 2011). It has been shown to be as valid and sensitive as a traditional neuropsychological assessment and takes approximately 35 minutes to administer (Keefe et al., 2004; Velligan et al., 2004). Six of the 8 subtests of the BAC-A match those found in the BAC-S. These tests are the Token Motor Task, Symbol Coding, List Learning, Digit Sequencing Task, Category Instances (Animals) and

Controlled Oral Word Association Test (F and S-words), Tower of London (Keefe et al., 2004). In addition to these 6 subtests the BAC-A comprises the Emotion Inhibition Test (a modified version of the Emotional Stroop task (LaMonica, Keefe, Harvey, Gold, & Goldberg, 2010; Williams, Mathews, & MacLeod, 1996)) and the affective auditory verbal learning test (Affective interference test). The latter task is similar to the Affective Auditory Verbal Learning Test (AAVLT) (Snyder & Harrison, 1997). Assessments will be conducted prior to the treatment period, 4, and 8 weeks into the treatment. To avoid potential learning bias we will use parallel versions of the word lists for the Emotion Inhibition Test, Tower of London, and the Verbal Memory Tests to assess cognitive changes over the course of the ketamine treatment.

Study design

We will follow an AB design and clinical/cognitive assessments will be taken at baseline, week 4, week 8, and week 12. Given the preliminary nature of this treatment study this open label trial aims to generate an effect size for a subsequent RCT and/or future grant application. No *a priori* estimates of the power/effect size were therefore calculated.

Timeline	**After Each Infusion**	**Baseline**	**Week 4**	**Week 8**	**Weekly Follow-up Phone Calls**	**Week 12**
SCID-I		X				
Clinical scales (MADRS, CGI, YMRS)		X	X	X	X	X
PANAS, Q-LES-Q, self-report	X					
BAC-A		X	X	X		X
Blood tests/Sample		X	X	X		X
Urine drug test	X	X				

Study sample

We will recruit adult patients aged 18-65 years with MDD or BD, with documented TRD (according to DSM-IV TR), and who have failed (defined as patient does not reach remission within the 8 week trial of an antidepressant or combination at a therapeutic dose) of at least two trials of first line evidence-based treatments and/or ECT.

Exclusion criteria

1) Being younger than 18 of age or older than 65.
2) Diagnosed with intellectual disability, e.g. mental retardation (MR), neurodegenerative diseases, e.g. early-onset neurocognitive disturbances such as frontotemporal dementia (FTD) or behavioral disorders, e.g. adult onset Attention Deficit Hyperactivity Disorder (ADHD).
3) Diagnosed with BD-NOS or rapid cycling BD
4) Diagnosed with personality disorders (PD).
5) Previously or currently diagnosed with psychosis (schizoaffective disorder - SAD) or schizophrenia - SCZ).
6) Current major medical problems that affect brain anatomy, neurochemistry, or function, e.g., obstructive sleep apnea requiring Continuous Positive Airway Pressure (CPAP), liver insufficiency, kidney insufficiency, cardiovascular problems, systemic infections, cancer, auto-immune diseases, and any brain disorder (seizure disorder, stroke, dementia, degenerative neurologic diseases); history of any brain diseases, including seizures, stroke, meningitis, encephalitis, dementia, degenerative brain diseases, and head injury with loss of consciousness for any period of time.
7) Diagnosed specifically with a cardiovascular disorders such as Arrhythmias, Chronic Heart Failure, Myocardial Infarction (MI) or suffering from Chronic Obstructive Pulmonary Disease (COPD) or asthma. Suffering from uncontrolled hypertension or diastolic BP over 100. Cardiac clearance prior to enrolling in the study/medical records from physician will be required *per patient's PCP. (*Diastolic BP must be less than 100 Systolic BP less than 165 and greater than 85 Heart rate less than 100.)
8) Patients with thyroid condition and are not currently euthyroid or on stable treatment regimen.
9)
10) Patients with increased risk of laryngospasm, active upper respiratory infections, respiratory depression, increased intracranial pressure, hyperthyroidism, or porphyria.

11) Current substance abuse or dependence. Only patients who achieved stable, full remission for at least 6 months will be included.
12) Pregnancy or Breast feeding. All female in reproductive age will undergo pregnancy tests. Female participants will be required to provide evidence of use of contraceptives during the course of the study.
13) Unable to understand the design and requirements of the study
14) Unable to sign the informed consent for any reason
15) An assigned responsible adult has provided assent to assist in patient's study participation. The responsible adult agrees to be present at each study appointment as well as provide transportation to study appointments for the patient.

Non responders

If a patient does not respond to the study treatment by their 4th treatment they will be removed from the study due to non-response. A successful response to study treatment will be at least a 30% reduction in MADRS scores from screening until the 4th treatment. Again if a patient does not respond by the 4th treatment, they will be excluded from the study.

Unanticipated Hospitalizations

If a patient needs to be hospitalized for worsening of symptoms or for their own personal safety, they will be removed from their study participation and their study treatment will end at that time.

Feasibility

Subject recruitment: Our center has access to a large patient pool (drawing from a metropolitan area of about 5.5 million people) and well-established ability to recruit patients with mood disorders. Dr. Jair Soares is the department chair for Psychiatry and Behavioral Sciences and Director of the University of Texas, Center of Excellence on Mood Disorders. He successfully completed a large number of studies over the past 20 years with excellent recruitment of MDD and BD subjects at this site. We will also recruit participants through doctor referrals. Participants will be exclusively outpatients.

Funding of the study: given the preliminary nature of this study we plan to use departmental funding for the current study and then possibly apply for a larger grant later on once we have collected preliminary data and calculated optimal power/effect sizes for ketamine treatment in individuals with TRD.

Data analysis

Normality assumptions for continuous variables will be examined. Where appropriate, outliers will be winsorised and log, square root or reciprocal transformations applied to achieve normality if appropriate. If normality cannot not been achieved, either untransformed or dichotomized scores were used. Baseline characteristics will be compared between responders and non-responders with the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Changes between two time-points for continuous variables were tested with paired t tests, and associations between continuous variables will be quantified with the Spearman correlation coefficient. Random effects models will be performed to quantify changes in clinical score and its component items over time and to compare temporal differences between eventual responders and non-responders. Splines will be used to determine differences in the pattern of response over time among all patients and to identify the time at which there was no additional improvement in depressive symptoms. Additionally, the relationship between response status between baseline and end of study calculating sensitivity, specificity, and positive and negative predictive values will be reported. Time to relapse for patients who met response criteria at end point will be estimated with the Kaplan-Meier method. Analyses will be performed with IBM SPSS Statistics (version 19; SPSS, Chicago, Illinois) and SAS (version 9.2; SAS, Cary, North Carolina).

Study timetable

Activities	Months											
	1	2	3	4	5	6	7	8	9	10	11	12
Obtain IRB approval at UTHealth and HCPC		x	x							•		•
Set up the Ketamine Ambulatory Clinic at HCPC			x	x								
Start recruiting patients and collecting data					x	x	x	x				•
Analyses of initial dataset								x	x	x		•
Submit a poster to International meeting with final results									x	x	x	•
Submit result to high-impact peer-reviewed journals											x	x

Importance of the knowledge to be gained

Our findings will enhance our understanding of the safety, tolerability and efficacy of ketamine infusion in adults with TRD. Further it will help us understand the feasibility of this treatment in a psychiatric setting. The findings of the present study will also constitute an important foundation for future grant proposals investigating the efficacy of this intervention as a measure of suicide prevention.

Women and Minority Inclusion in Clinical Research

Inclusion of Women

The subjects will include males and females, ages 18-65 years old, from various race/ethnic backgrounds, as reflected in the local community in the greater Houston area.

Inclusion of Minorities

Our study will include minority groups in proportions that will be representative of the ethnic/racial composition of the local community in Houston, Texas. Our projected numbers for minority enrollment are detailed in the enrollment table attached.

Inclusion of Children

Children will not be included in the study. The inclusion of children at this early stage would increase substantially the number of subjects needed for the overall project. At this time, we will focus on an adult population (ages 18-65 years old), which will also allow us to limit some of the potential confounding factors to our brain imaging and neurocognitive findings. Depending on our results these investigations will be extended to children and individuals over 65 years old in future studies.

Prisoners and pregnant women

We are aware of the special protections afforded to prisoners per federal regulations. We will not actively recruit people who are incarcerated to participate in this study. We do, however, acknowledge the possibility of research participants in our target population being incarcerated during the study. If an active participant is incarcerated for an extended period of time, disenrollment from the study will be necessary. No research interaction or intervention will take place until an incarcerated participant is released from jail. Finally, neither pregnant woman nor neonates will be enrolled in this study.

Potential Risks

Loss of confidentiality is a highly unlikely but potential risk associated with this study. Some participants may find questions annoying or intrusive and neuropsychological testing might induce some fatigue and sensation of boredom. The venipuncture (insertion of small IV due to need for IV infusion of ketamine) might produce some mild pain, bruising, bleeding, infection, and in some cases even induce fainting. Side effects associated with ketamine injection are rare and, if any, of transient duration. The most commonly reported side effects during the 4-hour period after each infusion include feeling strange or unreal (58.3%), abnormal sensations

(54.2%), blurred vision (50.0%), feeling drowsy or sleepy (45.8%) (Murrough et al., 2013b) and headaches (30-40%) (aan her Rot et al., 2010). Based on previous evidence we do not expect ketamine to impair cognitive functions such as memory, attention and language (aan her Rot et al., 2010).

One third of the patients exposed to standard repeated infusions of IV ketamine reported some kind of hemodynamic change such as elevated blood pressure (BP) and/or heart rate (Murrough et al., 2013b) that usually resolves shortly after the ketamine infusion (aan het Rot et al., 2010; Murrough et al., 2013b). It has been reported that initial hypertensive episodes and transient tachycardia are predictive of hemodynamic changes with subsequent repeated ketamine infusions (aan het Rot et al., 2010). Ventricular premature contractions, hypotension, and non-significant changes in oxygen saturation have also been reported with low-dose (0.5mg/kg) ketamine infusions over 40 minutes.

Risk of other medications

If patients are currently taking certain medications on a daily basis within 24 hours prior to and / or after receiving ketamine, they will not be able to take these medication(s) while receiving a ketamine infusion without clearance or approval of the physicians involved in administering ketamine. This is due to concerns for potential increased sedation and / or trouble breathing.

Medications include:

- Sedatives (e.g., clonazepam, lorazepam, alprazolam)
- Antibiotics (e.g., azithromycin, clarithromycin)
- Antifungal agents (e.g., ketoconazole)
- Tramadol

Potential Benefits

There are direct potential benefits for the individual subject as a result of participating in the planned work. First of all, ketamine serial IV infusions will alleviate potentially disturbing, life-threating depressive symptoms such as suicidal ideation. Moreover, participants might be able not only respond but also remit from other resistant/refractory depressive symptoms that reduce their quality of life and everyday functional outcome. There are no direct benefits associated with the completion of questionnaires, simple computer tests, and routine medical diagnostic and treatment procedures. Therefore we believe the risk-benefit ratio to be favorable for every subject involved in this naturalistic study.

Potential subjects will contact the UTHealth Center of Excellence on Mood Disorders group in response to flyers, advertisements or recommendation from their attending psychiatrist treating TRD or TRBD. Potential participants will undergo a brief telephone screening. If they meet the eligibility criteria and are still interested in taking part in the study, a first appointment will be scheduled to discuss the study with the researchers. If suitable the participant will be asked to read and signs the consent document if all questions have been discussed and answered to the potential subject's satisfaction.

Data and Safety Monitoring Plan

This study will be performed in accordance as provided by law under the resolution Nº 008430 of 1993 emitted by the Ministry of Health about medical research focused on health issues. This is a low-risk project in terms of ethical concerns.

This study will acquire, use and create individually identifiable health information (known as Protected Health Information or PHI). Confidentiality will be protected at all times by having research records identified by code number only. All research information will be stored in locked files at all times. Only authorized research staff will have access to the information gathered in this study. Only subjects capable to provide consent will be included in the study.

As per the Health Insurance Portability and Accountability Act (HIPAA) all individuals who are eligible and agree to participate in this research study will be required to sign a HIPAA research authorization prior to participation. If an individual refuses to sign the HIPAA research authorization, they will not be able to participate in this study. The HIPAA form is part of the official consent form.

Data will be stored separately from participants' identifiers. Both will be stored on encrypted drives on computers in locked offices. Confidentiality will be protected by having research records identified by code number only. All research information will be stored in locked files at all times. Only authorized research staff will have access to the information gathered in this study. All paper data will be stored [redacted] in a double locked cabinet. The electronic data will be stored [redacted].

An Accounting of Disclosure (AOD) will be created and maintained for any disclosure of individually identifiable information (III) outside the UTHSC-Houston. The manual spreadsheet will include the date of the disclosure, nature or description of the III disclosed purpose of each disclosure and the name and address of person or agency to which the disclosure was made.
The study imparts only minimal risk to included subjects. Strict monitoring of hemodynamic and respiratory changes as well as psychiatric screening will be performed during each infusion of ketamine.

Reimbursement

Patients will pay for the ketamine treatment ($400 for each of the 12 injections that are part of the main treatment, $400 for each maintenance treatment) and no reimbursement will be provided for their participation in the study.

Currently costs related to this study are not likely to be covered by insurance, and a proportion of eligible candidates may not be able to participate. It is however important to highlight that determining the effectiveness of a promising treatment for a severely ill patient group such as TRD-- for whom standard treatments have failed – has significant clinical relevance and needs to be tested in a timely fashion.

References

Abdallah CG, Fasula M, Kelmendi B, Sanacora G, Ostroff R (2012) Rapid antidepressant effect of ketamine in the electroconvulsive therapy setting. J ECT 28:157–161.

aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, Mathew SJ. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010 Jan 15;67(2):139-45.

Bauer M, Ritter P, Grunze H, Pfennig A. Treatment options for acute depression in bipolar disorder. Bipolar Disord 2012; 14 (Suppl. 2): 37–50.

Beck AT, Kovacs M and Weissman A. Assessment of suicidal ideation: The Scale for Suicide Ideation. J Consult Clin Psychol 1979;47: 343–352.

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351–354.

Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000;157(12):1925-32.

Bulloch A, Williams J, Lavorato D, Patten S. Recurrence of major depressive episodes is strongly dependent on the number of previous episodes. Depress Anxiety 2014;31(1):72-6.

Calabrese JR, Huffman RF,White RL, Edwards S, Thompson TR, Ascher JA,Monaghan ET, Leadbetter RA. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo controlled clinical trials. Bipolar Disord. 2008;10(2):323-333

Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J. A randomized, double-blind, placebo controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005;162(7):1351-1360.

Carlson PJ, Diazgranados N, Nugent AC, Ibrahim L, Luckenbaugh DA, Brutsche N, et al. Neural correlates of rapid antidepressant response to ketamine in treatment-resistant unipolar

depression: a preliminary positron emission tomography study. Biol Psychiatry 2013;73(12):1213-21.

Charlson F, Siskind D, Doi SA, McCallum E, Broome A, Lie DC. ECT efficacy and treatment course: a systematic review and meta-analysis of twice vs thrice weekly schedules. J Affect Disord 2012;138(1-2):1-8.

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, Scientific Advisory B, the Executive Committee of the Grand Challenges on Global Mental H, Anderson W, Dhansay MA, Phillips A, Shurin S, Walport M, Ewart W, Savill SJ, Bordin IA, Costello EJ, Durkin M, Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K, Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo
MM, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ. Grand challenges in global mental health. Nature 2011;475:27–30.

Conrad AK, Jacoby AM, Jobes DA, et al. A psychometric investigation of the Suicide Status Form II with a psychiatric inpatient sample. Suicide Life Threat Behav 2009; 39: 307–320.

Cuesta MJ, Pino O, Guilera G, Rojo JE, Gómez-Benito J, Purdon SE, et al. Brief cognitive assessment instruments in schizophrenia and bipolar patients, and healthy control subjects: A comparison study between the Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) and the Screen for Cognitive Impairment in Psychiatry (SCIP). Schizophrenia research. 2011;130(1):137-42.

De Fruyt J, Deschepper E, Audenaert K et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacology 2012; 26: 603–617.

De Hert M, Cohen D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndetei DM, et al. Physical illness in patients with severe mental disorders II Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 2011;10(2):138-51.

Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010a; 67:793– 802.

Diazgranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010b;71:1605–1611.

Dodd S, Horgan D, Malhi GS, Berk M. To combine or not to combine? A literature review of antidepressant combination therapy. J Affect Disord 2005;89(1-3):1-11.

Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53(8):649-59.

Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 2013;10(11):e1001547.

First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID – CV). Washington, DC: American Psychiatric Press. 1996.

Fond G, Loundou A, Rabu C, Macgregor A, Lançon C, Brittner M, Micoulaud-Franchi JA, Richieri R, Courtet P, Abbar M, Roger M, Leboyer M, Boyer L. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl). 2014;231(18):3663-76

Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv 2009;60(11):1439-45.

Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomized trials. Br J Psychiatry 2009; 194: 4–9.

Guy W. ECDEU Assessment manual for psychopharmacology – revised (DHEW Publ No ADM 76–338). 1996. Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, pp. 218–222

Haile CN, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, Iqbal S, Mahoney JJ 3rd, De La Garza R 2nd, Charney DS, Newton TF, Mathew SJ. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. Int J Neuropsychopharmacol. 2014;17(2):331-6.

Hauptman JS, DeSalles AA, Espinoza R, Sedrak M, Ishida W. Potential surgical targets for deep brain stimulation in treatment-resistant depression. Neurosurg Focus 2008;25(1):E3.

Hill SK, Reilly JL, Keefe RS, Gold JM, Bishop JR, Gershon ES, et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. American Journal of Psychiatry. 2013;170(11):1275-84.

Ibrahim L, Diazgranados N, Luckenbaugh DA, Machado-Vieira R, Baumann J, Mallinger AG, et al. Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(4):1155-9.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005a;62(6):593-602.

Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, et al. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med 2005b;352(24):2515-23.

Kollmar R, Markovic K, Thurauf N, et al. Ketamine followed by memantine for the treatment of major depression. (Letter) Aus N Z J Psychiatry 2008;42: 170.

Kranaster L,Hoyer C, Janke C, Sartorius A. Preliminary evaluation of clinical outcome and safety of ketamine as an anesthetic for electroconvulsive therapy in schizophrenia.World J Biol Psychiatry 2014;15(3):242-50.

Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002;95:114–118.

Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. JAMA. 2004;292(3):338-343.

Judd LL, Akiskal HS, Schettler PJ et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003; 60: 261–269.

Judd LL, Akiskal HS, Schettler PJ et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. Arch Gen Psychiatry 2005; 62: 1322–1330.

Judd LL, Akiskal HS, Schettler PJ et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002; 59: 530–537.

Keefe R, Goldberg T, Harvey P, Gold J, Poe M, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophrenia Research. 2004;68(2–3):283-97.

Kuswanto CN, Sum MY, Sim K. Neurocognitive functioning in schizophrenia and bipolar disorder: clarifying concepts of diagnostic dichotomy vs. continuum. Frontiers in psychiatry. 2013;4(162).

LaMonica HM, Keefe RS, Harvey PD, Gold JM, Goldberg TE. Differential effects of emotional information on interference task performance across the life span. Frontiers in aging neuroscience. 2010;2(141).

Larkin GL, Beautrais AL. A preliminary naturalistic study of lowdose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol 2011; 14:1127–1131.

Leung YW, Flora DB, Gravely S, Irvine J, Carney RM, Grace SL. The impact of premorbid and postmorbid depression onset on mortality and cardiac morbidity among patients with coronary heart disease: meta-analysis. Psychosom Med 2012;74(8):786-801.

Liebrenz M, Borgeat A, Leisinger R, Stohler R. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. Swiss Med Wkly 2007;137(15-16):234-6.

Lipsman N, McIntyre RS, Giacobbe P, Torres C, Kennedy SH, Lozano AM. Neurosurgical treatment of bipolar depression: defining treatment resistance and identifying surgical targets. Bipolar Disord 2010; 12: 691–701.

Loo CK, Katalinic N, Garfield JB, Sainsbury K, Hadzi-Pavlovic D,Mac- Pherson R. Neuropsychological and mood effects of ketamine in electroconvulsive therapy: a randomised controlled trial. J Affect Disord 2012;142:233–240.

Machado-Vieira R, Salvadore G, Luckenbaugh DA, Manji HK, Zarate CA Jr. Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. J Clin Psychiatry. 2008;69(6):946-958.

Malhi GS, Bargh DM, Cashman E, Frye MA, Gitlin M. The clinical management of bipolar disorder complexity using a stratified model. Bipolar Disord 2012; 14 (Suppl.2): 66–89.

McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. J Affect Disord 2014;156:1-7.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64(5):543-552.

Messer M, Haller IV, Larson P, et al. The use of a series of ketamine infusions in two patients with treatment-resistant major depression. J Neuropsychiatry Clin Neurosci 2010;22: 442–444.

Montgomery SA and Asberg M. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134: 382–389.

Morgan CJ, Curran HV. Ketamine use: a review. Addiction 2011;107:27–38.

Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. Psychiatr Serv. 2014 Aug 1;65(8):977-87.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2197-223.

Murrough JW. Ketamine as a novel antidepressant: from synapse to behavior. Clin Pharmacol Ther 2012;91(2):303-9.

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CM, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013a;170(10):1134-42.

Murrough JW, Perez AM, Mathew SJ, et al. A case of sustained remission following an acute course of ketamine in treatment-resistant depression. (Letter) J Clin Psychiatry 2011;72: 414–415.

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry. 2013b;74(4):250-6.
Murrough JW, Wan LB, Iacoviello B, Collins KA, Solon C, Glicksberg B, Perez AM, Mathew SJ, Charney DS, Iosifescu DV, Burdick KE. Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. Psychopharmacology (Berl) 2014;231:481–488

Murrough, J. W., Burdick, K. E., Levitch, C. F., Perez, A. M., Brallier, J. W., Chang, L. C., ... & Iosifescu, D. V. (2015). Neurocognitive Effects of Ketamine and Association with Antidepressant Response in Individuals with Treatment-Resistant Depression: A Randomized Controlled Trial. Neuropsychopharmacology.

Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 2009;166(9):980-91.

Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68 Suppl 8:17-25.

Niciu MJ, Luckenbaugh DA, Ionescu DF, Guevara S, Machado-Vieira R, Richards EM, Brutsche NE, Nolan NM, Zarate CA Jr. Clinical predictors of ketamine response in treatment-resistant major depression. J Clin Psychiatry 2014;75(5):e417-23.

Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, Miyahara S, Bauer MS, Thase ME, Wisniewski SR, Sachs GS. Treatmen tresistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry. 2006;163(2):210-216.

Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: Findings from the WHO World Mental Health Surveys. PLoS Med 2009;6:e1000123.

Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. Arch Gen Psychiatry 2011;68:1058 –1064.

Nugent AC, Diazgranados N, Carlson PJ, Ibrahim L, Luckenbaugh DA, Brutsche N, et al. Neural correlates of rapid antidepressant response to ketamine in bipolar disorder. Bipolar Disord 2014;16(2):119-28.

Okamoto N, Nakai T, Sakamoto K, Nagafusa Y, Higuchi T, Nishikawa T. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: comparing ketamine and propofol anesthesia. J ECT 2010;26: 223–227.
Overall JE and Gorham DR. The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. Psychopharmacol Bull 1988;24: 97–99.

Pacchiarotti I, Mazzarini L, Colom F et al. Treatment resistant bipolar depression: towards a new definition. Acta Psychiatr Scand 2009; 120: 429–440.

Post RM, Leverich GS, Altshuler LL, Frye MA, Suppes T, Keck PE, et al. Differential clinical characteristics, medication usage, and treatment response of bipolar disorder in the US versus The Netherlands and Germany. Int Clin Psychopharmacol 2011; 26:96 –106.

Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment resistant depression. Biol Psychiatry 2009;66:522–526.

Prudic J, Haskett RF, McCall WV, Isenberg K, Cooper T, Rosenquist PB, et al. Pharmacological strategies in the prevention of relapse after electroconvulsive therapy. J ECT 2013;29(1):3-12.

Rabheru K. Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how?.J ECT 2012;28(1):39-47.

Rasmussen KG, Lineberry TW, Galardy CW, Kung S, Lapid MI, Palmer BA, Ritter MJ, Schak KM, Sola CL, Hanson AJ, Frye MA. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol. 2013 May;27(5):444-50.

Rosa AR, Magalhães PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, Gama CS, Kapczinski F. Clinical staging in bipolar disorder: focus on cognition and functioning. J Clin Psychiatry. 2014;75(5):e450-6.
Rush AJ, Thase ME, Dubé S. Research issues in the study of difficult-to-treat depression. Biol Psychiatry 2003;53(8):743-53.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H. & Keller, M. B. (2003). The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biological Psychiatry, 54, 573-583.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711-1722.

Sahakian BJ, Morris R, Evenden JX et aL A comparative study of visuospatial memory and learning in Alzheimer type dementia and Parkinson's disease. Brain 1988;111:695-718.

Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. Journal of the Royal Society of Medicine 1992;85:399-402.

Salgado JV, Carvalhaes CFR, Pires A, Neves M, Cruz BF, Cardoso CS. Sensitivity and applicability of the Brazilian version of the Brief Assessment of Cognition in Schizophrenia (BACS). Dement Neuropsychol. 2007;1(3):260-5.

Salvadore G, Cornwell BR, Sambataro F, Latov D, Colon-Rosario V, Carver F, et al. Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology 2010;35(7):1415-22.

Segarra N, Bernardo M, Gutierrez F, Justicia A, Fernadez-Egea E, Allas M, et al. Spanish validation of the Brief Assessment in Cognition in Schizophrenia (BACS) in patients with schizophrenia and healthy controls. European Psychiatry. 2011;26(2):69-73.

Shiroma, P. R., Albott, C. S., Johns, B., Thuras, P., Wels, J., & Lim, K. O. (2014). Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. International Journal of Neuropsychopharmacology, 17(11), 1805-1813.

Sienaert P, Lambrichts L, Dols A, et al. Evidence-based treatment strategies for treatment-resistant bipolar depression: a systematic review. Bipolar Disord 2013. 15: p. 61–69.

Sidor MM, MacQueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry 2011; 72: 156–167.

Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. PLoS Med 2013;10(3):e1001403.

Snyder KA, Harrison DW. The affective auditory verbal learning test. Archives of Clinical Neuropsychology. 1997;12(5):477-82.

Stefanczyk-Sapieha L, Oneschuk K and Demas M. Intravenous ketamine -burstǁ for refractory depression in a patient with advanced cancer. J Palliat Med 2008;11:1268-1271.

ten Doesschate MC, Bockting CL, Koeter MW, Schene AH; DELTA Study Group. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. J Clin Psychiatry. 2010;71(8):984-91.

Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol. 2006;26(6):600-609.

Velligan DI, DiCocco M, Bow-Thomas CC, Cadle C, Glahn DC, Miller AL, et al. A brief cognitive assessment for use with schizophrenia patients in community clinics. Schizophrenia research. 2004;71(2):273-83.

Zarate, C. A., Brutsche, N. E., Ibrahim, L., Franco-Chaves, J., Diazgranados, N., Cravchik, A., ... & Luckenbaugh, D. A. (2012). Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biological psychiatry, 71(11), 939-946.

Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep 2007;9(6):449-59.

Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, Suppes T. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 doubleblind, randomized, placebo-controlled studies. J Clin Psychiatry. 2008;69(5): 769-782.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013;382(9904):1575-86.

Williams JMG, Mathews A, MacLeod C. The emotional Stroop task and psychopathology. Psychological bulletin. 1996;120(1):3-24.

Yatham LN, Calabrese JR, Kusumakar V. Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. Bipolar Disord 2003; 5: 85–97.

Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: Reliability, validity, and sensitivity. Br J Psychiatry 1978;133: 429–435.

Zanicotti CG, Perez D and Glue P. Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. J Palliat Med 2012;15: 400–403.

Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, Luckenbaugh DA. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012; 71(11):939-46.

Zarate CA Jr., Duman RS, Liu G, Sartori S, Quiroz J, Murck H. New paradigms for treatment-resistant depression. Ann N Y Acad Sci 2013b;1292:21-31.

Zarate Jr. CA, Mathews DC, and Furey ML. Human Biomarkers of Rapid Antidepressant Effects. Biol Psychiatry 2013a;73:1142–1155