Pharmacologic Attenuation of Ketamine Using Nitroprusside
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Mount Sinai	Protocol Title:	Pharmacologic attenuation of ketamine using nitroprusside
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MSSM Protocol Template HRP-503a

Brief Summary of Research (250-400 words):

Ketamine is an effective fast-acting therapeutic intervention for patients with treatment refractory depression that is known to have the unwanted effect of inducing temporary psychotomimetic symptoms (i.e., delusions, hallucinations and thought disorganization) in some patients. The precise mechanisms of these psychotropic effects remain to be elucidated, but for several decades the NMDA-type glutamate receptor has been hypothesized to be of central importance. In this vain, recent studies of the antihypertensive agent nitroprusside – which increases the availability of the molecular nitric oxide, a known by-product of NMDA activity – have found evidence for antipsychotic properties both in humans with psychotic illness and healthy subjects given ketamine. Here, we propose a study that will build on this work by evaluate the effects of nitroprusside on both the antidepressant and psychotomimetic effects of ketamine given to patients to treat refractory depression. In addition, as an exploratory aim, by collecting serial blood samples from participants as they are administered ketamine and nitroprusside, we will seek to determine functional markers of therapeutic effect and the mechanisms by which ketamine modulates both mood and psychotic states.

1) Objectives:

Research Question

We will test whether the effects of ketamine (KET) on mood and psychotic states is modified by co-administration with sodium nitroprusside (NP) in patients with depression. Furthermore, we will evaluate the extent to which the underlying biology of disease states and drug mechanisms can be inferred through analysis of peripheral blood biomarkers.

Specific Aims

Aim I. To test whether co-administration with NP has any impact on the efficacy of KET as an antidepressant.

Aim II: To test the ability of NP to prevent the psychotomimetic effects of KET in patients with depression.

Aim III. Evaluate whether the neurobiological mechanisms governing changes in psychiatric states can be inferred through analysis of peripheral biomarkers isolated from blood.

Research Hypotheses

Research Hypothesis I. Patients pre-treated with NP will experience attenuated antidepressant effects (measured by MADRS score) following KET compared to pre-treatment with placebo.

Research Hypothesis II: Patients pre-treated with NP will experience attenuated psychotomimetic effects (e.g., CADSS score) immediately following KET compared to pre-treatment with placebo.

Research Hypothesis III. Changes in peripheral biomarkers profiles will be correlated with changes in mental status (e.g., mood, perception) in depressed patients treated with KET with and without NP pre-treatment.

2) Background

KET has both rapid onset antidepressant (Berman et al. 2000) and psychotomimetic (Krystal et al. 1994) effects in humans. Among the many biochemical properties of this molecule is antagonism at the NMDA receptor (Anis et al. 1983), an ion channel that is highly permeable to calcium. There are a multitude of downstream processes affected by NMDA receptor modulation, one of which is nitric oxide (NO) synthesis (Bredt and Snyder 1989; Sattler et al. 1999). Taken together, these findings for several decades have formed the scientific basis for the hypothesis that the psychotropic properties of KET occur through modulation of NO homeostasis via NMDA activity.

There is some direct evidence to support this notion with regard to psychosis. Studies of rodents co-administered the NO donor NP and either PCP or KET, for instance, support the idea that **NMDA hypoactivity results in psychotic phenotypes through decreased NO synthesis** (Bujas-Bobanovic et al. 2000; Kandratavicius et al. 2015). In humans, a molecular neuroimaging study of healthy subjects found KET-induced reduction of NMDA receptor availability was associated with increased psychotic phenomena (Stone et al. 2008). Similarly, a decrease in psychotic phenomena has been observed when the NP is administered to patients with primary psychotic illness (Hallak et al. 2013) as well as healthy human subjects given KET (personal communication with Dr. Jaime Hallak). NP administration may therefore block KET-induced psychosis via enhancing NO availability (NP is a potent NO donor).

With regard to depression, there is less data. In a rodent model of depression, the antidepressant effects of KET were not reversed by NP (Vogt et al. 2015), suggesting regulation of psychotic and affective symptoms through different pathways. However, more recently a rodent model pointed to NO synthesis as being an indispensable component of the antidepressant mechanism of KET (Harraz et al. 2016). Therefore, it is unclear if antidepressant effects of KET are related to NO availability.

Building on this previous work, the proposed study seeks to characterize the effects of KET and NP on depressive and pro-psychotic states in patients with depression. This line of research has the potential to shed new light on the basic mechanisms of depression and psychosis, and to suggest a novel strategy to minimize unwanted side effects of KET for the treatment of depression.

3) Setting of the Human Research

The human research will be conducted at the Mood and Anxiety Disorders Program (MAP) outpatient clinic located in the Atran building , at the Adult Psychopharmacology Program suite of Mount Sinai School of Medicine, at the Clinical Research Center (CRC) and at the Psychiatry Infusion Suite located in the Icahn Building of Mount Sinai School of Medicine.

4) Resources Available to Conduct the Human Research

We will be recruiting from various sources in the community for this research study. They include online recruitment sources, community outreach and physician referrals. Dr. Murrough has years of experience conducting research studies and is well-suited to conduct human research. Our coordinators have experience conducting human research and are very well qualified. All staff members assisting with this trial are adequately informed about the protocol, the investigational products, and their trial-related duties and functions. An anesthesiologist or other appropriately trained physician (e.g., Intensivist) will administer the study drugs to subjects.

The following emergency equipment will be available in setting of study drug administration:

- Defibrillator, suction device, two oxygen cylinders
- Oxygen delivery devices (nasal cannulae)

- ECG monitor, pulse oximeter, and an expired carbon dioxide detection device (e.g., EasyCap, etc).
- emergency benzodiazepine reversal, emergency opioid reversal, and resuscitation drugs
- manual resuscitation bag, tracheal intubation equipment
- IV equipment: Angiocath, IV tubing, Saline Bag, IV starter kit
- Saline flush, syringes, needles

Code protocol: A study physician will be available throughout the infusion and during the subsequent monitoring period. In the event that additional medical back up is required, study personnel will call a "Team 7000" to activate the Hospital emergency response team, as well as call 911, which is the standard procedure for emergencies occurring in non-hospital space.

5) Study Design

a) Recruitment Methods

The primary source of patients will be self-referrals generated from media advertisements. In addition, we anticipate referrals from clinicians in the Mount Sinai Medical Center, New York City area hospitals affiliated with Mount Sinai, and community clinics, who are aware of our clinical and research program. If the participant is interested, he or she will contact the study team directly. Subjects will be compensated for the time and inconvenience associated with participation in this protocol. Screening is done under GCO 06-0945: A Screening Protocol for Adult Patients with Mood and Anxiety Disorders. Advertisements include the link to an online pre-screening survey, which is IRB approved under GCO 06-0945. Any media advertisements will first be sent to the IRB for approval.

b) Inclusion and Exclusion Criteria

Inclusion Criteria:

1) Male or female patients, 21-65 years of age;
2) Female individuals who are not of childbearing potential (i.e., surgically sterile, postmenopausal for at least one year) or using a medically accepted reliable means of contraception. Women using oral contraceptive medication for birth control must also be using a barrier contraceptive. Women of

childbearing potential must also have a negative pregnancy test at screening and at pre-infusion;

3) Participants must fulfill current DSM-5 criteria for Major Depression without psychotic features or Persistent Depressive Disorder with specifier of "with persistent major depressive episode";
4) Depression is at least moderate severity, defined as a CGI-S score of ≥ 4;
5) Current major depressive episode is of at least 4 weeks duration;
6) Each participant must have a level of understanding sufficient to agree to all tests and examinations required by the protocol and must sign an informed consent document;
7) Each participant will agree to be compliant with study procedures required by the protocol;
8) Each participant must be able to identify a family member, physician, or friend who will act as an emergency contact.

Exclusion Criteria:

1) Lifetime history of psychotic features, diagnosis of schizophrenia or any other psychotic disorder, or diagnosis of bipolar disorder;
2) Lifetime histories of autism, mental retardation, pervasive developmental disorders, or Tourette's syndrome;
3) Current diagnosis of OCD or eating disorder (bulimia nervosa or anorexia nervosa);
4) Subjects with DSM-V drug or alcohol abuse/dependence within the preceding 2 years;
5) Patients with schizotypal or antisocial personality disorder, or any clinically significant axis II disorder that would, in the investigator's judgment, preclude safe study participation;
6) Patients judged clinically to be at serious and imminent suicidal or homicidal risk, or suicide attempt within the past 1 year;
7) Women who are either pregnant or nursing;
8) Any serious, unstable medical illnesses including hepatic, renal impairment, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunologic, or hematologic disease;
9) History of congestive heart failure, established coronary artery disease, or valvular disease;
10) History of cerebrovascular insufficiency;
11) History of intrapulmonary arteriovenous shunts, co-arctation of the aorta or other conditions where cardiac outflow tract is obstructed;
12) Vitamin B12 deficiency;

13) Clinically significant abnormal findings of laboratory parameters, physical examination, or ECG;
14) Renal impairment, as reflected by a BUN > 20 mg/dL and/or creatinin clearance of >1.3 mg/dL;
15) Thyroid impairment, as reflected by a TSH > 4.2 mU/L;
16) Hepatic injury, as reflected by AST or ALT greater than twice the upper limit of the reference range (AST: >80; ALT >110);
17) Patients who have a positive urine toxicology for illicit substances at screening and within 24 hours of the infusion;
18) Treatment with an irreversible MAOI within 2 weeks prior to randomization or fluoxetine within 4 weeks prior to randomization;
19) Treatment with other antidepressants (classified as SSRIs, SNRIs, Atypical Antidepressants, MAOIs, TCAs) within one week of randomization;
20) Previous recreational use of PCP or KET;
21) Hypertension with systolic BP >160 mm Hg or diastolic BP >90 mm Hg at screening, systolic BP > 165 mm Hg or diastolic BP > 95 mm Hg immediately prior to treatment with study drug or hypotension with systolic BP < 90 or diastolic < 60 at screening or immediately prior to treatment with study drug; heart rate >110 or <60 at either of these time points;
22) Treatment with sildenafil (Viagra), tadalafil (Cialis), Avanafil (Stendra), Vardenafil (Levitra) or other drugs in the same category of phosphodiesterase-5 enzyme inhibitors within 2 weeks of infusion.

In no case will it be recommended to a participant to discontinue a particular treatment if there is any evidence that the treatment is providing clinical benefit. Additionally, only the patient's prescribing physician, and never the study physician, will take a patient off a medication.

If urine toxicology is positive and not explained by a prescribed medication at any point during the study, the participant will be disqualified from the study. If this occurs, the patient will be provided with a referral for drug counseling and treatment if the patient wishes to seek treatment.

As part of the initial screening, subjects will be asked to provide emergency contact information, and their consent obtained to call the emergency contact to confirm that they are willing and able to serve as such.

Finally, a capacity evaluation will be conducted by an independent psychiatrist in order to ensure sufficient subject understanding of the potential risks and benefits or participating in the study.

c) Number of Subjects

Our goal is for 40 individuals to be randomized in this study. Based on our expected screen fail rate, we expect to enroll approximately 100 patients who will sign the consent for and be screened for study eligibility.

d) Study Timelines

Subjects undergo a screening period that may last up to four weeks (Visit 0). Eligible subjects then undergo the PLC/KET Test Infusion (Visit 1) and undergo evaluation of treatment response 24 hours following the infusion (Visit 2). For subjects who meet criteria to continue in the study, they are randomized to one of two treatment conditions (PLC/KET or NP/KET) to take place up to four weeks from the Test Infusion (Visit 3). Subjects will again return for evaluation 1 week (+/- 2 days) following Visit 1(Visit 2a). After the second infusion (Visit 3), subjects will return for evaluation at 24 hours (Visit 4) and 1 week (+/- 2 days) following Visit 3 (Visit 5). Subjects will return for a final exit visit (Visit 6) 14 days (+/- 2 days) following the second infusion (Visit 3). Therefore, the total study participation time will be up to 10 weeks.

We anticipate a 2-year project period, during which time approximately 100 patients will be screened, with 40 patients randomized. However, after 8 patients have completed the study, the results will be unblinded to an independent statistician and an interim analysis conducted. On this basis, the study may be terminated, or it may be continued towards the goal of randomizing 40 total patients. A second interim analysis will be conducted once the sample size has doubled, and 16 patients have completed the study. The statistician will receive de-identified coded data only.

e) Study Endpoints

<u>Primary Outcomes</u>

(a) Change in Montgomery–Asberg Depression Rating Scale (MADRS) compared across PLC/KET and NP/KET administrations.

(b) Change in four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS), Clinician-Administered Dissociative States Scale (CADSS) and Visual Analog Scale (VAS) scores from Time 0 to Time 40 minutes compared across PLC/KET and NP/KET administrations.

Secondary Outcome

Change in molecular profiles obtained from blood draws of subjects at set time points that parallel clinical ratings during infusions of the agents under investigation and post-infusion follow up.

Statistical Analysis

The null hypotheses of this study are that (a) pre-treatment with NP does not attenuate the antidepressant effects of KET (b) pre-treatment with NP does not reduce psychotic rating scores induced by KET, and (c) there are no changes in molecular measurements over the course of KET and/or NP infusions that correlate with clinical ratings. These hypotheses will be tested against their corresponding alternatives, namely that pre-treatment with NP effectively attenuates both the antidepressant and pro-psychotic effects of KET and that molecular changes in reflecting real-time changes in mental status can be tracked using serial blood draws.

Data will be analyzed using repeated measures General Linear Models with Time and Treatment Condition as within-subject variables. Overall F tests for significance will be followed up by post-hoc t-tests comparing rating scores between the treatment conditions.

The statistician will receive de-identified coded data only.

f) Procedures Involved in the Human Research

The current protocol consists of 8 study visits, as well as a phone call check-in (Study Visit 0: Screening; Study Visit 1: PLC/KET infusion; Study Visit 2: 24-hour follow-up of Study Visit 1; Study Visit 2a: 7-day follow-up of Study Visit 1; Phone-call follow-up of Study Visit 1; Study Visit 3: PLC/KET or NP/KET infusion; Study Visit 4: 24-hour follow-up of Study Visit 3; Study Visit 5: 7-day follow-up of Study Visit 3; Study Visit 6: study exit evaluation). Below, we first outline procedures for study drug administration that apply to both Study Visits 1 and 3. Then, we describe in more detail the procedures that will occur on each of the Study Visits. See Table 1 for an outline of the events occurring at all visits.

Description of Study Drug Procedures

Study drugs are administered on Study Visits 1 (single-blind) and 3 (double-blind). Visits 1 and 3 will occur up to four weeks apart to allow subject depression levels to return to baseline, a necessary component of the study design in order to test whether NP has any effect on the antidepressant action of KET. At Visit 1, participants will receive single-blind placebo (PLC) followed by KET (0.5 mg/kg/hour for 40 minutes), in which they are blind to the PLC/NP condition but are aware they are receiving KET. Subjects return to the clinic 24 hours following Visit 1, at which time their eligibility to continue and be randomized in the study is determined. The criteria for continuing is a significant antidepressant response to KET as demonstrated by MADRS score of >= 50% improvement from baseline. Eligible subjects are randomized to one of two treatment conditions for Visit 3 (double-blind): PLC/KET or NP/KET (NP dose: 0.5 micrograms/kg/minute for 240 minutes), where again, the blinded condition is PLC/NP, but the subjects are aware they are receiving KET. Ineligible subjects (i.e., ketamine non-responders) will be scheduled to return to the clinic for an exit visit 1 week (7 +/- 2 days) following the first infusion. The appearance of the nitroprusside will be protected to allow this drug to be blinded. Given the potential lengthy duration between visits (between 2 and 4 weeks), subjects will return to the clinic approximately 1 week (7 +/- 2 days) following V1 (PLC/KET) for a check-in (Visit 2a) with the study doctor in order to ensure subject safety, as well as to be evaluated for remission of depressive symptoms. Additionally, a phone call MADRS will be administered 3 to 4 days following the in-person check-in, which will serve as the final determinant of the subject's return to baseline (defined as receiving a score within 20% of the baseline MADRS). If the subject has not returned to baseline, the V3 will be rescheduled for a date approximately two weeks following its initial appointment in order to allow maximum time (4 weeks) for a return to baseline, and the two check-ins (Visit 2a and by-phone check-in) will be repeated for the next two weeks, for a total of 4 additional check-ins. Following the V3 infusion visit, subjects again return to the clinic at 24 hours (Visit 4) and at 7 +/- 2 days (Visit 5) following the second infusion day, and once more 14 +/- 2 days after the infusion for the Exit Visit (Visit 6).

Each treatment day (Visit 1 and 3) involves Infusion 1 (PLC or NP) and Infusion 2 (KET). Prior to Infusion 1 (PLC on Study Visit 1; PLC or NP on Study Visit 3) an indwelling catheter will be placed in the antecubital veins of each arm, and pulse, blood pressure, pulse-oximetry, and an EKG strip will be placed for continuous vital monitoring, which will be performed throughout the infusions. One of these catheters will be used for the administration of NP/PLC, and one will be used for the administration of KET; this is to ensure no interaction effects between the drugs given in the same line. At Time 0, Infusion 1 will begin through an infusion pump and will continue until Time 240 minutes. At Time 200

minutes, Infusion 2 (KET on both Study Visits 1 and 3) will begin and will continue until Time 240 minutes, at which point all medication administration will be complete for the Study Visit. Clinical ratings (BPRS, CADSS, VAS; see below) will be collected at regular intervals before, during and after the infusion period by clinical raters. Blood draws may be conducted at baseline and Time +240 min on V1 and V3 infusion days, as well as at the 24-hour V2 and V4 visits, for a total of six blood draws; however, this is an optional procedure that will occur under a different protocol (GCO 11-1617). On the two infusion days, the blood will be drawn through one of the indwelling catheters that are used for study drug administration.

A urine toxicology screen will be performed before the first infusion and must be negative for illicit substances in order to proceed with the infusion. For females, a urine pregnancy test will confirm non-pregnancy prior to the infusions.
Prior to the infusion VS will be assessed by nursing staff and confirmed by an MD and will need to be stable as per inclusion/exclusion criteria. Patients will be monitored by study nursing staff and by an MD throughout the infusions and for 1 hour of observation after the infusions end. Furthermore, a study anesthesiologist will oversee the study drug infusions. At the end of the observation period a study doctor will evaluate the patient, then the patient will be discharged home accompanied by a responsible adult. Patients will be instructed not to drive for 24 hours following the infusions.

Description of Study Visit Procedures:

Study Visit 0: Screening

Summary of study procedures during this phase:

- *Informed Consent*
- *Structured Psychiatric Interview (SCID)*
- *Physician Evaluation*
- *Medical History*
- *Adverse Events Documentation*
- *Concomitant Medication Documentation*
- *Physical Exam*
- *Vital Signs*
- *Routine Laboratory Tests*
- *Urine Toxicology*
- *Urine Pregnancy Test (if applicable)*
- *EKG*

After receiving complete disclosure about the research and opportunity to fully review the consent form, potential participants will be given the opportunity to ask questions. If they choose to take part in the study, then they will be asked to sign the written informed consent form. Psychiatric history will be obtained by a member of the research team using the SCID and the DSM-5 Diagnostic Criteria. A medical history and physical examination will be performed for each patient and basic laboratory tests ordered. This will include: ECG, vital signs (including orthostatic blood pressure measurements), complete blood cell counts, electrolytes, thyroid functioning test, liver function tests, urinalysis, and toxicology screening. A urine pregnancy test will be performed in premenopausal women. Results of these tests will identify patients who should be included or excluded based on criteria stated earlier in this protocol.

Study Visits 1 and 3: Test days

Summary of study procedures during this phase:

- *Vital Signs*
- *Urine Toxicology*
- *Urine Pregnancy Test (if applicable)*
- *Study Drug Infusion 1 and Infusion 2*
- *Blood draws before/after infusion (if applicable)*
- *Clinical ratings before/during/following infusion*

Study Visit 1 will occur up to 4 weeks after Study Visit 0. At this Visit, all participants will first receive PLC for Infusion 1 and KET for Infusion 2. Details of the dosing and timing for these infusion sequences, as well as the associated clinical ratings and blood draws, is explained in the "Description of Study Drug Procedures" section above.

Study Visits 2 and 4 (24-h follow ups)

Participants will return to the study site 24 hours after Study Visit 1 for Study Visit 2. At this visit, safety and efficacy assessments will be performed (no drugs will be administered). The research team will analyze the outcomes of the MADRS and CADDS for each participant obtained on this day. In order to best assess the capacity of NP to attenuate the pro-psychotic and antidepressant effects of KET, only those participants who show improvement in MADRS $\geq$ 50% compared to baseline will be eligible to return for Study Visit 3.

Participants who meet these criteria will return for Study Visit 3 up to 4 weeks later (depending on the amount of time required for the patient's MADRS score to return to baseline). These participants will be randomized to receive a drug administration sequence of either PLC/KET or NP/KET at Study Visit 3.

All patients who return for Study Visit 3 will return to the study site within 24 hours for Study Visit 4. At this visit, safety and efficacy assessments will be performed (no drugs will be administered).

Study Visits 2a and 5 (7-day follow-ups) and Phone Call Check-In

Approximately 1 week (7 +/- 2 days) after Visit 1, participants will return to the study site for an in-person visit (Visit 2a), which will consist of meeting with the study doctor and completing a MADRS with the clinical rater. Provided that there are no clinical concerns, a phone call MADRS will be scheduled 3-4 days following the in-person check-in in order to determine whether the patient has returned to baseline (within 20% of baseline MADRS). As stated above, if the participant has not returned to baseline before the second infusion, the infusion will be rescheduled to a date approximately 2 weeks ahead of the original appointment, and these two check-ins will be repeated twice more over the course of the next 2 weeks (visit 2b, 2c and two phone calls), for a total of four additional check-ins.

Approximately 1 week (7+/- 2 days) after Visit 3, participants will return to the study site for an in-person visit (Visit 5), which will consist of meeting with the study doctor and completing a MADRS with the clinical rater.

Visit 6 (Exit Visit)

14 days +/- 2 days after Visit 3, and 7 days after Visit 5, all participants will return for Study Visit 6 (Exit Visit). Safety and efficacy assessments will be performed, and the patient will have completed the study.

Description of Study Instruments

The **Structured Clinical Interview for DSM-5 Axis I Disorders (SCID)** (First et al. 2012) is a semi-structured interview that provides probe questions as well as follow-up questions to be asked by the clinician to assist in diagnosis. It includes an overview to obtain information about demographics, work, chief complaint, history of present illness, past history, treatment history, and current functioning.

The main body of SCID (patient edition) includes 9 modules that are designed to diagnose 51 mental illnesses in all.

The **Brief Psychiatric Rating Scale (BPRS)** (Overall and Gorham 1962) is used to assess acute behavioral changes during the infusions. Four key BPRS items for the positive (+) symptoms of psychosis will be used: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Three items representing the negative (-) symptoms of psychosis will also be used: blunted affect, emotional withdrawal, and motor retardation.

The **Clinician-Administered Dissociative States Scale (CADSS)** (Bremner et al. 1998) is used to measure dissociative effects during the infusions. The scale includes 19 questions and 8 observer ratings scored from 0 (not at all) to 4 (extremely). The CADSS measures impairment in body perception, environmental perception, time perception, memory impairment, and feelings of unreality.

Visual Analog Scales. These scales are scored in millimeters from the left-hand side of a 100-mm line to a perpendicular mark made by the patient at a point corresponding to the apparent magnitude of the feeling state. Range: 0 ("not at all") to 100 ("most ever").

Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). This is a 10-item instrument used for the evaluation of depressive symptoms in adults and for the assessment of any changes to those symptoms. Each of the 10 items is rated on a scale of 0 to 6, with differing descriptors for each item. These individual item scores are added together to form a total score, which can range between 0 and 60 points. The estimated time to administer this scale is 20 minutes. Inter-rater reliability of the scale is high and scores correlate significantly with those of the HAM-D. On the infusion days a modified MADRS will be used that will exclude the sleep and appetite items.

Quick Inventory of Depressive Symptomatology, Self Report (QIDS-SR): The Quick Inventory of Depressive Symptomatology, Self Report (QIDS-SR) is a 16-item self rated instrument designed to assess the severity of depressive symptoms. The 16 items cover the nine symptom domains of major depression as indicated by the DSM, and are rated on a scale of 0-3. Total scores range from 0 to 27, with ranges of 0-5 (normal), 6-10 (mild), 11-15 (moderate), 16-20 (moderate to severe), and 21+ (severe).

Columbia-Suicide Severity Rating Scale (C-SSRS): The Columbia-Suicide Severity Rating Scale (C-SSRS) is a comprehensive, semi-

structured interview that uniquely measures the full spectrum of suicidality including passive and active suicidal ideation, suicidal intent as well as suicidal behaviors. Subjects will be assessed at every visit with the CSSRS by a study clinician. Any subject with an increase in suicidality and all those subjects found to have a plan or intent will undergo thorough assessment by the study psychiatrist who will determine the appropriate course of action, including whether acute intervention is needed and whether it is in the best interest of the subject to continue in the study. If necessary, the study psychiatrist will seek consultation from the study PI or medical monitor. If continued participation is deemed not to be in the best interest of study subject, s/he will be discontinued from the study.

g) Data Management and Confidentiality

Case report forms and source documents are completed electronically using the institution's REDCap data capture system, a secure web-based application protected by Mount Sinai's server and managed by IT, which will obviate the need for data entry and data cleaning at time points separate from data capture, reducing the risk of error. The case report forms and source documents are based on established instruments or are developed from adaptations of NIH and industry-sponsored clinical trial protocols. Study data are recorded without specific patient identifying information. Patient identifiers are sequestered in a separate REDCap database. Access to both study databases is password protected and only IRB approved study members have access.

All data will be obtained for research purposes only. We will collect information about participants' psychiatric history, including previous treatments, medical history, and family history. As part of the medical evaluation, we will collect blood and urine specimens for analysis, and perform an ECG. The outcome of these tests will be shared with the participant. In the event that we detect a medical condition that requires treatment, we will provide the participant with an appropriate referral.
In addition, data will include clinical ratings and patient self-ratings. These data will not be shared with the participants.

h) Provisions to Monitor the Data to Ensure the Safety of subjects

This information is only required when Human Research involves more than minimal risk to subjects.

Part I describes the safety monitoring activities that will be undertaken in during the study. This should be completed for all studies that require more than the basic minimum Data and Safety Monitoring Plan **(DSMP)**.

Part II describes Data and Safety Monitoring Committees or Boards and should be completed when one is needed for the DSMP.

Part I: Elements of a Data and Safety Monitoring Plan (DSMP)

1. List the name(s) of the individual(s) at MSSM who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information. The Principal Investigator may be the only monitor of a study.

If the qualifications of an individual to serve as a monitor are not contained in the PPHS application, they must be added to the DSMP either as a narrative description or as a CV.

MSSM Principal Monitor: James Murrough, MD PI

Indicate whether this person is the PI, a Team Member, or is Independent:

Last Name: James

First Name: Murrough

Academic Title: Assistant Professor

Department: Psychiatry

Mailing Address: 1 Gustave L. Levy Place, Box 1230

Phone: 212-241-7574

Fax: 212-241-3354

E-mail: james.murrough@mssm.edu

2. Justify your choice of principal monitor in terms of the assessed risk to the research subject‘s health and wellbeing. In high risk studies when the principal monitor is independent of the study staff, indicate the individual’s credentials, relationship to the PI, and the rationale for selection.

Dr. Murrough is intimately knowledgeable of this study and also be involved in the clinical care of the subjects and will provide oversight of

the entire study. He has been involved in many KET studies in Mood and Anxiety Program (MAP).

3. List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

Adverse events, subject compliance with the protocol, side effects and dropouts will be closely monitored.

4. Indicate the frequency at which ACCUMULATED safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.

All accumulated data will be reviewed annually by the PI and the IRB. In addition, data and safety will be monitored in an ongoing fashion by the PI.

5. Where applicable, describe rules which will guide interruption or alteration of the study design.

N/A

6. Where applicable, indicate dose selection procedures that will be used to minimize toxicity.

The dose of KET is fixed with 0.5 milligrams/kg/hour infusion over 40 min. NP is administered at the lowest therapeutic dose used for treatment of hypertension, 0.5micrograms/kg/min. The time of 240 minutes for the infusion was determined through the only published study of the use of NP as a psychotropic medication in humans (Hallak, 2013).

7. List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).

Grading of severity and attribution to research will be conducted at each visit and noted on the treating cover sheet.

(1) Attribution of adverse events:
Unrelated: Adverse event(s) will clearly not related to the investigational agent(s)
Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
Possible: The adverse(s) events may be related to the intervention(s)

Probably: The adverse(s) event is likely related to the intervention(s)
Definite: The adverse(s) event is clearly related to the intervention(s)

(2) Plan for Grading Adverse Events:
The FDA's definition of serious adverse events (21CRF 312) (AE) include any untoward medical occurrence that at any age results in death or the immediate risk of death, hospitalization or the prolongation of an existing hospitalization, persistence or significant disability/incapacity or congenital anomaly/birth defect (NH Guide, 6/11/99).

Grade of Risk:
1= Non Serious Adverse Event
2=Serious Adverse Event

8. Describe procedures that will be used to assure data accuracy and completeness.

The PI will monitor the accuracy and completeness of the data. The following elements will be monitored: recruitment procedures and pace; adherence to the exclusion/inclusion criteria; deviation from protocol; the timeliness of documentation and data entry; and the accuracy and confidentiality of all information both in study documents and study database.

9. Should a temporary or permanent suspension of your study occur, in addition to the PPHS, indicate to whom (NIH, FDA, sponsor, IRB) will you report the occurrence.

N/A

Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

A local Data Safety and Monitoring Board (DSMB) for ketamine depression protocols is currently in place at Mount Sinai and will provide oversight for the current trial.

The DSMB will ensure the safety of study participants and the integrity of the data collection in the projects. To achieve this goal, the DSMB will perform an ongoing evaluation of the safety of patients participating in the clinical outcomes in the clinical trial. This includes monitoring adverse events and overall clinical outcomes in the studies. Through this process the board will evaluate the need for study termination and/or modification of study criteria for inclusion, exclusion, or discontinuation. In

addition, the DSMB will be responsible for the evaluation of the adherence to written protocols regarding the protection of human subjects and the assurance of identity protection as specified in the Data Sharing Section. The DSMB will expeditiously review all serious adverse events and perform ongoing scheduled reviews of non-serious adverse events and study dropouts. The DSMB includes the following members: The Oversight Committee members are to include: Lawrence Price, MD, Professor of Psychiatry, Brown University; Menachem Weiner, MD, Icahn School of Medicine Professor of Anesthesiology; Charles Kellner, MD, Professor of Psychiatry, Icahn School of Medicine at Mount Sinai; and Dr. Mark Green, Professor of Neurology and Professor of Anesthesiology, Icahn School of Medicine at Mount Sinai. The board will review the project's data and safety on bi-annual basis and report their findings to the PI.

i) Withdrawal of Subjects

Investigators may elect to withdraw the patient due to safety concern or non-adherence to the study protocol. Subjects may withdraw at any point in the study.

6) Risks to Subjects

Risks associated with NP [The following information was derived from the FDA package insert for NP (Nitropress [package insert]. Lake Forest, IL: Hospira Inc; 2014).]

The principal hazards of NP excessive hypotension and excessive accumulation of cyanide. Transient excesses in the infusion rate of NP can result in excessive hypotension, sometimes to levels so low as to compromise the

perfusion of vital organs. These hemodynamic changes may lead to a variety of associated symptoms. Hypertensive patients, and patients concomitantly receiving other antihypertensive medications, may be more sensitive to the effects of NP than normal subjects. NP infusions at rates above 2 μg/kg/min generate cyanide ion (CN^-) faster than the body can normally dispose of it. The true rates of clinically important cyanide toxicity cannot be assessed from spontaneous reports or published data. Most patients reported to have experienced such toxicity have received relatively prolonged infusions, and the only patients whose deaths have been unequivocally attributed to NP-induced cyanide toxicity have been patients who had received NP infusions at rates (30-120 μg/kg/min) much greater than those now recommended. Elevated cyanide levels, metabolic acidosis, and marked clinical deterioration, however, have occasionally been reported in patients who received infusions at recommended rates for only a few hours and even, in one case, for only 35 minutes. Cyanide toxicity may manifest itself as venous hyperoxemia with bright red venous blood, as cells become

unable to extract the oxygen delivered to them; metabolic (lactic) acidosis; air hunger; confusion; and death. Cyanide toxicity due to causes other than NP has been associated with angina pectoris and myocardial infarction; ataxia, seizures, and stroke; and other diffuse ischemic damage.

The adverse reactions described in this section develop less rapidly and less commonly than the hypotension and cyanide toxicity highlighted above. NP can cause sequestration of hemoglobin as methemoglobin. The back-conversion process is normally rapid, and clinically significant methemoglobinemia (>10%) is seen only rarely in patients receiving NP; even patients congenitally incapable of back-converting methemoglobin should demonstrate 10% methemoglobinemia only after they have received about 10 mg/kg of NP (a patient receiving NP at the maximum recommended rate (10 µg/kg/min) would take over 16 hours to reach this total accumulated dose). Thiocyanate build-up may occur in NP infusions at high doses and rates. It is mildly neurotoxic (tinnitus, miosis, hyperreflexia) at serum levels of 1 mmol/L (60 mg/L) and life-threatening when levels are 3 or 4 times higher (200 mg/L). To keep the steady-state thiocyanate level below 1 mmol/L, a prolonged infusion of NP should not be more rapid than 3µg/kg/min. Other, nonspecific adverse reactions that have been reported with NP include abdominal pain, apprehension, diaphoresis, “dizziness,” headache, muscle twitching, nausea, palpitations, restlessness, retching, retrosternal discomfort, bradycardia, electrocardiographic changes, tachycardia, rash, hypothyroidism, ileus, decreased platelet aggregation, flushing, venous streaking, and irritation at the infusion site.

NP should not be used in the setting of compensatory hypertension, where the primary hemodynamic lesion is aortic coarctation or arteriovenous shunting. NP should not be used to produce hypotension during surgery in patients with known inadequate cerebral circulation, or in moribund patients (A.S.A. Class 5E) coming to emergency surgery. Patients with congenital (Leber’s) optic atrophy or with tobacco amblyopia have unusually high cyanide/thiocyanate ratios, and NP should be avoided in these patients. NP should not be used for the treatment of acute congestive heart failure associated with reduced peripheral vascular resistance such as high-output heart failure that may be seen in endotoxic sepsis. Like other vasodilators, NP can cause increases in intracranial pressure. In patients whose intracranial pressure is already elevated, NP should be used only with extreme caution. The hypotensive effect of NP is augmented by that of most other hypotensive drugs, including ganglionic blocking agents, negative inotropic agents, and inhaled anesthetics. Caution should also be exercised in patients with hepatic insufficiency, anemia, hypovolemia, abnormalities of the pulmonary ventilation/perfusion ratio, and high surgical risks. NP has not been tested for effects on fertility.

Risks associated with KET

KET is a sedative/analgesic and general anesthetic for human and veterinary use. It may produce mild to moderate increases in blood pressure, heart rate, and cardiac output due to its sympathomimetic effects and can provoke ischemia in patients with underlying coronary artery disease. Overall, however, KET has a favorable acute safety profile. Over the past several decades, KET has been administered as an anesthetic to several million adults and children.

The reported incidence of KET-induced perceptual disturbances varies from less than 5% to greater than 30% (Knox et al. 1970; White et al. 1980) and may manifest as vivid dreaming, visualization of psychedelic color, suspension in space, kaleidoscopic floating, and out-of-body experiences. Some patients describe these psychic experiences as bizarre or frightening, while others find them pleasurable, joyful, and fascinating. Indeed, KET is also known as "Special K" as a drug of abuse related to PCP. For that reason KET was placed in Schedule III of the Controlled Substance Act in 1999. Nonetheless, when perceptual disturbances occur, they are usually mild and of short duration (Green and Johnson 1990). KET administration has transient effects on symptoms, usually lasting less than 60 minutes and rarely lasting longer than 2 hours (Carpenter 1999). The perceptual disturbances may be more common in those with preexisting psychosis (Lahti et al. 1995).

Several studies have addressed the question of prolonged psychological effects in the general population secondary to its anesthetic use and concluded that KET does not place patients at a greater risk than other anesthetics (Hersack 1994; Reich and Silvay 1989; Schorn and Witwam 1980). There is no evidence in these long-term studies that individuals exposed to KET are at risk of abusing it on follow-up.

Both ourselves and others have safely used KET in a large number of psychophysiological studies in patients with psychiatric disorders as well as in healthy with doses similar to that of the present study. A meta-analysis of a number of these studies found no evidence of behavioral sensitization following repeated KET exposure (Cho et al. 2005).

7) Provisions for Research Related Injury

We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of research participation if it is believed that such participation endangers a patient's welfare. Monitoring procedures are used to evaluate potential side effects of treatment or of research procedures. The protocol stipulates an extensive medical and psychiatric evaluation of all patients as a condition for research participation.

Patients are monitored for potential reactions during the clinical trial. A physician is on-call at all times between clinic visits so that adverse reactions can be evaluated and treated promptly.

In general, if subjects are injured or made sick from taking part in this research study, medical care will be provided. Generally this medical care will be billed to the health care insurance. However, ISMMS may be responsible for the costs of any direct research-related injury.

8) Potential Benefits to Subjects

The possible benefits to the patient (remission or improvement of MDD symptoms) and to others (development of a new drug with rapid antidepressant effects based on the elucidation of a new molecular pathway and/or development of a new drug that minimizes the pro-psychotic side effects of KET) are reasonable in relation to the risks of this study. All study participants will receive without cost an extensive psychiatric and medical evaluation. All participants will receive reimbursement of travel expenses. No other direct benefits result from study participation.

9) Provisions to Protect the Privacy Interests of Subjects

Adequacy of Protection Against Risks Recruitment and Informed Consent

Interested individuals contacting the clinic by phone will be informed that the information they give over the phone is written down and discussed by the research team. They will be advised that if they do not enroll in research with the clinic, the information will be destroyed, and that if they do enroll, the information becomes part of their research chart, which is destroyed after seven years. An initial phone screening is completed after they give verbal authorization.

If an individual appears to meet enrollment criteria and is interested in participating, a face-to-face interview will be conducted by one of the project investigators. Referring clinicians will be asked to inform potential participants of the possible alternatives to participating in the study. A release of information will be obtained for review of any available historical and clinical data. A written authorization form is also obtained from each patient, permitting the research team to use, create, or disclose his or her PHI for research purposes. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project will be discussed with each patient. Following this discussion, he or she will be given a copy of the consent form to review at their leisure, and any questions are answered. Study

visits and procedures will take place at the MAP clinic in the Atran Building. The PI or one of the co-Is of the protocol will seek written voluntary informed consent from all participants prior to study entry. The initial consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research participants. If the individual remains interested in the project, written informed consent is obtained, and medical and psychiatric screening procedures are undertaken to confirm eligibility. A copy of the consent form is provided to all participants.

If the individual decides not to participate in this study, a staff member provides reasonable and timely assistance in obtaining an alternative referral, if so desired. The decision not to participate does not affect eligibility to participate in future studies, to receive treatment at Mount Sinai, or to receive treatment on a private basis from a referring clinician.

The consent process also includes documentation of permission to obtain previous medical records, including contact with previous physicians, pharmacies, and family members. The IRB-approved forms for informed consent are made part of the patient's permanent medical record, with a copy filed in the research chart.

End of Study

There are three areas in which safeguards to protect research participants from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to insure confidentiality of the participants' data, and the procedures used to minimize possible risks associated with the study procedures. In the consent form and discussion with an investigator, patients are advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the PI.

In the informed consent form, patients are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff at the research sites and the possible exception of state or federal regulatory personnel. No one but the Project Manager has access to the master list linking patients' names to code numbers. All information obtained is coded. The respective master lists are kept under strict lock and key. Identifiable information is kept in locked file drawers and password protected computer files. Results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity.

10) Economic Impact on Subjects

The study drug will be provided at no cost to the subjects.

11) Payment to Subjects

Participants will be paid according to the following schedule:

Visit	Compensation
Screening Visit	$50
Treatment Day 1	$100
Post-Treatment Assessment Visit (24-hour)	$25
Post-Treatment Assessment Visit (7-day) *	$25
Treatment Day 2	$100
Post-Treatment Assessment Visit (24-hour)	$25
Post-Treatment Assessment Visit (7-day)	$25
Study Exit Visit	$25
Total for participation in all parts of the study:	$375

* this visit may be repeated up to 2 times, for a total additional payment of $50.

12) Consent Process

If an individual appears to meet enrollment criteria and is interested in participating, a face-to-face interview will be conducted by one of the project investigators. Referring clinicians will be asked to inform potential participants of the possible alternatives to participating in the study. A release of information will be obtained for review of any available historical and clinical data. A written authorization form is also obtained from each patient, permitting the research team to use, create, or disclose his or her PHI for research purposes. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project will be discussed with each patient. Following this discussion, he or she will be given a copy of the consent form to review at their leisure, and any questions are answered. Study visits and procedures will take place at the Mood and Anxiety Disorders Program (MAP) outpatient clinic , the Clinical Research Center (CRC), the Adult Psychopharmacology Program suite, and the Psychiatry Infusion Suite.

The PI of the protocol will seek written voluntary informed consent from all participants prior to study entry. The initial consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information,

and the rights of research participants. If the individual remains interested in the project, written informed consent is obtained, and medical and psychiatric screening procedures are undertaken to confirm eligibility. A copy of the consent form is provided to all participants.

If the individual decides not to participate in this study, a staff member provides reasonable and timely assistance in obtaining an alternative referral, if so desired. The decision not to participate does not affect eligibility to participate in future studies, to receive treatment at Mount Sinai, or to receive treatment on a private basis from a referring clinician. Patients will be also given the opportunity to withdraw from the study prior to analysis of their data.

The consent process also includes documentation of permission to obtain previous medical records, including contact with previous physicians, pharmacies, and family members. The IRB-approved forms for informed consent are made part of the patient's permanent medical record, with a copy filed in the research chart.

13) Process to Document Consent in Writing

We will be using the standard PPHS consent template

14) Vulnerable Populations

Indicate specifically whether you will include or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	X	*Adults unable to consent*
	X	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	X	*Wards of the State (e.g. foster children)*
	X	*Pregnant women*
	X	*Prisoners*

The proportion of ethnic minorities (vs. Caucasian) in the total sample will be consistent

with the population proportions in the NYC metropolitan areas. We appreciate that minority groups tend to be underrepresented in research samples of major depressive disorder. Therefore, we will specifically aim to recruit minority patients to assure that the sample represents the community. However, the size of the racial sub-samples may be too small to identify statistically meaningful differences.

Anticipated ethnic/racial distribution: Patients will be recruited from the catchment area of the Mount Sinai Medical Center, which is characterized by a diverse ethnic distribution consisting of 49 percent Hispanics, 38 percent Blacks and 7 percent Whites, and from the catchment area of our affiliated hospitals which are comprised of 22 percent Hispanics, 23 percent White non-Hispanics, 26 percent Asians and 24 percent Blacks. The diversity of the population in our catchment areas permits the recruitment of patients from most of the major ethnic groups including Asians and Pacific Islanders, Blacks, Hispanics from Mexico, Puerto Rico, Cuba, Central and South America, and Caucasians.

There is general agreement in the literature that the prevalence of MDD is greater in women than in men. Therefore, we expect to recruit about 2/3 women and 1/3 men.

Inclusion of Children

This study will not include individuals under the age of 21. The rationale for this exclusion is that insufficient data are available in adults to judge the potential risk in children.

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

N/A

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The pharmacist prepares the IV medication (KET and NP) in a 100 ml NS bag, and a nurse from the GCRC comes to retrieve it the morning of infusion, such that a fixed dose of ml per kg is administered.

At approximately 9 am each patient will begin Infusion 1 (NP or PLC), then 200 minutes later Infusion 2 (KET) will commence. The KET and NP will be stored and dispensed by the research pharmacy.

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