New York State Psychiatric Institute

Institutional Review Board

July 01, 2019

To: Dr. Michael Grunebaum

From: Dr. Edward Nunes, Co-Chair
Dr. Agnes Whitaker, Co-Chair

Subject: Approval Notice: Continuation expedited per 45CFR46.110(b)(1)(f)(8c)

Your protocol # **6785** entitled: **KETAMINE VS MIDAZOLAM IN BIPOLAR DEPRESSION (ADD-ON TO # 6598)** Protocol version date 07/01/2018 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **July 04, 2019 to July 03, 2020.**

Consent requirements:
√ Not applicable: Data Analysis Only
☐ 45CFR46.116 (f)(3) waiver of consent
☐ Signature by the person(s) obtaining consent is required to document the consent process
☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: ☐ No ☐ Yes

Field Monitoring Requirements: ☐ Routine ☐Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.
✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.
✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.
✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

* Enrollment closed for bipolar population only. Recruitment of healthy controls continues.

Cc: CU Business Office (NARSAD and Internal Acct GT002345)

EN/AHW/alw

Signed copy on file at IRB

Protocol Title:
Ketamine in Bipolar Depression (Add-on to # 6598)

Version Date:
07/01/2019

Protocol Number:
6785

First Approval:
07/31/2013

Clinic:
MIND Clinic

Expiration Date:
07/03/2020

Contact Principal Investigator:
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Research Chief:
J. John Mann, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
MIND
Within the division/department, what Center or group are you affiliated with, if any?
None

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Outside Investigators: None

Consultant:

Vivek K. Moitra, MD

Associate Clinical Professor of Anesthesiology

Associate Medical Director, Surgical ICU

Associate Program Director, Critical Care Medicine Fellowship

Division of Critical Care, Columbia University College of Physicians and Surgeons

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
In the past year there was no further recruitment or enrollment of new subjects. The only study activity in the past year was secondary data analysis. We request the ACAR only for data analysis purposes. The study is closed to recruitment.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No

Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
14
Total number of participants enrolled to date
7
Number of participants who have completed the study to date
7
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Bipolar depression
Total number of participants enrolled from this population to date
5
Specify population #2
Healthy volunteers
Total number of participants enrolled from this population to date
2
Gender, Racial and Ethnic Breakdown
Female: 3
Male: 4
Transgender male to female: 1

Non-Hispanic: 8
Hispanic: 0

White: 6
African American or Black: 1
Asian: 1

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year

0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ MRI
✓ Off-label Use of Drug or Device
✓ Somatic Treatment or Intervention

Population

Indicate which of the following populations will be included in this research

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50
✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?
Yes
Describe internal account
The Nina S. Rahn account GT002345
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes

Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
NARSAD/BBRF
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research
Enrollment was completed for this study in suicidal, bipolar, depressed patients to test random assignment to intravenous infusion of ketamine or midazolam control. We then enrolled 5 more subjects to collect pilot data from MRI scans done before and after the same ketamine infusion procedure that was done in the original randomized clinical trial. The primary aim is to gather pilot data exploring neuroimaging (MRI) correlates of the clinical effects of ketamine. We plan to enroll two healthy controls to evaluate whether differences in performance on the memory task during the MRI scans in the patient sample from pre- to post-infusion is associated with ketamine or simply due to practice effects.

Background, Significance and Rationale

Background, Significance and Rationale
There is a shortage of antidepressant options and an absence of antisuicidal treatments of demonstrable efficacy for depressed bipolar (BD) patients. Few double-blind randomized controlled trials (RCT) have examined suicidal behavior in bipolar samples. We are conducting an RCT of the glutamate antagonist ketamine versus midazolam control in suicidal, unipolar depressed patients (IRB 6598), which presented the opportunity for an add-on study in a bipolar depressed sample. Two RCTs by Zarate et al in 33 BD subjects, showed rapid reduction in depressive symptoms or suicidal thoughts after ketamine but not saline infusion

(1,2). We recently completed enrollment of the feasibility study of suicidal, depressed BD patients to extend our actively recruiting protocol to this clinically important population and to test ketamine infusion versus a more rigorous, active control medication (midazolam).
One double-blind, crossover RCT in 18 BD patients with treatment resistant depression on lithium or depakote maintenance compared antidepressant response after add-on ketamine versus saline infusion (1). Results showed markedly superior response to ketamine at 40 minutes post-infusion remaining significant until Day 3, but change in the Montgomery-Asberg Depression Rating Scale (MADRS) suicide item did not differ by treatment (1). This group conducted a replication trial in an independent sample of 15 depressed BD patients and found similar antidepressant effects as well as reduction in the suicide items of the MADRS, Hamilton Depression Rating Scale (HDRS), and Beck Depression Inventory from 40 minutes to several days after ketamine but not saline infusion (2). Neither trial explicitly sought enrollment of suicidal patients, a key issue since pre-treatment suicidal ideation severity appears to be a moderator of treatment effect on suicidal ideation itself (3). Both studies used single scale items rather than a state of the art suicidal ideation rating instrument, such as the Beck Scale for Suicidal Ideation (SSI) (4). Saline control was used in both studies, which given ketamine's dissociative and psychotomimetic effects, may compromise blinding. Both trials were remarkable for a lack of adverse events and absence of a significant signal for ketamine-induced mania, an obvious concern in this population (1, 2).
In unipolar Major Depressive Disorder (MDD), several studies found reduction of suicidal ideation in as little as 40 minutes after sub-anesthetic, intravenous (iv) ketamine infusion (5-9). Improvement in suicidal ideation lasted up to 4 hours, and up to 12 days with repeat infusions. A recent study added open ketamine infusion to emergency department patients' current medication and/or psychosocial treatment and found improvement in suicidal ideation lasted for 10 days. We have replicated these antisuicidal results in an ongoing study of ketamine in depression: In N=6 patients who presented with HDRS suicide item score of 1 or higher, all scored zero 24 hours post-ketamine. Two ketamine studies in MDD used a saline control, which is suboptimal due to ketamine's dissociative and psychotomimetic side effects, and testing for adequacy of the blind was not reported.
Given the public health importance of suicidal behavior, lack of antisuicidal treatments for patients with BD who are at higher risk, and promising early results for ketamine, we propose to enroll 5 additional depressed BD patients with moderate to severe suicidal ideation. Subjects will undergo a 1-hour structural and functional MRI within 2 days before and 2 days after an open ketamine infusion following the same procedure is in the currently approved protocol, but without blinding or randomization.

Specific Aims and Hypotheses

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PRIMARY AIM: The primary study aim will be to explore structural and functional MRI effects from before to after ketamine infusion in Bipolar Disorder during a major depressive episode with moderate to severe suicidal ideation. Unless contraindicated, patients will continue their current psychotropic medication. The goal will be to use pilot data for a neuroimaging grant application. Subjects will be administered the same clinical and neuropsychological assessments as in the currently approved protocol.
Exploratory AIM 1: Cognitive dysfunction is associated with suicide attempt (Keilp et al 2001). Therefore we will compare neurocognitive effects of ketamine vs. midazolam as in our R01-funded study. Our pilot data show that memory improvement correlates with reduction in suicidal ideation, even after adjusting for

depression improvement. We will explore this further by measuring performance on the Buschke Selective Reminding Task and other brief cognitive tests at baseline and post-infusion.
Exploratory AIM 2: To assess suicidal ideation and behavior using the SSI and the Columbia-Suicide Severity Rating Scale (C-SSRS)(Posner et al 2011) during the initial 6 weeks of clinical follow-up after infusion.

Description of Subject Population

Sample #1

Specify subject population
Bipolar depression with moderate to severe suicidal ideation
Number of completers required to accomplish study aims
N=5
Projected number of subjects who will be enrolled to obtain required number of completers
10
Age range of subject population
18-65

Sample #2

Specify subject population
Healthy controls
Number of completers required to accomplish study aims
2
Projected number of subjects who will be enrolled to obtain required number of completers
4
Age range of subject population
18-65

Gender, Racial and Ethnic Breakdown

We expect the gender and ethnic breakdown to be consistent with the cumulative sample to date (N=16):

Male = 6 (37.5%)
Female = 10 (62.5%)

Hispanic = 1 (6%)
Non-Hispanic - 15 (94%)

White = 14 (88%)
Asian = 1 (6%)

Mixed race = 1 (6%)

Description of subject population

Patients
The goal is to recruit bipolar depressed patients with current Scale for Suicidal Ideation (SSI) score of 4 or greater, to result in a sample with, overall, moderate to severe suicidal ideation. Based on studies in our clinic, subjects come from the 5 boroughs of New York City and the nearby tri-state suburbs.

Healthy Controls
The two healthy control subjects will not have any Axis I diagnosis (specific phobia acceptable), borderline personality disorder, or antisocial personality disorder.

Recruitment Procedures

Describe settings where recruitment will occur
Patients are recruited through advertisements, clinician referrals, and hospital clinic, inpatient and emergency services.
How and by whom will subjects be approached and/or recruited?
Subjects will be approached/recruited by study research assistants, psychologists and psychiatrists.
How will the study be advertised/publicized?
Local media, internet, mailings to clinicians, outreach to the CPMC and other local emergency departments, clinical facilities, or relevant organizations. CUMC's research study search engine, RecruitMe, is one web-based tool that will be used.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
01944293

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
MIND umbrella protocol (IRB 4815) and screening protocol (IRB 5880R).

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Bipolar ketamine vs midazolam
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. Bipolar, major depressive episode, with 17-item HDRS score of 16 or greater. Patients may be psychiatric medication-free, or if on psychiatric medication, not responding adequately given current MDE with suicidal ideation (see 2).	DSMIV criteria by SCID-I administered by trained assessors; medication history; clinical evaluation; HDRS.
2. Moderate to severe suicidal ideation as indicated by Beck Scale for Suicidal Ideation (SSI) score of 4 or greater.	SSI scale, clinical assessment.
3. 18-65 years old	Interview
4. Patient must agree to voluntary admission to NYSPI inpatient research unit for infusion phase.	Interview, informed consent.
5. Female patients of child-bearing age must be willing to use an acceptable form of birth control during participation, such as condoms, diaphragm, oral contraceptive pills.	Interview, informed consent.
6. Must be co-enrolled in IRB#4815 (PI: Oquendo)	Informed consent.
7. Able to provide informed consent.	Interview
8. Subjects 61-65 years old must score 25 or higher on MMSE at screening.	Mini Mental State Exam

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. Unstable medical or neurological illness including baseline hypertension (BP $\geq$ 140/90) or significant history of cardiovascular illness.*	Baseline medical evaluation including blood pressure, heart rate, physical exam, routine labs, and electrocardiogram (ECG).
2. Significant ECG abnormality (e.g. ventricular tachycardia, evidence of ischemia, symptomatic bradycardia, unstable tachycardia, second degree or	Baseline ECG.

greater AV block).	
3. Pregnancy/lactation.	Baseline serum pregnancy test.
4. Current psychotic symptoms.	Clinical assessment and baseline SCID-I.
5. Contraindication to any study treatment.	Medical assessment and history.
6. Current or past ketamine abuse or dependence; any drug or alcohol dependence within past 6 months; suicidality only due to binge substance use or withdrawal.	Clinical assessment, SCID-I, urine drug screen.
7. Inadequate understanding of English.	Clinical assessment.
8. Prior ineffective trial of or adverse reaction to ketamine or midazolam.	Clinical assessment.
9. Opiate use greater than total daily dose of 20mg oxycodone or equivalent during the 3 days pre-infusion.	Clinical assessment and medical records.
10. A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of prior head trauma and score 1.5 standard deviations below the mean on Trail-making B will be excluded from study participation.	Clinical interview and medical history. Trail-making A & B, as needed.
11. Metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or interfere with the MR scan, according to the guidelines set forth in the following reference book commonly used by neuroradiologists: "Guide to MR procedures and metallic objects", F. G. Shellock, Lippincott Williams and Wilkins NY 2001. Additionally transdermal patches will be removed during the MRI study at the discretion of the investigator.	Interview, MRI Safety screening form
12. Claustrophobia significant enough to interfere with MRI scanning	Clinical interview
13. Weight over 350 lbs or inability to fit into MRI scanner.	Weight and maximal body

	circumference (if necessary) as part of physical exam; visit to MRI suite if necessary.**

*HIV is not an exclusion if the subject's depressive illness pre-dates HIV diagnosis, and the HIV is well-controlled as indicated by: 1) Undetectable viral load (plasma HIV-1 RNA level < 50 copies/mL) to be confirmed by lab result provided by potential subject and/or discussion between study staff and subject's HIV treatment provider; and 2) Potential subject has a normal finger-tapping test at screening evaluation.
**In cases where there is a question about whether a participant's dimensions are compatible with the MRI scanner, a subject's circumference may be measured to determine if the subject's circumference is less than the MRI scanner limit, 55cm. The subject also may be brought to the MRI center so that the MRI technologist can assess whether or not the subject will fit safely inside the MRI scanner. Metal screening and urine pregnancy testing will be done before this brief visit. Subjects who cannot safely enter the scanner will not be eligible to participate in the study and will be provided with referrals.

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Healthy Controls
Create or insert table to describe the inclusion criteria and methods to ascertain them

1. Absence of major psychiatric illness (specific phobia permissible), borderline personality disorder, and antisocial personality disorder.	DSMIV criteria by SCID-I and SCID-II administered by trained assessors; clinical evaluation.
2. 18-65 years old.	Interview
3. Female subjects of child-bearing age must be willing to use an acceptable form of birth control during participation, such as condoms, diaphragm, oral contraceptive pills.	Interview, informed consent.
4. Must be co-enrolled in IRB#4815 (PI: Sublette)	Informed consent
5. Able to provide informed consent.	Interview
6. Subjects 61-65 years old must score 25 or higher on MMSE at screening.	Mini Mental State Exam

Create or insert table to describe the exclusion criteria and methods to ascertain them

1. Unstable medical or neurological illness including	Baseline

baseline hypertension (BP ≥ 140/90) or significant history of cardiovascular illness.*	medical evaluation including blood pressure, heart rate, physical exam, and routine labs.
2. Pregnancy/lactation.	Baseline serum pregnancy test.
3. Inadequate understanding of English.	Clinical assessment.
4. A neurological disease or prior head trauma with evidence of cognitive impairment. Subjects who endorse a history of major head trauma and score 1.5 standard deviations below the mean on Trail-making B will be excluded from study participation.	Clinical interview and medical history. Trail-making A & B, as needed.
5. Metal implants or paramagnetic objects contained within the body (including heart pacemaker, shrapnel, or surgical prostheses) which may present a risk to the subject or interfere with the MRI scan, according to the guidelines set forth in the following reference book commonly used by neuroradiologists: "Guide to MR procedures and metallic objects", F. G. Shellock, Lippincott Williams and Wilkins NY 2001. Additionally transdermal patches will be removed during the MRI study at the discretion of the investigator.	Interview, MRI Safety screening form
6. Claustrophobia significant enough to interfere with MRI scanning	Clinical interview
7. Weight over 350 lbs or inability to fit into MRI scanner.	Weight and maximal body circumference (if necessary) as part of physical exam; visit to MRI suite if necessary.**

*HIV is not an exclusion if the HIV is well-controlled as indicated by: 1) Undetectable viral load (plasma HIV-1 RNA level < 50 copies/mL) to be confirmed by lab result provided by potential subject and/or discussion between study staff and subject's HIV treatment provider; and 2) Potential subject has a normal finger-tapping test at screening evaluation.
**In cases where there is a question about whether a participant's dimensions are compatible with the MRI scanner, a subject's circumference may be measured to determine if the subject's circumference is less than the MRI scanner limit, 55cm. The subject also may be brought to the MRI center so that the MRI technologist can assess whether or not the subject will fit safely inside the MRI scanner. Metal screening and urine pregnancy testing will be done before this brief visit. Subjects who cannot safely enter the scanner will not be eligible to participate in the study and will be provided with referrals.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
Yes
Indicate NYSPI IRB #
5880R, 4815
Describe Study Consent Procedures
a. Subject is given a detailed, verbal explanation of this study and IRB #5880R, 4815 and given a signed copy of all consent forms.
b. Subject gives written informed consent to participate in IRB #5880R, 4815 and this study.
c. Subject receives medical evaluation under 4815 and this study. Genetics blood sample is under IRB #4815 (Biological and neuropsychological measures for genetic studies of psychiatric populations—PI: Oquendo).
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

✓ Information Sheet

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Grunebaum, Michael, MD
Lan, Martin, MD
Miller, Jeffrey, MD
Sublette, M, MD
Type in the name(s) not found in the above list

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
No

Study Procedures

Describe the procedures required for this study
1. Screening
a. We will recruit inpatients or outpatients with bipolar disorder during a major depressive episode. We will also recruit two healthy control subjects who will not receive a ketamine infusion but who will only complete the two MRI scan procedures.
b. Subject completes phone screen, approved under IRB #5880R. If subject appears eligible based on the phone screen, they will be scheduled for an in-person screening visit under Screening Protocol IRB #5880R to determine whether inclusion/exclusion criteria (excluding medical screening) are met.
c. Subject is given a detailed, verbal explanation of this study and IRB #4815.
d. Subject gives written informed consent to participate in IRB #4815 and this study and is given a copy of both signed consent forms.
e. Subject receives medical evaluation under IRB 4815 and this study. Genetics blood sample is under IRB #4815 (Biological and neuropsychological measures for genetic studies of psychiatric populations—PI: Oquendo).
f. During the period between enrollment and the infusion, the treating physician will assess the patient weekly in person or by phone, including a Clinical Global Impression (CGI) scale. If concerns are noted during a telephone contact, subjects will be brought in for an in-person visit. If someone has a CGI-I >5 then a repeat CGI-I will be done within 3-4 days and if it remains >5 then the subject will be withdrawn; or 2) their CGI Improvement score is six or seven on one occasion and the treating psychiatrist

assesses that they cannot safely continue research participation. If after enrollment a subject refuses inpatient admission that is deemed clinically necessary by the research team they will be withdrawn from research.

2. Prior Psychiatric Medication

a . During the 72 hours before baseline MRI scans, PRN diphenhydramine, hydroxyzine, or quetiapine will be permitted for insomnia or anxiety. No zolpidem, benzodiazepine, or stimulant will be permitted during this time. Subjects who at enrollment are taking a benzodiazepine or stimulant will be tapered during the weeks between enrollment and the scan/infusion phase. We will monitor patients for signs of withdrawal, such as severe anxiety, diaphoresis, tachycardia
(HR greater than 100), or hypertension (BP greater than 140/90) and if such signs are present, or subjects cannot tolerate the taper, then the taper will be extended, if possible, or if not then the subject will be withdrawn from the protocol.
b. Current mood stabilizers, antipsychotic and antidepressant medications will be maintained at a stable dose during the 2 weeks prior to scanning/infusion. Minor dose adjustments may be made pre-infusion, such as to reduce side effects.

3. Actively Suicidal Patients

a. Patients with imminent (next few days) suicidal plan or intent will only be enrolled as inpatients. The independent inpatient treatment team must agree that study participation is clinically reasonable.
b. For patients who require hospitalization because of destabilization or suicidal risk, we will attempt to arrange admission to NYSPI. Hospitalized patients will be discharged from the hospital when stable as judged by the inpatient staff and the treating psychiatrist as not being in imminent risk of harm to self/other.
c. A research psychiatrist will be available by cellphone 24 hours a day, seven days a week. Patients requiring urgent admission will be brought to the CUMC Emergency Dept. by the study physician with security assistance, if needed. Non-emergent admissions will be arranged by the treating psychiatrist, if possible to NYSPI. Patients who are deemed to require hospitalization, but who refuse, will receive all necessary interventions such as contacting the local crisis team, family, or Emergency Medical Services.

4. Pre-Infusion Research Measures

a. Baseline clinical and neuropsychological ratings (See Figure 2, attached).
b. Saliva Cortisol: We will measure salivary cortisol using Salivettes (Sarstedt, Germany) at the following time-points for both the initial infusion and the optional open ketamine infusion: Time-Sensitive (within 72 hours pre-infusion) and 24 HR Post-Infusion Day (i.e., Day 1 Follow-Up). The samples will be collected fasting and before the patient has taken any medication that day. At each time point, patients will be asked to provide two samples, one immediately on waking in the morning and a second sample 30 minutes later. Samples will be processed in the Nathan Kline Institute laboratory of Thomas Cooper, M.A..

5. Inpatient Research Phase

a. To participate in the study, patients must agree to inpatient hospitalization at NYSPI (4-Center or 5-South units) for the MRI scans and infusion. The duration of the inpatient study phase will be 1-2 weeks. Our goal will be for the admission to be as short as possible, though participants will be offered

further inpatient treatment if clinically indicated. Patients will be evaluated by a research physician and the inpatient unit's independent clinical team and will be discharged when assessed, according to standard practice, as safe for outpatient treatment. Patients who need to be kept involuntarily for safety reasons will be withdrawn from research and treated clinically.
b. We will attempt to schedule the study infusion as close as possible to the date of enrollment, given time for screening lab results, inpatient admission and BSU and MRI scheduling.
c. MRI/fMRI Scan:
MRI scans will be performed at the New York State Psychiatric Institute MRI facility. Subjects will receive an array of structural and functional MRI scans lasting 60 minutes at baseline, within 48 hours prior to ketamine infusion, and the scans will be repeated within 48 hours post-infusion. For the two healthy control subjects who will not receive a ketamine infusion, the two MRI scans will be separated by a period of 48 to 96 hours. We will attempt to perform the follow-up MRI scanning session prior to initiating other treatments if possible. Structural scans will include T1-weighted images and DTI. Scans will include high-resolution imaging of the hippocampus. The procedure will be stopped if subjects exhibit significant distress.
Because this MRI scan is being performed for research purposes, it may not show problems that would normally be found in a typical clinical MRI scan ordered by a doctor for a specific medical problem. The T1-weighted and T2* echoplanar images acquired in this study, regardless of resolution of other image characteristics, do not, in general, yield adequate information for a clinical quality read. However, for the baseline MRI scan, gross structural abnormalities such as the presence of mass effects or hydrocephalus will be examined and documented by an appropriately qualified radiologist. Upon request, results will be shared with research subjects or a physician designated by them. When there is evidence of a mass lesion, hydrocephalus or other significant abnormality, a qualified clinician will call the subject and then a letter will be sent, depending on the urgency, and at the discretion of the investigator and neuroradiologist.

d. All patients will be NPO after midnight prior to study infusion and will be escorted by study staff to and from the BSU where the infusion will occur.
e. For subjects currently taking psychiatric medication, we will give advance notice of infusion scheduling to anesthesiologist consultant, Dr. Moitra, to confirm his or a back-up anesthesiologist's availability for phone consultation during the infusion, if needed.
f. Pre-infusion blood level of BDNF will be measured by drawing a blood sample through the iv site. This will be analyzed in the NKI lab of Tom Cooper.

8. Ketamine Infusion
a. The infusion medication will be prepared by the NYSPI research pharmacy.
Patients will receive an open-label intravenous infusion of saline solution with ketamine hydrochloride (0.5 mg/kg; Abbott Laboratories, North Chicago, IL) over the course of approximately 40 minutes in the BSU of NYSPI with continuous monitoring of the subject by a study physician.

b. Vital Signs Monitoring: During study infusion(s), blood pressure, heart rate, respiratory rate, and oxygen saturation will be monitored as follows:
i. -5 minutes
ii. 0 (start of infusion)
iii. Post start of infusion: 5, 10, 15, 20, 25, 30, 35, and 40 minutes (end of infusion)

iv. Post end of infusion: Blood pressure will continue to be obtained until there are two measurements at least 15 minutes apart that are within 10 mmHg of the baseline diastolic blood pressure or diastolic blood pressure is below 85. Respiratory rate and oxygen saturation will continue to be obtained until there are two measurements at least 15 minutes apart that are within normal limits (RR of 10 or greater; 0xygen saturation of 94% or greater). Immediate post-infusion ratings, including suicidal ideation assessment, are done by the physician.

c. The physician and Research Assistant who remain in the patient's room during the infusion record the vital signs. After the subject is transferred back to their inpatient unit, the blood pressure and heart rate will be obtained manually by the unit nursing staff.

d. Intervention for Hypertension: If the systolic blood pressure increases to ≥ 200 or diastolic blood pressure increases to ≥115 mmHg during the ketamine infusion, the infusion will be discontinued. The blood pressure will be monitored and if there is no decrease after 15 minutes, then:
1) One dose of sublingual nitroglycerine, 0.3 mg, will be administered.
2) If there is no response within 10 minutes, clonidine 0.1 mg po will be administered every 30 minutes (total maximum dose 0.6 mg clonidine) until the desired blood pressure is reached. Desired blood pressure is defined as within normal range or 10 mmHg of baseline diastolic reading.
3) If high blood pressure is symptomatic, i.e., blurred vision, headache, chest pain, the subject will be transferred to the ER. If they do not respond to the above treatment (d.) then they will be transferred to the ER.

e. Intervention for Decreased Oxygen Saturation or Respiratory Rate:
1) If 02 saturation is <94%, the patient will be given oxygen via nasal canula; then if 02 saturation returns to ≥94%, the infusion will be continued. If 02 saturation remains <94% with nasal canula oxygen, then the infusion will be stopped, the anesthesiologist called, and if necessary the patient will be transferred to the ER.

9. Post-Infusion Lab Tests
a. BDNF, ketamine and norketamine levels will be measured by drawing blood samples with a blood-draw separate from the iv site. These will be analyzed in the NKI lab of Tom Cooper.
b. Post-infusion saliva cortisol: Same procedure as Pre-Infusion (4b above).

10. Post-Infusion Treatment
a. After the post-infusion MRI scan and related research measures are completed, all patients will receive open clinical treatment. Patients will be offered a total of 6 months treatment including inpatient and outpatient phases. During open clinical treatment, medication will be changed for those patients who don't respond or whose response is transient.
b. Follow-up clinical research ratings will be done for the first 6 weeks of post-infusion treatment.
c. Continuation appointments will be weekly for six weeks, then decreasing to

at least monthly, as clinically indicated, for the remainder of the six months.
d. In all follow-up treatments, psychiatrists will be available to patients between sessions for consultations and emergencies (a research psychiatrist is on-call at all times). Thus, clinical management will provide careful assessment of the patient's clinical condition to determine clinical changes, safety, and the need for withdrawal from the protocol. Psychiatrists will evaluate mood, suicidality, and treatment course to help determine if a patient's condition warrants removal from the study. Independent, masters or PhD level, raters will systematically assess suicidal ideation and/or behavior and depression weekly during the 6-week continuation phase for exploratory analysis.
f. At the end of the 6 months of treatment patients will be referred for ongoing care.

11. Outcome Measures: See Figure 2, Schedule of Research Procedures and Assessments (attached).

12. Safety Follow-up for Ketamine Abuse/Use:
a. At 3 and 6 months post-ketamine/midazolam, all patients we can contact will be evaluated to determine the absence of post-exposure ketamine use/abuse.
You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation
Criteria for Early Discontinuation
13. Withdrawal from Study: Subjects will be withdrawn from the study if:
a. They request it for any reason.
b. The PI judges that it is medically unwise to continue in the study, for example if the subjects are unable to comply with the study procedures.
c. They are unable to tolerate the delay to treatment because of pronounced worsening of symptoms such as marked agitation, mania, or psychotic symptoms. Worsening of suicidal ideation will not automatically require discontinuation from research, since this is the primary study aim, as long as the team judges that the patient can be managed safely as an outpatient (e.g. they have no plan or intent), or they agree to inpatient treatment and the inpatient staff agrees that the patient may continue research participation.
d. A rise in systolic blood pressure ≥ 200 mm Hg or diastolic blood pressure to ≥ 115 mm Hg during the infusion.
e. During infusion, if oxygen saturation remains <94% with nasal canula oxygen or respiratory rate <10, then patient will be withdrawn from research and treated clinically as described in Section 8.e.
f. Inability to tolerate MRI scanning.
g. Other criteria for discontinuation will be appearance of psychosis, mania, severe agitation, or other deterioration where the treating physician decides that research participation is unacceptable.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Patients

Sample	Timepoint	Total Collected Per Patient
Blood	Baseline Pre and Post-infusion	59 ml 32 ml total (64 ml if two infusions)
Saliva	Pre-infusion (2 samples) Post-infusion (2 samples)	1ml per sample = Total 4 ml

Healthy Controls

Sample	Timepoint	Total Collected Per Subject
Blood	Baseline screen	59 ml

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Informed consent
IRB approved form (30-45 min)
Diagnosis
SCID I, II (1-2 hrs)
Demographics
Division Baseline Demographic form (BDEMO) (30 min)
Clinical State
24-item Hamilton Depression Rating Scale (HDRS) (15-20 min)
Beck Depression Inventory (BDI) (5 min)
Profile of Mood States (POMS) (10 min)
Global Assessment Score (GAS) (1 min)
Anxiety Visual Analog Scale (5 min)
Clinical Global Impressions (CGI) (1 min)
Young Mania Rating Scale (YMRS) (10 min)
Suicidal Ideation and behavior
Columbia Suicide History (CSH) and Lethality Rating Scale (LRS) (up to 20 min)
Beck Scale for Suicidal Ideation (SSI) (10 min)
Columbia Suicide Severity Rating Scale (C-SSRS) (10 min)
Beck Suicide Intent Scale (SIS) (10 min)
Brown Goodwin Aggression Inventory (BGAI) (up to 20 min)
Life Events

St. Paul Ramsey scale (SPR) (15 min)
Axis IV (5 min)
Medication
Antidepressant Treatment History Form (ATHF) (20 min)
Systematic Assessment for Treatment Emergent Events-General Inquiry (SAFTEE) (10 min)
Clinician-Administered Dissociative States Scale (CADSS) (15 min)
Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale only (10 min)
Biomarkers
Saliva cortisol (10 min)
Neuropsychological tests (60 min at Baseline and 60 min on Day 1 post-infusion):
- WAIS-III Vocabulary (pre-infusion only)
- WAIS-III Digit Symbol
- Letter and Category Fluency
- Buschke Selective Reminding Test
- Computerized Choice Reaction Time
- Computerized CPT
- Computerized Stroop Task
- Computerized A, Not B
- Computerized Go-No Go Task
- Computerized Fish/Face Task
- Cambridge Gambling Task
- Implicit Associations Task (Suicide version)

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
1

Drug #1

Name of the drug
Ketamine
Manufacturer and other information
Multiple generic manufacturers.
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
This is a clinical study involving a marketed drug and the study meets all of the following

conditions:
1. It is not intended to be reported to the FDA in support of a new indication for use or to support any other significant change in the labeling; and
2. It is not intended to support a significant change in the advertising for the product; and
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; and
4. It is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 50 and 56 respectively]; and
5. It is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
Patients will continue their current psychiatric medication (as described in Procedures). The delay to inpatient admission will generally not exceed 2 weeks**;** if a subject needs a longer delay between consent and beginning treatment it will be determined by the study clinician on a case-by-case basis based on need for delay, clinical stability, and ability to comply with the plan for monitoring**.** This period allows the time required for processing lab samples, completion of baseline research measures, and scheduling inpatient admission, MRI scans, and the infusion procedure in the BSU. We will attempt to minimize this delay. During this time the treating physician will contact the participant to assess their clinical condition weekly, either in person or via phone, including the Clinical Global Impressions (CGI) scale. If items of concern are noted during a telephone contact, the participant will be brought in for an in-person visit. If someone has a CGI-I >5 then a repeat CGI-I will be done within 3-4 days and if it remains >5 then the subject will be withdrawn from research and start clinical treatment. Additionally, if the team judges that this delay is not clinically acceptable or the participant does not agree to the delay, then the patient will be withdrawn from research.
Maximum duration of delay to standard care or treatment of known efficacy

For subjects not already taking medication for bipolar disorder, treatment with standard medication will begin on the day after the post-infusion MRI scan. This may add approximately 3-5 inpatient days to the delay described above, depending on MRI and infusion scheduling, since patients will usually be admitted to NYSPI a day or two before the baseline MRI scan. This delay may be slightly longer if a patient needs or wants to be admitted further in advance of the infusion.

Treatment to be provided at the end of the study
Described in Procedures (Section 10) above.

Clinical Treatment Alternatives

Clinical treatment alternatives
This is a pilot study to test feasibility and potential neural correlates of MRI scans before and after a sub-anesthetic ketamine infusion in patients with bipolar depression and suicidal thoughts. Various treatments for bipolar depression exist, such as numerous approved antidepressant medications, ECT, and various psychotherapies. Relatively little is known about best practices for more suicidal depressed bipolar patients, or regarding the antidepressant mechanism of ketamine.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Potential Risks to Subjects and Procedures for Minimizing Risks:
Risks associated with participation in this study are related to 1) side effects of ketamine; 2) other medication related risks; 3) intravenous catheter; 4) blood drawing; 5) pregnancy; 6) MRI Scanning. We have experience with this ketamine dose in our ongoing trial in unipolar depression (IRB 6598). The latter study's consultant, Dr. Vivek Moitra, MD, Associate Clinical Professor of Anesthesiology, Associate Medical Director Surgical Intensive Care Unit, Associate Program Director, Critical Care Medicine Fellowship, Division of Critical Care, Columbia University College of Physicians and Surgeons, is experienced with ketamine and is a consultant on this study also.

1. Side effects of medications:

1.A. Side Effects of Intravenous Ketamine.
i) Medical Risks. Administration of sub-anesthetic doses of ketamine i.v., such as the 0.5 mg/kg dose to be used in this study, may induce a modest rise in blood pressure. We have administered sub-anesthetic doses of ketamine i.v. (0.5mg/kg over 40 minutes) in the setting of a brain imaging protocol at this institution (IRB #5786, PI: J. Mann). The resulting effects on vital signs for the eleven patients scanned under protocol #5786 are presented as a function of time in Table 1 below for the duration of the ketamine injection. These modest increases all peaked and largely resolved by 75 minutes, with vitals returning to near baseline.

Table 1. Effects of ketamine on systolic and diastolic blood pressure in a group of patients (n=11). The dose of ketamine was 0.5 mg/kg given over 40 minutes.

Time (min)	Systolic BP during Ketamine (mm Hg)	Diastolic BP during Ketamine (mm Hg)	Pulse during Ketamine
0	111	70	69
5	113	72	63
10	116	73	69
15	116	73	72

20	121	75	68
25	121	78	73
30	120	77	72
35	124	78	73
40	122	78	79
45	122	78	74
50	116	75	73
55	121	76	74
60	123	76	75
65	124	79	75
70	121	81	76
75	114	75	76

2. MRI and fMRI Scan
The MRI scanner uses a large magnet (3 Tesla) to take pictures of the brain and is not associated with any known medical risks, except for persons who have a heart pacemaker, or have metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to notify us if this is the case. The long-term effects of being placed in a magnet of 3T are unknown. There is also the risk of burns from medicinal patches during the MRI; therefore, subjects will be asked to remove any patches prior to the scanning session. Some people have reported sensations during the
MRI scan, such as "tingling" or "twitching" (or, very rarely, a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in the body. Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner's small space. Despite these experiences, in our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped. The MRI scan is not painful, but having to lie still in the enclosed space of the scanning table is uncomfortable for some people.

c. Pregnancy
Although there are no known risks associated with pregnancy, we will not scan someone who is known to be pregnant.

Describe procedures for minimizing risks
Describe procedures for minimizing risks
ii) Specific measures and precautions
Any medical risks from increased blood pressure will be minimized through the careful screening of potential subjects. Subjects will be excluded for baseline hypertension or history of cardiovascular illness. A physician, Dr. Michael Grunebaum (ACLS certified 05/22/2012; copy of certification attached), will be present during the procedure. If physician coverage for Dr. Grunebaum is needed (such as vacation), then another ACLS-certified MIND physician (Drs. Matthew Milak or Martin Lan), who has been trained in the infusion procedure, will be present.

Procedures for hypertension that occurs during the infusion are described above under Study Procedures. Nausea and vomiting will be treated supportively and, if severe, with anti-emetic agents; if necessary, administration of ketamine will be discontinued. Subject will be informed that they should be fasting (12 hours no food, 4 hours no liquids) prior to the ketamine infusion. For these reasons, the medical risks involved in participation in this study will be minimized.

iii) Psychiatric or Behavioral Risks. Ketamine is an FDA-approved dissociative anesthetic. Ketamine exposure at the sub-anesthetic dose to be used in this study can be associated with a moderate dissociative state, which is well tolerated in the majority of cases and is spontaneously reversible (10). There is extensive clinical experience with ketamine used at anesthetic doses, and no long-term detrimental effects of ketamine exposure have been reported. It is possible that ketamine administration will increase the risk of psychosis, even in normal subjects. Ketamine is a street drug of abuse. As such, it poses the risk that exposure during this study may predispose subjects to subsequent abuse of this drug. To minimize this risk, current drug or alcohol dependence or any history of ketamine abuse or dependence will be excluded. We will follow patients while they are receiving clinical treatment and review any evidence of abuse that may appear after the ketamine infusion. This dose of ketamine has been safely administered in similar settings to N=27 depressed bipolar patients without any serious adverse events (1, 2). Subjects will be informed that immediate effects of the infusion may be unpleasant and they may feel worse.

iv) Specific measures and precautions
The experiment will be carried out in the presence of at least one psychiatrist. Severe agitation, hyperarousal, or psychosis will be treated with benzodiazepine (lorazepam) or neuroleptics, as indicated. The risks of exposing subjects to a drug of abuse potential will be minimized by explaining this risk to prospective subjects, and by excluding from the study any subjects with documented or suspected current substance or alcohol dependence. Immediate post-infusion ratings will include safety questions about suicidal ideation**.**

2.A.3. Side Effects of Other Medications
Diphenhydramine, hydroxyzine: The potential side effects are dizziness, drowsiness, a drugged feeling, and dry mouth.

2.B. Other medication related risks:
Benzodiazepine/Stimulant taper: As described under Study Procedures, During the 72 hours before baseline MRI scans, PRN diphenhydramine, hydroxyzine, or quetiapine will be permitted for insomnia or anxiety. No zolpidem, benzodiazepine, or stimulant will be permitted during this time. Subjects who at enrollment are taking a benzodiazepine or stimulant will be tapered during the weeks between enrollment and the scan/infusion phase. We will monitor patients for signs of withdrawal, such as severe anxiety, diaphoresis, tachycardia (HR greater than 100), or hypertension (BP greater than 140/90) and if such signs are present, or subjects cannot tolerate the taper, or feel a need for an adjustment, then the taper will be extended or the subject can be withdrawn from the protocol.
Fixed Dose: Current mood stabilizers, antipsychotic and antidepressant medications will be maintained at a stable dose during the 2 weeks prior to scanning/infusion. Minor dose adjustments may be made pre-infusion, such as to reduce side effects. If a subject feels they need an adjustment, they can be withdrawn from the protocol.

Delay to Treatment: We will schedule the scans and infusion as soon as possible. Patients on psychotropic medications may continue them as described in Procedures. Patients may experience worsening of their depressive symptoms during this period and this will be discussed with all subjects as part of the consent process.
Non-response: There is a chance that the medications and/or dosages used in this study will not be helpful or that a participant may feel worse during participation in the study. Participants will be encouraged to tell their doctor if they feel worse during the study.

Other Risks Associated with Antidepressant Use:
The Food and Drug Administration (FDA) has issued a public health advisory concerning a possible link between worsening depression, and, in rare cases, suicidal thoughts or behavior in adults younger than 25 years of age treated with certain antidepressant medications (including those in this study). This FDA advisory will be discussed with all subjects as part of the consent process.

2.C. Risks from Intravenous Catheters. There is a small risk of infection and bleeding associated with intravenous catheters, which are prevented by proper techniques. Placement of IVs will be by a physician, nurse, or technician trained and certified in aseptic technique for catheter placement to minimize this risk.

2.D. Blood Drawing: The risks associated with drawing blood are slight discomfort and occasional bruising. There is no risk of anemia in a physically healthy person with the amounts of blood drawn in this study.

2.E. Interviews: Psychiatric interviews and neuropsychological testing can sometimes be stressful, but some people find talking to a physician or psychologist helpful. The interviewers will all be experienced personnel. The research team may request permission to record the interview for teaching purposes with audiotape and/or videotape. In this event, a separate consent process will occur for this.

2.F. Saliva sampling: This procedure has no significant risks other than minor inconvenience.

2.G. Pregnancy: Pregnancy is one of the study's exclusion criteria and will be ascertained at screening with a pregnancy test. Patients must agree at the time of consent to use an effective form of birth control and to inform the treating psychiatrist in the event of pregnancy while in the study. A pregnancy test will be repeated within 24 hours pre-infusion. If a patient becomes pregnant during the study, they will be withdrawn from research and treated clinically.

2. H. Electrocardiogram
An electrocardiogram has no serious risks. On rare occasions a rash may develop where the electrodes are placed which usually resolves without treatment.

3. Data and Safety Monitoring Plan: The Principal Investigator will be responsible for monitoring the safety and sound clinical care of all study participants through a weekly team meeting and as needed.

3.a. Adverse events. Serious adverse events will be reported per regulatory requirements. Other adverse events will be monitored using the SAFTEE-GI (17) and a weekly meeting of the research team.

3.b. Data and Safety Monitoring Board

i) Membership: The Data Safety Monitoring Board (DSMB) that is already in place for our ongoing ketamine/midazolam study in unipolar depression (IRB 6598) will also monitor the add-on study described in this protocol. The three DSMB members are experienced researchers from other institutions.

ii) Responsibilities: Throughout the study, notification of any Serious Adverse Events (SAEs) as well as any investigator-initiated changes in the protocol will be submitted to the DSMB when they are submitted to the IRB. Based on its review of the protocol, the DSMB will identify the data parameters and format of the information to be regularly reported. The DSMB may at any time request additional information from the Principal Investigator. The DSMB may monitor study charts or delegate this task to the personnel of the New York State Psychiatric Institute IRB.
Other than SAEs, adverse events will be tabulated and submitted to the IRB and DSMB annually. SAEs are also reviewed by the Incident Review Committee of the New York State Psychiatric Institute. The DSMB will initially be given data blinded to treatment status but may request unblinding if there is a safety concern.
Based on review of safety data, the DSMB will make recommendations concerning the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed.
iii) DSMB Meetings will be on a semi-annual basis but can be more frequent as indicated.
Meetings:
iv) Reports: The discussions and decisions of the DSMB will be summarized in written reports and provided to the NIMH Program Officer in annual reports.
v) HIPAA Procedures: This grant will go through Columbia University and will be conducted at the New York State Psychiatric Institute and Columbia University Medical Center. All HIPAA requirements will be followed including forms for patients to sign and receive a copy to keep as part of the informed consent process.

4. Discomfort during MRI scanning

Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the scanner if requested. Our research staff will be present at all times, and a staff psychologist or psychiatrist will be available at all times. If subjects experience significant anxiety or claustrophobia, we will offer them the option of administering a short-acting benzodiazepine, and performing only structural and DTI scans. If subjects do not complete fMRI tasks due to anxiety/claustrophobia, they may perform these tasks on a computer outside of the scanner.

Pregnancy:

Women of child-bearing age will be required to have a pregnancy test administered after enrolling in the study as well as on the day of each MRI scan prior to scanning, and within 24 hours of the ketamine infusion. In addition, nursing mothers will also be excluded from the study.

Methods to Protect Confidentiality

Describe methods to protect confidentiality
Records will be kept in locked storage and access will be allowed only to members of the research team or institutional personnel as part of a routine audit. Research records, like other medical and clinical records, will be kept confidential to the extent permitted by law. Once a patient enrolls in the project they are given a code number for all subsequent computer data and/or lab forms. The code list and patient names as well as all data are kept in locked offices with access limited to those directly responsible for maintenance of these files by the research team. The data capture system we will use in this study, StudyTRAX, has been used as a data repository for NIH sponsored projects at NYSPI and is HIPAA compliant. Data sets are de-identified as defined in HIPAA 45 C.F.R. §164.514 (b)(2).
Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
Subjects will receive a complete medical, neurological and psychiatric evaluation, results of which will be communicated to them. Subjects are not expected to benefit directly from participation in this study, however, patients will be offered a total of six months of medication based treatment for depression.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
We will give patients a modest inconvenience payment of $20 cash for each outpatient visit at which research data are collected, which we believe will not be coercive but will help recruitment and decrease attrition. Patients will not receive payment for research assessments, MRI scans or procedures during the inpatient stay. Healthy controls will be compensated with $75 for completing the first MRI scan and $125 for completing the second MRI scan. Compensation for the second scan is higher to incentivize completion of both scans, which is necessary for the data to be of use.

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References

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Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of unbolded Information Sheet(s)
Upload copy(ies) of bolded Information Sheet(s)
Upload copy(ies) of recruitment materials/ads to be reviewed
Upload copy(ies) of the HIPAA form
IRB_HIPAA_Form_6785_10-6-16.pdf
Upload any additional documents that may be related to this study

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 6785 **Principal Investigator:** Michael F. Grunebaum, MD

Name of Study: Ketamine in bipolar depression

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form**.**

1. The Health Information that may be used and/or disclosed for this Research includes:

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**
☑ Researchers and their staff at the following organizations involved with this Research:
Columbia University Medical Center

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. Please note that:

- You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

  Michael Grunebaum, MD, New York State Psychiatric Institute, 1051 Riverside Drive, Box 42, New York, NY 10032

- While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. This Authorization does not have an end date.

6. You will be given a copy of this form after you have signed it.

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**