A Randomized, Double-Blind, Placebo-Controlled Trial of the Rapid Antisuicidal Effects of Intranasal Ketamine in Comorbid Depression and Alcohol Abuse

NCT03539887

Version Date: 10/09/2019

IRB NUMBER: HSC-MS-17-0903
IRB APPROVAL DATE: 10/09/2019

A Randomized, Double-Blind, Placebo-Controlled Trial of the Rapid Antisuicidal Effects of Intranasal Ketamine in Comorbid Depression and Alcohol Abuse

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General Information

Clinicians have a limited ability to predict imminent suicidal behavior and efficacious treatments are not available to treat suicidal patients. Thus, Rapid-acting treatments for suicidal individuals are truly needed. This project aims to evaluate the potential rapid and sustained antisuicidal and antidepressant effects of a single intranasal dose of ketamine in inpatients during a mood episode (in Major Depressive Disorder, MDD or Bipolar Disorder, BD) with or without comorbid recent abuse of alcohol. These results will elucidate the antisuicidal effects of ketamine using the intranasal route along with the identification of associated mediators or moderators; this approach has the potential for enormous public health impact.

Background

Suicide: A Major Public Health Problem

Suicide occurs across demographics and psychiatric disorders, killing at least one million individuals worldwide each year. In contrast to other injury-related death such as homicide or motor vehicle accidents, suicide rates have increased, particularly among middle-aged adults. In the US, each year, hundreds of thousands of Americans seek emergency treatment for suicidal thoughts or behaviors. Unfortunately, even when these individuals are hospitalized on inpatient units or connected with longterm psychiatric resources, they remain at acute risk for suicidal behavior. Over 40,000 Americans killed themselves in 2013 and over 380,000 presented to emergency services for suicidal thoughts and behaviors. In contrast, other forms of preventable death, such as motor vehicle accidents, have declined making suicide the leading cause of injury-related death in the U.S, and arguably, the leading cause of psychiatry-related mortality (Rockett et al 2009).

Multiple studies have identified inpatient psychiatric hospitalization as a critical time period for increased suicidal ideation and behaviors. Times of highest suicide risk are also associated with transitions in care, most typically the transfer of a patient from emergency services to the psychiatric inpatient unit or the first week after inpatient discharge. Also, the period between antidepressant initiation and antidepressant effectiveness has been shown to be a particularly high-risk period for psychiatric patients at risk for suicide (Pompili et al 2010). There is some evidence that reductions in prescriptions due to these warnings have resulted in increased suicide attempts among adolescents and young adults (Lu et al 2014). There is no approved pharmacotherapy specific for suicidality in patients with mood disorders.

Lack of Effectiveness of Current Treatments for Suicidality

When treating acutely suicidal patients, clinicians have somewhat few resources at their disposal. The only FDA approved medication for suicide risk is clozapine, which is limited to individuals with

schizophrenia diagnoses. Psychotherapeutic approaches have been shown to reduce suicide re-attempt rates, but usually require months to take effect.

There are few, if any, well-researched interventions for suicidal individuals, meaning that hundreds of thousands of mental health professionals in this country see suicidal clients with little to no effective treatments at their disposal. While lithium treatment of BD has shown long-term effectiveness in suicide prevention, its short-term effectiveness may be limited by a slow time course of change in suicidal thoughts (Lewitzka et al 2015).

Advances in the treatment of the suicidal patients have been also hampered by an incomplete understanding of the neurobiological underpinnings of the suicidal crisis, as suicidal thoughts and behaviors have not been clearly linked with specific neural circuits.

Thus, there remains a critical need to identify interventions associated with a rapid reduction in acute suicide risk, especially right after admission. In the absence of such knowledge, the most vulnerable patients may remain undertreated before they can be connected with short-term effective agents and access to long-term resources.

Suicide and Psychiatric disorders: Shared Clinical and Biological Basis between Mood Disorders and Alcoholism

-Clinical and Biological Basis between Mood Disorders and Alcoholism: The Glutamate System:

Almost 90% of suicide cases are associated with some form of psychiatric illness (Soleimani et al 2015). Mood disorders (MDD and BD) and alcohol dependence are both within the ten disorders for highest worldwide disease burden as identified by the World Health Organization (WHO). In addition, the National Comorbidity Study found that men with alcohol dependence had rates of depression three times higher than the general population; alcohol dependent women had four times the rates of depression (Kessler 1995). Studies of clinical populations also show high rates of these combined disorders (Daley et al 2000). It is observed that mood disorders, mainly major depressive disorder (MDD) and bipolar disorder (BD), are associated with about 60% of all suicides. High levels of alcohol use and alcohol-related problems are also associated with suicide and suicidal behaviors (Cherpitel et al 2004). The data gathered during recent years suggests that abnormalities within glutamatergic transmission, especially NMDA (N-methyl-D-aspartate) receptor dysfunction, are associated with more generalized mechanisms of brain dysfunctions underlying various psychiatric disorders. Glutamatergic dysfunction has been involved in the pathophysiology of both BD and MDD (Phelps et al 2012). Similarly, previous studies have demonstrated that glutamatergic system alterations may also be involved in the pathophysiology of alcohol dependence (Hermann et al 2012, Krystal et al 2003). Further supporting the association between NMDA and alcoholism, Schumann and colleagues (Schumann et al 2008) observed that ten genes involved in glutamatergic pathways showed a significant association between risky drinking behavior, which encoded for the *NR2A* subunit of the NMDA receptor. The authors suggested that a genetic variation in the *NR2A* gene that expresses the NMDA receptor could be involved in susceptibility to alcohol dependence.

Glutamate dysfunction has also underlain the dual diagnosis of mood disorders and alcoholism (Nery et al 2010, Krystal et al 2003). One magnetic resonance spectroscopy (MRS) study found that BD patients in long-term remission from alcoholism showed reduced dorsolateral prefrontal cortex glutamate levels, as well as glutamate plus glutamine levels, compared to BD adults who never developed alcoholism (Nery et al 2010). These studies support the glutamate system as an underlying biological substrate interconnecting the pathophysiology of both disorders.

-*The Potential role of Ketamine:* This convergent biology may be also impacting therapeutics. A recent study showed that a positive family history of alcohol dependence was associated with better

antidepressant response with the NMDA antagonist ketamine in both MDD and bipolar depression (Luckenbaugh et al 2012). Individuals with treatment-resistant depression and positive family history for alcohol (FHA) showed significantly greater and more durable improvements in depressive symptoms in response to a single intravenous infusion of ketamine than those with negative FHA. Lower dissociation was also observed with ketamine in those with FHA, as indicated by lower scores on the CADSS scale (which measures dissociation) (Luckenbaugh et al 2014).

It is known that chronic alcohol use upregulates NMDA receptor function and that ketamine administration in recovering alcoholism reverses NMDA receptor overactivation, and was associated with reduced psychotomimetic symptoms in this group of patients (Krystal et al 2003). It was also suggested that these results were consistent with a defect in the glutamatergic system that might function as a risk factor for the development of alcoholism in individuals with BD (Krystal et al 2003). Thus, changes in NMDA receptors in subjects with a genetic heritability to alcoholism could be a distinct neurobiological subtype that leads to a differential (improved) response to ketamine, and potentially other NMDA antagonists studied in mood disorders. In depression, a systematic review on the benefits of IV ketamine in patients with treatment-resistant depression showed that success rates following intravenous doses of ketamine range from 25% to 85% at 24 hours post-administration and from 14% to 70% at 72 hours post administration (Fond et al 2014).

-*Ketamine and Suicidality:* Regarding the antisuicidal effects of ketamine, there are only few studies evaluating the antisuicidal effects of ketamine. All of them used IV route and with exception of one double-blind placebo controlled study (Murrough et al 2015), all others all open-label trials and information was obtained from suicide items from depression rating scales (Wilkinson and Sanacora 2016). In the randomized controlled trial using IV route, there was no dropout and IV ketamine was superior to active placebo (midazolam) as antisuicidal agent at 48hs post-infusion (Murrough et al 2015). Furthermore, our prior research has shown that intravenous (IV) ketamine improves outcomes by reducing suicidal ideation and significantly improving depressive symptoms within 24 hours of administration (with effects lasting up to ten days) (DiazGranados et al 2010).

Interestingly, evidence suggests that ketamine exerted an independent effect on SI as opposed to this effect being mediated solely by an overall reduction in depressive or anxiety symptoms. Recent analysis suggests that ketamine's effects on SI may in fact be independent of its effects on other depression or anxiety symptoms (Wilkinson and Sanacora 2016). The recent reviews on the antisuicidal effects of ketamine (Reinstatler and Youssef 2015, Wilkinson and Sanacora 2016) concluded that further studies are needed to better identify the best delivery method of ketamine and assess SI as the primary, not secondary, outcome as well as patients at imminent risk of suicide with significant suicidal ideation scores at baseline.

-*CNS Studies with Intranasal Ketamine:* Intranasal ketamine seems a reasonable choice for further studies in the field. Intranasal ketamine has been successfully used in the treatment of headache and pain in ambulatory patients (Kaube et al 2000, Huge et al 2010, Carr et al 2004). In one study, 50 mg of ketamine administered intranasal was well tolerated and led to symptomatic improvement in chronic pain (Carr et al 2004). In psychiatry, Lapidus et al investigated the potential rapid antidepressant effects of intranasal ketamine (50mg) in subjects with MDD. Patients showed significant improvement in depressive symptoms at 24 hours after ketamine compared to placebo. Response criteria were met by 8 of 18 patients (44%) 24 hours after ketamine administration compared with 1 of 18 (6%) after placebo. Intranasal ketamine was well tolerated with minimal psychotomimetic or dissociative effects and was not associated with clinically significant changes in hemodynamic parameters (Lapidus et al 2014).

Scientific Impact: The opportunity to intervene quickly and decisively to prevent suicidal ideation may improve clinical practice and outcomes for subjects at high risk for suicide. A rapid-acting suicide intervention strategy to prevent suicidal ideation and behavior using a feasible and safe route such as the intranasal for ketamine studies, nested with a comprehensive intervention that addresses underlying suicide risk and protective factors, has the potential for enormous public health impact. There is no study evaluating the rapid antisuicidal effects of intranasal ketamine in patients with suicidal ideation. Also, no study has evaluated the role of alcohol abuse as a moderator of clinical response in depression and suicidality.

Since there is no available studies in this field using the intranasal route and considering that the highest risk times for suicidal behavior are the week after admission to an inpatient psychiatric unit and the week after discharge (Qin & Nordentoft 2005), we aim to investigate the rapid antisuicidal effects of intranasal ketamine in patients with suicidal ideation during depressive episodes with or without recent use of alcohol. We hypothesize that a single dose of intranasal ketamine will induce a rapid, robust and sustained decrease in suicidal ideation in subjects with a comorbid major depressive episode and alcohol dependence relative to only depression and placebo as defined by changes in suicidal ideation scales after 24hrs.

Objectives

Primary objective: To evaluate the rapid antisuicidal effects on a single dose of intranasal ketamine (50mg) in a sample of depression comorbid or not with alcohol abuse compared to placebo.

Secondary objectives:

-To identify clinical variables and dimensions associated with the potential antisuicidal efficacy of intranasal ketamine.

-To identify post-treatment biomarkers associated with the antisuicidal response to ketamine.

-To evaluate the role of recent alcohol abuse in the antisuicidal and antidepressant effects of ketamine

-To identify clinical and biological predictors of response to ketamine

-To evaluate safety and tolerability of intranasal ketamine

Hypothesis:

-Primary: A single dose of ketamine will induce a rapid, robust and sustained decrease in suicidal ideation in subjects with a comorbid major depressive episode and alcohol dependence relative to placebo as defined by change in SSI scale after 24hrs.

-Secondary:

-The antisuicidal efficacy of intranasal ketamine will be independent from its rapid antidepressant efficacy.

-Intranasal ketamine will present superior antisuicidal efficacy in the group with comorbid depression and alcohol compared to depression only.

- Antisuicidal response to ketamine will be correlated with changes in neurotrophic factors and inflammatory markers at one day after ketamine infusion. -Intranasal ketamine (50mg) will be safe and well-tolerated.

-Alcohol use and/or family history of alcohol abuse will be associated with better antisuicidal and antidepressants response to ketamine.

Description of Study Populations: A total of 60 individuals (males and females) between the ages of 2160 will be enrolled in the study. Two participant populations will be recruited into this protocol. Participant populations are individuals with the following conditions: 1.) current suicidal ideation and past suicide attempt under intranasal ketamine (Group 1, n= 30) and current suicidal ideation and past/recent suicide attempt under placebo (Group 2, n= 15). Group 1 will include two subgroups, with (n=15) or without (n=15) recent abuse of alcohol plus positive personal/family history for alcoholism. The study will take place at a Research Unit at the Harris County Psychiatric Center, UT Houston. Participants at acute risk will be admitted to the HCPC 2D Unit, a secure, but voluntary psychiatric unit, in which there will be nursing staff and physicians available at all hours to respond to any crisis as needed. Subjects will complete an informed consent process and will be systematically screened for inclusion and exclusion criteria. Only participants with a lifetime history of suicide attempt will be enrolled.

Design

This study will be a double-blind, randomized, placebo controlled trial, evaluating drug-free inpatients (at least 24hs period pre-admission) with depressive episode associated with past suicidal attempt and current active suicidal ideation. Patients will be randomly assigned to intranasal ketamine hydrochloride (50 mg) or saline solution (1 to 1 in both groups, suicide or suicide plus alcohol, with a total of 4 groups). After the single intranasal administration, assessments will occur at +40 min, +240 min, +24 h (phase 1), and +48 h (phase 2). For phase 2, patient may receive their regularly scheduled daily medications if improvement less than 50%. Pts will be subsequently followed up on the suicidal ideation scores until discharge once a day with treatment as usual. This study is expected to take one year to be concluded. Medication should be applied in the first 24hs after admission. There is no approved treatment for suicidal ideation and just a few trials used ketamine for suicidal ideation, none of them evaluating the intranasal route. Thus, a placebo-controlled study is warranted to prevent potential methodological issues. The use of ketamine plus standard care would bias the evaluation of the specific antisuicidal efficacy of intranasal ketamine since standard treatments in some cases may also target suicidality and mood in the short-term.

Assessment of antisuicidal efficacy will be obtained using the Columbia-Suicide Severity Rating Scale (CSSRS) as a screening tool for inclusion (based on “yes” or “no” questions) at HCPC. MADRS item 10 score of 5 or 6 suggests active suicidal risk and will be also used as the threshold for patient inclusion in the ketamine intervention. For those enrolled, the primary efficacy outcome measure will be changes in suicide severity at 24hr post-treatment based on the Scale for Suicide Ideation (SSI) scores, which assesses presence of suicidal ideation and history of suicidal behavior. Secondary outcomes to be administered at each visit include the Montgomery-Åsberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Clinician-Administered Dissociative States Scale (CADSS), SnaithHamilton Pleasure Scale (SHAPS) Alcohol Urge Questionnaire (AUQ) and the Clinician-Administered National Institutes of Health-Brief Fatigue Inventory (NIH-BFI). Inter-rater reliability will be assessed for all ratings, with accepted kappa over 0.8.

Potential psychotomimetic, dissociative, hemodynamic, and general adverse effects associated with ketamine will be also measured. Safety and tolerability will be specifically assessed the ClinicianAdministered Dissociative States Scale (CADSS) and the mood item of the Young Mania Rating

Scale (YMRS). Clinically significant changes will be characterized as systolic or diastolic blood pressure (BP) >180/100 mmHg or heart rate >110 beats/minute.

Clinician Administered Measures

1) The *Scale for Suicide Ideation* (SSI) is a 21-item clinician-administered scale designed to quantify the intensity of current conscious suicidal ideation in various dimensions of self-destructive thoughts or wishes: the extent of the wish to die, the desire to make an actual suicide attempt, and details of any plans; also, internal deterrents to an active attempt, and subjective feelings of control and/or courage regarding a proposed attempt. Individuals are asked to report their current and worst-point suicidal thoughts (Beck et al 1979).
2) The *Columbia Suicide Severity Rating Scale* (C-SSRS) is a widely used measure of suicidal ideation and behavior. The "Screening/Baseline" version of the measure evaluates suicidal ideation and behavior both lifetime and in the last six months. The "Since Last Visit" version assesses suicidal thoughts and behavior since the last assessment. The C-SSRS takes 15 minutes to administer (Posner et al 2011).
3) Montgomery-Asberg Depression Rating Scale (MADRS) is a widely-used ten item instrument evaluating depressive symptoms in adults. The estimated time to completion is 20 minutes. Interrater reliability is high and scores correlate significantly with those of other validated depression measure, e.g. HDRS. Each of the ten items is rated on a scale of 0-to-6, with differing anchors describing escalating psychiatric severity (Montgomery et al 1979).
4) *Young Mania Rating Scale (YMRS*) consists of 11 items used to assess hypomanic/manic symptoms. The time for administration is 15-30 minutes (Young et al 1978).
5) *Clinician-Administered Dissociative States Scale* (CADSS) is a clinician-administered measure of perceptual, behavioral and attentional changes occurring during dissociative experiences that has been tested in healthy subjects and post-traumatic stress disorder (PTSD). This scale involves 19 self-reported questions and eight observer ratings scored from 0 (not at all) to 4 (extremely). To characterize dissociative responses to ketamine, the CADSS will be sorted into five subscores with apparent face validity based on published scales that also assess dissociative states: body perception, environmental perception, feelings of unreality, memory impairment and time perception (Bremner et al 1998).
6) The *Snaith-Hamilton Pleasure Scale (SHAPS)* is an assessment of anhedonia, which has been extensively used by our group. The 14-item measure takes 5 minutes to complete (Snaith et al 1995).
7) The *Clinician-Administered National Institutes of Health-Brief Fatigue Inventory (NIH-BFI*) is an assessment of fatigue in the context of depression (Saligan et al 2015).
8) *Self-Report: Alcohol Urge Questionnaire* (AUQ) is a multi-item measure of self- reported urges to drink alcohol, predictor of drinking abuse and relapse (Bohn MJ, Krahn DD, Staehler BA 1995) and AUDIT/CIWA.

Although the primary aim of this study to investigate the efficacy of ketamine as a treatment for suicidal thoughts, this investigation is also designed to provide initial data for potential biomarkers of antisuicidal response and the neurobiology of the response process. Sixty six percent of all patients will

receive intranasal ketamine, while only 33.3% will be receiving placebo. We decided not to use active placebo (midazolam) due to the risk of increasing craving for alcohol. After the end of the trial (48hs), all patients will receive treatment as usual as well as lithium, which is a medication that has shown significant antisuicidal properties (Lewitzka et al 2015). All patients will be discharge when presenting no acute suicidal ideation based on *C-SSRS* and SSI.

Study Population

All study investigators and raters will be blind to assignment. Subjects will complete an informed consent process and will be systematically screened for inclusion and exclusion criteria, as follows:

Inclusion Criteria:

1. Male or female between the age of 21 and 60 years old, voluntary admission.
2. Able to provide written informed consent
3. Current suicidal ideation and depressive symptoms and DSM-IV-TR depressive episode (also MADRS score ¬>12).
4. DSM-IV-TR criteria for current alcohol abuse (but not intoxicated/withdrawal, abstinent from drinking for > 5 days prior to admission).
5. Lifetime history of suicide attempt (patient)
6. Not taking any medication in the last 24hs.
7. SSI score over 4 (first five items) and Columbia scale score 4 or 5

Exclusion Criteria:

- Unstable medical condition or medical problem with known CNS effects, e.g. uncontrolled hypertension (SBP≥170 and/or DBP≥100) or recent history (6 months) of alcohol-withdrawal seizures or significant abnormal laboratory tests (LFT 3 times higher than normal).
- Currently having a manic episode.
- Prior diagnosis of a DSM-IV-TR psychotic spectrum disorder a personality disorder or current psychotic symptoms.
- Currently under the acute effects of an illicit substance.
- Pregnant or nursing women.

As the only public-academic teaching psychiatric hospital in Houston, Texas, the University of Texas Harris County Psychiatric Center serves a large and diverse patient population. Last year, HCPC served 2443 adult psychiatric patients who had a primary diagnosis of BD (35.2% of patients served) and a similar number with MDD. More than half (52.2%) of the patients admitted to HCPC were on suicide precautions, and the mean patient length of stay was 8.8 days. We estimate being able to assess approximately 1200 patients per year (n = 3600) for study eligibility and recruitment.

Regarding the recruitment strategy, we will only recruit participants who seek care for suicidal thoughts or behaviors at the HCPC. Recruitment strategies will not include local advertising in any type of media. Potential participant will be seen by a treating clinician who will complete routine assessment according to standards of care for their facility. Study staff will speak with clinician in person on site in the

emergency department or at the research unit. Study staff will review the Inclusion/Exclusion Checklist and Study Summary. If potential participant appears eligible for study, study staff will speak with potential participant in person. Study staff will again re-review Inclusion/Exclusion Checklist with the potential participant to assess eligibility and interest in the study.

On the inpatient unit (Experimental Therapeutics and Molecular Pathophysiology Program), participant will sign informed consent for the protocol. In case a participant is brought onto the unit and are determined to be ineligible for study participation or cannot provide informed consent due to any reason, this participant will be provided appropriate standard clinical care. There is no washout period after admission to HCPC for this study. Since there is no specific treatment for suicidal ideation (that is a key justification for this study), standard of care after the trial will be based on the specific pharmacological approaches for the different ICD-10 diagnoses that any patient may present during hospitalization. A level of understanding sufficient to agree to all required tests and examinations, sign an informed consent document and verify understanding. Only patients admitted to the HCPC as voluntary will be enrolled in the study.

The standard non-medical care includes possible psychotherapy, daily group therapy, recreation, and other therapeutic daily activities. Thus patients will be provided a supportive care during the 48hrs of treatment duration, even those in the placebo group.

Human Subjects Protection

Inclusion of Women

The subjects will include males and females, ages 21-60 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 21-60 years old), which will also allow us to limit some of the potential confounding factors related to administration of ketamine to minors. .

Cognitively Impaired Persons

We are excluding cognitively impaired persons as we feel preliminary safety and efficacy data should be obtained in non-impaired adults before proceeding to vulnerable populations. We also want to ensure that all participants understand the consenting process as well as the study tests and measures.

Women Who are Pregnant, Plan to Become Pregnant, or are Breast-feeding

Ketamine is generally considered unsafe for use during pregnancy and breast-feeding, and so we will exclude this population

Potential Benefits

There are potential direct potential benefits for the individual subject as a result of participating in the planned work. First of all, intranasal ketamine is expected to alleviate potentially suicidal ideation and other clinical dimensions such as anhedonia and depression. There are no direct benefits associated with the rating scales or blood withdrawal. Overall we believe the risk-benefit ratio to be favorable for every subject involved in this study due to the inpatient setting and offer of treatment as usual following the short duration of this trial. Note that all suicidal patients at the hospital will be on active suicidal watch and precautions, researches will not change that aspect of treatment and the follow up treatment will be per clinical recommendations, with other medications allowed the 2-day period post-ketamine.

Qualifications of Investigators

The Investigators have a strong track record in recruiting, studying and publishing novel research findings and mentoring junior colleagues in this area of expertise. This study will be sponsored by the Department of Psychiatry, UT Health and HCPC; Dr. Machado-Vieira has led and participated in previous studies with ketamine for Mood Disorders (e.g. Machado-Vieira et al 2009 b, c).

Study Procedures

Intranasal ketamine will be prepared as 100mg/ml ketamine in 0.9% saline or saline alone. An LMA MADgic mucosal atomization device will be used to provide 5 intranasal applications of solution (volume 100 µl), separated by 3 minutes. Each of five ketamine applications will provide 10 mg of study drug. Ketamine administrations will be provided over 15 min by the principal investigator or attending psychiatrist in a psychiatric unit. Patients will be monitored for at least 4 hours in the psychiatric unit (observation room at 2D unit) after ketamine/placebo administration, including continuous monitoring of vital signs (i.e., heart rate, blood pressure, respiration, and pulse oximetry). The proposed dose does not induce sedation/anesthesia (the required dose for sedation would be 6-9mg/Kg) and here the dose to be used in 6 to 18 times lower than the sedation dose (between 0.5-1mg/Kg). Besides, the investigator has extensive experience using the proposed dose, with no reports of any serious adverse effect in a sample of over 100 patients.

Ratings of suicidal thoughts, depression, anxiety, anhedonia, fatigue, dissociation and other clinical symptoms will be collected during this trial, at the following time points: baseline (pre-ketamine), then 40 and 240minutes, 1 day and day 2 (+48h) post-ketamine. Blood will be collected at the same timepoints, except for 40 minutes and 48 hours post-ketamine.

In order to ensure pregnant women are excluded from the study, a urine pregnancy test will be performed on female patients that meet all other inclusion criteria. We will also collect blood for the purpose of transcriptional profiling, metabolomics, proteomics, and the measurements of inflammatory measures including cytokines and kynurenine pathway metabolites. We will also evaluate Brain-derived

neurotrophic factor (BDNF) as well other neurotrophic factors and cytokines in plasma and mRNA expression. Our recent studies support the role of these markers in depression (Zarate and MachadoVieira 2017) and the present investigation will address the effects in suicidal ideation. Samples will be collected via antecubital intravenous line. Samples will be collected via venipuncture. If sample collection is difficult via venipuncture a PIV catheter may be used for no more than 24hrs in order to decrease discomfort.

The patient will be withdrawn from the study if the clinical condition gets significantly worse according to the clinicians' judgment or if patients withdraw their consent. The date and the reason for discontinuation will be noted. All patients prematurely discontinuing the trial must be seen for a final evaluation.

We have a team of individuals, including a full-time social worker, who is involved in ensuring that the participant has access to appropriate mental health and medical providers. We will also provide a clinical summary of the participant's stay at the Harris County Psychiatric Center (HCPC) in order to facilitate the transition from one provider to another. Once the participant is discharged from the unit, clinical care will transition to the participant's outside providers. If a participant is determined to be at imminent suicide risk and wants to leave the inpatient unit, the patient will be excluded from the study and involuntary commitment procedures may take place.

Research data will be stored in a locked filing cabinet in the investigator's dedicated locked offices to protect subject anonymity. Data will be de-identified and stored using codes assigned by the investigators.

The key to the code will be kept in a separate, secure area. Biological samples will be centrifuged and stored in secured freezers without patient identifiers at the Harris County Psychiatric Center (HCPC). The samples will be kept in laboratory 3D-05. This lab requires a unique key that is only given to researchers that need to utilize the facility. The sample(s) and date(s) will be stored using assigned code(s) and kept in locked storage. The samples will then be transferred to the Laboratory of the Center of Excellence in Mood Disorders at Behavioral and Biomedical Sciences Building (BBSB) for analysis. They will not be discarded until fully utilized. Biomarkers related to glutamate function, plasticity and immune function in blood samples (plasma, platelets and lymphocytes) will be evaluated. Each patient will receive the total amount of $250, based on the application of rating scales ($100) and three blood draws ($150) throughout the study.

Data and Safety Monitoring

The Principal Investigator will be responsible for knowing the policies of the local IRB (the UT – Houston Committee for the Protection of Human Subjects, CPHS). The PI will adhere to CPHS policies and maintain accurate documentation of CPHS correspondence and reports (e.g., annual report). The Principal Investigator (PI) is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations Relatedness to the research of all serious adverse events will be determined by the PI. Dissociation with ketamine does not last more than 40 minutes after ketamine use in Depression and its presence has been associated with a better rapid antidepressant response (Luckenbaugh et al 2014). We expect that dissociation does

not affect the anti-suicide efficacy, being mild and transitory (if present) using the safer intranasal route. In addition, all patients will be strictly monitored at the hospital for at least 48hs after ketamine use, which provides safety for all patient, either responders or not.
There are minimal risks to subjects involved in this study related to the participation in this study. The proposed dose (50 mg) has been safely given to human subjects in previous clinical trials. Ketamine was well tolerated at low doses, with the most common side effects being transient and limited. Based on a similar study evaluating the same dose of intranasal ketamine for depression (Lapidus et al 2014), ketamine was well tolerated with showed minimal psychotomimetic or dissociative effects as well as was not associated with any clinically significant change in hemodynamic parameters. The same findings were observed in additional studies using intranasal ketamine in chronic pain (previously described). 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). Thus, we considered that intranasal ketamine in the proposed dose will be safe and well-tolerated. Besides, the PI has extensive experience with ketamine in terms of safety and efficacy from the trials he has done at the National Institutes of Health. Patients will follow all routines at the unit after the initial 4hs of initial observation (groups, etc).
Adequate monitoring and management of suicidal thoughts and behaviors will be critical to the safe conduct of this study. For this reason, we propose a comprehensive and multi-disciplinary approach to assess, and if necessary, treat, study participants. Monitoring for suicide risk over the course of the study will be assessed frequently through: the SSI, C-SSRS, MADRS item #10. In addition, research staff will conduct a clinical evaluation on a daily basis. During the first 4hs after the intranasal spray, inpatient research assistant-to-patient staffing ratio will be 1:1 in the first hour after treatment and in the next 3hrs a team member (PI, or MD trainee) will be with the patient and also supported by the research staff, both continuously monitoring vitals and be doing the ratings. Additionally, nursing staff and physicians are available at all hours to respond to any crisis if needed.

The following conditions would increase concern for suicidal behavior:

- SSI score of 6 or above
- C-SSRS endorsement of items #4 or #5
- MADRS item #10 score ≥ 4
- Clinical assessment of suicidal thoughts/behavior

Procedure in case of adverse events:
In addition to the nursing staff and physicians in the unit, a medical monitor will provide independent oversight of data related to subject safety. Dr. Sudhakar Selvaraj, Assistant Professor at the Department of Psychiatry and Behavioral Sciences, will be the independent medical monitor of the study. He will be blind to study medication, unless he believes that termination of the trial is warranted.
As a medical monitor, Dr. Selvaraj will meet twice per year with the PI, Dr. Machado, and the study team. In each meeting, the following items will be discussed:

- List and summary of adverse events.
- Whether adverse event rates are consistent with pre-study assumptions.
- Summary of recruitment and retention and reason for dropouts.
- Whether the study is on track to be completed and accomplish the stated aims.

An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these. An adverse event can be an expected side effect that is of a serious nature, or an unexpected side effect/event regardless of severity. All adverse events will be graded as to their attribution (related or unrelated) and their severity.

A Serious Adverse Event (SAE) is any adverse event that meets one of these criteria:

- The event results in death
- The event is life-threatening
- The event results in an inpatient hospitalization or prolongation of existing hospitalization
- The event results in permanent or severe disability or permanent damage
- A pregnancy results in a congenital anomaly or birth defect
- Based on appropriate medical judgment, the event may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above

Adverse event documentation

1. Every event that is reported to the principal investigator or research staff by the subject or medical staff caring for the subject which meets the criteria for adverse event will be documented in the Case Report Form (CRF). Additionally, the event will be documented in the **adverse events log** located on the study folder within an encrypted drive.
2. Adverse event documentation will include description of the event, when and how it was reported, as well as any official chart records or documentation to corroborate the event; determination of attribution)
3. Adverse events will be reported to the CPHS as per CPHS policy.

Stopping Rules

In case a patient enrolled in the study presents an emergency condition, the following steps are to be followed in addition to regular clinical procedure:

1. The Principal Investigator will be contacted in order to report the serious incident. His office number and cellphone are located on a binder in unit 2D.
2. Dr. Machado will then determine whether the incident is related to the Ketamine/Placebo administration and give further instruction.
    a. Should staff be instructed to break the blind, they can look up a specific patient in the **2D ketamine trial enrollment list**. This list is the first page of the binder located in unit 2D. The binder also contains possible side effects and the contact information of the PI, the medical monitor and the study team.
    b. In the Nurse Supervisor's Office there is an Orange container. The staff will ask the nurse supervisor to break the seal on the container and locate the list on the bottom slot. (This is only to be used for emergencies with Dr. Machado's approval.) After locating the file, staff will match the patient's medication number to determine the medication given.
3. The medical monitor will be informed of the event within 48 hours.

Safety Review Plan and Monitoring

Oversight of participant safety includes review of adverse events as well as study progress, data integrity and study outcomes.

1. The principal investigator will review all adverse events immediately if he is at the facility. If the event occurs while the PI is not at the facility, the staff will contact the PI via cellphone. In turn, the PI will make determinations on whether the adverse event is serious, related and or expected.
2. All serious adverse events such as changes in systolic or diastolic blood pressure (BP) >180/100 mmHg or heart rate >110 beats/minute, will be reported to the independent medical monitor within 48 hours.
3. The Principal Investigator is responsible for reviewing study progress (e.g., recruitment, retention, protocol adherence) on a quarterly basis.
4. The Principal Investigator will submit an annual report to the independent medical monitor including a summary of the items covered in the biannual meetings-- List and summary of adverse events, whether adverse event rates are consistent with pre-study assumptions, summary of recruitment and retention and reason for dropouts and whether the study is on track to be completed and accomplish the stated aims.
5. The annual report will be reviewed and signed by the medical monitor and submitted annually to CPHS.

Alternative therapies for depression: Currently available antidepressants, i.e. tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants (bupropion, mirtazapine, vilazodone, etc.), and neuromodulatory therapies, i.e. electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS), are effective treatments for Depression. Several psychotherapeutic modalities, i.e. cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT), are also effective and are frequently used in combination with medications. While individuals with depression often report suicidal thoughts, none of these treatments have a demonstrated rapid effect of suicidal ideation.

Participants will be informed and/or reminded that these alternative treatments for suicide or depression are available to them in the community before enrollment into this protocol. They will be informed that standard of care on psychiatric inpatient units may include pharmacologic and psychotherapeutic approaches which will be started right away. They will also be reminded that they can be transferred to a different psychiatric facility for follow-up care. This approach will ensure that patients are clearly informed of the standard of care that is available to them before being exposed to experimental risks.

Early holding rule includes an overall improvement lower than 20% (based on SSI scores) in first 15 patients randomized and the present of any serious and unexpected adverse effect.

Data handling and record keeping

As is standard of care on our unit, we will require participant authorization to release any medical information. Hard copy research data/records will be de-identified (so no individual will be identified by name) and stored double-locked (in locked cabinets in a room that is locked when unoccupied). Electronic data with identifiers (including biomarkers) will be saved on password-protected computers on secured servers (encrypted drives). Biomarkers data will be maintained on a secure internet-based

server. Only study investigators will have access to the data. De-identified results from clinical trials will be posted on ClinicalTrials.gov.

For Stored Samples: Biological samples will be kept in dedicated freezers without patient identifiers. Results will be published as group data without the use of specific identify identifiers. Sample(s) and date(s) will be stored using assigned code(s) and kept in locked storage. Electronic health information and research data will be kept on password-protected computers with encrypted drives. Only study investigators will have access to the stored samples.

Special Precautions: Samples and data will be stored using codes that we assign. Data will be kept in password-protected computers. Samples will be kept in locked storage. Only study investigators will have access to the samples and data.

Statistics

Our outcome analyses will focus on examining the acute effects and duration of intranasal ketamine treatment during inpatient psychiatric hospitalization. As a primary outcome, we will examine the efficacy of intranasal ketamine for preventing suicidal behavior and ideation among adult patients in a current depressive episode at day 1. Our primary outcome analysis seeks to answer two questions: 1) will intranasal ketamine work acutely compared to placebo, and 2) how long will this effect persist? Effect sizes will be calculated for intranasal ketamine treatment. In the primary outcome analysis, two dichotomous primary outcome measures will be examined in the evaluation: 1) the presence or absence of suicidal ideation, and 2) the presence or absence of suicidal behavior as measured using the C-SSRS and SSI. Our secondary outcome analysis will include an examination of 1) the effects of intranasal ketamine for suicidal ideation while controlling for improvements in depression and other dimensions 2) the potential role of recent alcohol abuse and previous alcohol dependence in the rapid anti-suicidal effects of intranasal ketamine. The symptom severity ratings of SSI, the C-SSRS total score and, as well as changes in MADRS scores will be utilized as primary and secondary outcomes, respectively. Normality assumptions for continuous variables will be examined. 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.

Analyses of cross-sectional data with missing values will utilize multiple imputation (Proc MI and Proc MIANALYZE, SAS v. 9.3), while longitudinal analyses will rely on maximum likelihood (in the Bayesian context). Multiple imputation, maximum likelihood, and explicitly modeling missing data in the Bayesian approach are all robust to data missing at random. Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. Pattern-mixture modeling methods will address any identified non-ignorable missing data patterns.

Preliminary data analyses will inspect baseline group differences as well as correlations between baseline covariates and specified criterion variables. Baseline covariates demonstrating a correlation

with both predictors and outcome variables, meet criteria for being potential confounders, and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will determine the degree to which any group differences might confound conclusions regarding treatment. Analyses will proceed in parallel using conventional, Frequentist and Bayesian approaches. Frequentist results yield the probability of the observed data, or data more extreme, given that the null hypothesis holds. Bayesian results yield the probability that an alternative holds. Eleven patients per group are required using confidence level of 95% (with $P<0.05$, two-tailed) and power 0.8, based on previous studies using ketamine for depression in placebo-controlled studies reporting response rates of 60% with ketamine and 10% with placebo. The study was designed to detect a moderate to large difference ($d=0.7$) between ketamine *vs* placebo, based on previous studies using IV ketamine (Wilkinson et al 2018). Treatment effects may be also quantified as mean differences between groups and associated effect sizes are based on standardized mean difference (Cohen's *d*). All statistical tests were two-sided with an alpha set at 0.05. All analyses were performed using SPSS v. 20 (SPSS Inc., USA) and SAS (version 9.2; SAS, Cary, North Carolina).

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