

New York State Psychiatric Institute
Institutional Review Board

June 23, 2015

To: Dr. Michael Grunebaum
From: Dr. Edward Nunes, Co-Chairman
Dr. Laurence Greenhill, Co-Chairman
Subject: Approval Notice: CONTINUATION

Your protocol # **6785** entitled: **KETAMINE VS MIDAZOLAM IN BIPOLAR DEPRESSION (ADD-ON TO # 6598)** Protocol version date 06/23/2015 and consent forms have been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **July 08, 2015 to July 07, 2016**. (Reviewed at the Full Board meeting on June 15, 2015.)

Consent requirements:

- Not applicable:
- 45CFR46.117 (c)(2) waiver of documentation of consent for the telephone interview
- ✓ 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.

Cc: CU Business Office (NARSAD); CUMC IRB

Encl: CF, recruitment materials, HIPAA

EN/LG/alw

Protocol Title:
**Ketamine vs midazolam in bipolar
depression (Add-on to # 6598)**

Version Date:
06/23/2015

Protocol Number:
6785

First Approval:
07/31/2013

Clinic:
MIND Clinic

Expiration Date:
07/07/2015

Principal Investigator:
Michael Grunebaum, MD
Email: mfg14@columbia.edu
Telephone: 646-774-7573

Research Chief:
J. John Mann, MD

Cover Sheet

Choose from the following that is applicable to your study

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:

Subject enrollment is ongoing.

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 occurring 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 occurred in the past year)?

Yes

Please describe them and indicate resultant protocol modifications made.

Subject 32003: 55yo man with Bipolar I enrolled in study 3/25/14, had infusion 4/17/14 with positive response, then in open psychopharmacological treatment in MIND clinic plus day program. At most recent appointment 6/30/14, had been euthymic for several weeks on lithium, venlafaxine, mirtazapine, lurasidone, clonazepam, zolpidem. MIND doctor received call 7/11 that Pt had admitted self to NYPH-Westchester with worsening depression/suicidal thoughts. Pt had history of two suicide attempts and many past hospitalizations with similar presentation prior to study. SAE was reported to IRB which reviewed as NFAI.

32003 (same subject): 8/3/14 subject admitted self to NYPH-Westchester with depression/suicidal thoughts after death of girlfriend. SAE reported and IRB reviewed as NFAI.

32003 (same subject): 10/15/14 subject admitted self to NYPH-Westchester with increased depression/suicidal thoughts. SAE reported and IRB reviewed as NFAI.

Subject 32001: 35 year old woman with bipolar disorder, treatment resistant depression, and chronic suicidal thoughts, enrolled 1/13/15, had study infusion 1/27/15. On 1/28, she was a non-responder and un-blinding showed she had received ketamine. After discussion with her private psychiatrist, open clinical treatment was initiated by adding venlafaxine 37.5mg to her regimen (lithium 1200mg, quetiapine 400mg). Venlafaxine was titrated to 225mg without mixed or manic symptoms as of her 2/25 visit. During first week of March, Pt developed mixed symptoms and increased suicidal ideation. I arranged for re-admission to NYSPI, but she chose admission to NYH-Westchester, which occurred 3/4/15. IRB reviewed SAE report and replied NFAI.

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

30

Total number of participants enrolled to date

16

Number of participants who have completed the study to date

13

Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?

No

Comments / additional information

Numbers of participants:

16 enrolled to date

13 completed study procedures

2 in open treatment

1 had randomized infusion on 6/18/15; to enter open treatment

(13+2+1=16)

Sample Demographics

Specify population

Bipolar depression with moderate to severe suicidal ideation

Total number of participants enrolled from this population to date

16

Gender and Ethnic Breakdown

10 Female; 6 Male

1 Hispanic; 15 Non-Hispanic

12 White

1 Black

1 Asian

2 Other

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year

10

Number of participants currently enrolled

3

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
- ✓ Off-label Use of Drug or Device
- ✓ Somatic Treatment or Intervention

Population

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

- ✓ Adults
- ✓ Adults over 50
- ✓ Inpatients

Research Support/Funding

Will an existing internal account be used to support the project?

No

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**

We are conducting an NIMH-funded clinical trial in suicidal, depressed patients to test random assignment to intravenous infusion of ketamine or midazolam control followed by continuation treatment (IRB 6598). Here, we propose a pilot feasibility study to use essentially the same protocol in a sample of patients with bipolar disorder. The primary goal is to test the effectiveness of ketamine at reducing suicidal thoughts in patients with bipolar depression. Midazolam, the similarly sedative control medication, is not known to reduce depression or suicidal thoughts. We will also explore cognitive correlates as well as systematic, state of the art assessment of suicidal ideation and behavior during follow-up.

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 presents 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 propose

a 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 test its antisuicidal effects in a randomized, double-blind, pilot feasibility trial in a higher risk sample of depressed BD patients with moderate to severe suicidal ideation. We will use midazolam as control medication. We will follow a very similar protocol to our IRB-approved unipolar depression study (NYSPI IRB#6598).

Specific Aims and Hypotheses

Specific Aims and Hypotheses

PRIMARY AIM: The primary study aim will be to compare the effect of iv ketamine vs. midazolam infusion on suicidal ideation in a double-blind RCT in Bipolar Disorder during a major depressive episode with moderate to severe suicidal ideation. Unless contraindicated, patients will continue their current psychotropic medication and will be randomized to iv ketamine (0.5mg/kg) or midazolam (0.02mg/kg) 40-minute infusion. We hypothesize that ketamine will produce greater improvement in suicidal ideation compared to midazolam at 24 hours after infusion.

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=16

Projected number of subjects who will be enrolled to obtain required number of completers

30

Age range of subject population

18-65

Gender and Ethnic Breakdown

We expect the following gender and ethnic breakdown: Male (40%); Female (60%); White (67%); Black (24%); Hispanic (16%); Asian (9%).

Description of subject population

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.

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.

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	Interview, informed consent.

control during participation, such as condoms, diaphragm, oral contraceptive pills.

- | | |
|---|------------------------|
| 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 > 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 greater AV block). | Baseline ECG. |
| 3. Pregnancy/lactation. | Baseline urine 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 diagnosis of sleep apnea. | Clinical assessment and |

medical records.

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

- Subject is given a detailed, verbal explanation of this study and IRB #5880R, 4815 and given a signed copy of all consent forms.
- Subject gives written informed consent to participate in IRB #5880R, 4815 and this study.
- 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

Milak, Matthew, MD

Sublette, M, MD

Type in the name(s) not found in the above list

Martin Lan, MD, PhD

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.
- 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 . For insomnia or anxiety, PRN diphenhydramine, hydroxyzine, zolpidem, or a benzodiazepine will be permitted. The goal will be a maximum **total** daily dose of lorazepam 2mg (**or equivalent other benzodiazepine**) during the week pre-infusion. **No zolpidem or benzodiazepine** will be permitted during the 24 hours pre-infusion. Subjects who at enrollment are taking a higher benzodiazepine dose will be tapered during the pre- infusion week to the above maximum daily dose. Subjects who show signs of benzodiazepine withdrawal or cannot tolerate the 24-hours pre-infusion without zolpidem or benzodiazepine will be withdrawn from the protocol.

b. Current psychiatric medications other than benzodiazepines will be maintained at a stable dose until post-infusion treatment. 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. Randomization

- a. Patients will be assigned randomly to one of the two treatment conditions: ketamine or midazolam.
- b. Randomization will be stratified on two variables: 1) According to time-sensitive pre-infusion Scale for Suicidal Ideation (SSI) score of below 8 vs. 8 or above; and 2) According to whether the subject is currently taking psychiatric medication or not.
- c. The infusion medication will be prepared by the NYSPI research pharmacy.
- d. Codes linking patient numbers to treatment assignment will be sealed and kept under

lock-and-key for all study patients.

6. Blinding

- a. The patient, study psychiatrist, and assessors will be blind to infusion allocation.
- b. An un-blinded pharmacist, who is not part of the research team, will dispense the infusion treatments.
- c. To test adequacy of the blind, after completion of post-infusion research assessments, all subjects and research personnel will each complete a brief questionnaire asking them to guess subjects' infusion group status.
- d. Infusion responders will be informed by the pharmacy via a letter which infusion they received at the end of their 6-month participation in our clinic or when they stop treatment in our clinic, whichever comes first. Infusion non-responders will be informed which infusion they received after research measures are complete on the post-infusion day. The

DSMB may request unblinded data as needed.

7. Inpatient Infusion Phase

- a. To participate in the study, patients must agree to inpatient hospitalization at NYSPI (4-Center or 5-South units) for the infusion. Our goal will be for the admission to be as short as possible, approximately 3-5 days, or more 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 scheduling.
- c. 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.

d. No zolpidem or benzodiazepine will be permitted in the 24 hours pre-infusion. 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 then the infusion will be canceled and benzodiazepine restarted.

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. Blinded Ketamine/Midazolam Infusion

a. Dose:

i) Patients randomized to ketamine will receive an 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.

OR

ii) Patients randomized to midazolam will receive an intravenous infusion of saline solution with midazolam (0.02 mg/kg) over 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; Oxygen

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 O₂ saturation is $<94\%$, the patient will be given oxygen via nasal canula; then if O₂ saturation returns to $\geq 94\%$, the infusion will be continued. If O₂ saturation remains $<94\%$ with nasal canula oxygen, then the infusion will be stopped, the anesthesiologist called, the blind broken, and if the infusion drug was midazolam then the patient will be given flumazenil unless the anesthesiologist recommends other treatment.
- 2) If respiratory rate is <10 , the infusion will be stopped, the anesthesiologist called, the blind broken, and if the infusion drug was midazolam then the patient will be given flumazenil unless the anesthesiologist recommends other treatment.
- 3) If the patient does not respond to the above treatment, they 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 Day 01 post-infusion research measures are completed, all subjects 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. Non-responders: For patients who are non-responders at 24 Hrs Post-Infusion (Day 01), the blind will be broken after Day 01 post-infusion research measures are complete. Non-responders who received midazolam will be offered an optional open-label ketamine infusion, following the

same procedure as above. **Neuropsychological testing will be repeated on Day 01 after the open-label ketamine infusion, during the inpatient stay. Non-responders who opt for the open ketamine infusion will start the continuation phase after it.**

d. Continuation appointments will be weekly for six weeks, then decreasing to

at least monthly, as clinically indicated, for the remainder of the six months.

e. 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 subjects 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. 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

Sample	Timepoint	Total Collected Per Patient
Blood	Baseline	59 ml
	Pre and Post-infusion	32 ml total (64 ml if two infusions)

Saliva	Pre-infusion (2 samples)	1ml per sample = Total 4 ml
	Post-infusion (2 samples)	

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)

Adequacy of blind questionnaire (1 min)

Biomarkers

Neuropsychological testing (120 min)

Salivary cortisol (10 min)

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

2

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 two marketed drugs 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].

Drug #2

Name of the drug

midazolam

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 two marketed drugs 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. The delay to inpatient admission will 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 and the infusion procedure in the BSU. We will attempt to minimize this delay. During this time the treating physician will stay in contact with the participant and 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 plus supportive clinical management will begin on the day after the ketamine/midazolam infusion, after 24-hour research assessments are completed. This adds approximately 1-2 days to the delay described above since patients are usually admitted to NYSPI a day or two before the infusion. This delay may be slightly longer if a patient needs or wants to be admitted farther in advance of the infusion. Non-responders who received midazolam and who choose to receive a clinical ketamine infusion prior to beginning standard clinical treatment will have an additional delay of a few days for BSU scheduling, which we will try to minimize.

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 study of sub-anesthetic ketamine's effect on suicidal ideation in depressed patients with bipolar disorder, with midazolam as an active control. 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.

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 the medications; 2) other medication related risks; 3) intravenous catheters; 4) blood drawing; and 5) pregnancy. 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 both ketamine and midazolam, and will be 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

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. In case of severe agitation, hyperarousal, or psychosis, the blind will be broken. If the patient received ketamine, they will be treated with benzodiazepine (lorazepam) or neuroleptics, as indicated (see below for midazolam). 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 the Beck Scale of Suicidal Ideation.

2.A.2. Side Effects of Intravenous Midazolam

Midazolam is an imidazobenzodiazepine derivative in common use as a sedative and, like ketamine, anesthetic induction agent, including for routine outpatient procedures such as colonoscopy (11-13). It is the control medication at the same dose in our ongoing study IRB 6598.

i) Medical Risks.

a. Midazolam has anxiolytic, hypnotic, muscle relaxant, and antegrade amnesic effects (11-13). Midazolam is not known to have direct effects on glutamate or NMDA receptors (11,12). To investigate the potential relationship of anxiety or anxiolysis to infusion effects on suicidal ideation, we will systematically assess anxiety using a visual analog scale (14).

b. Midazolam may cause respiratory depression, decreased systolic and diastolic blood pressure and increased heart rate (11-13) The sub-anesthetic dose we plan to use requires the presence of a physician, but not an anesthesiologist (personal communication from Eric Heyer, MD, Chief of Neuro-Anesthesiology, Columbia University Medical Center).

c. Cardio-respiratory effects are usually absent at intravenous sedative doses (0.05-0.15 mg/kg) and our planned dose is below the low end of this range (11-13). Midazolam has an onset of CNS activity within minutes, a half-life of 2-4 hours, and psychomotor performance returns to normal approximately 2 hours after administration (11-13). It is relatively free of other side effects such as nausea, vomiting, or venous irritation (11-13). Midazolam may cause confusion, but an RCT found it

to be safe even in the elderly (15).

ii) Specific measures and precautions

The risk of respiratory depression with the midazolam dose in this study is expected to be “miniscule” (personal communication, Dr. Moitra, study consultant). Adverse effects of midazolam can be reversed with administration of the benzodiazepine antagonist flumazenil (11-13). Specific interventions for respiratory depression or low oxygen saturation are described under Study

Procedures.

iii) Psychiatric or Behavioral Risks. Midazolam has anxiolytic, hypnotic, muscle relaxant, and

antegrade amnesic effects substantially mediated by its binding to CNS benzodiazepine receptors and increased GABA activity (11-13). It is not known to have direct effects on glutamate or NMDA receptors (11-13). Midazolam may cause confusion, but an RCT found it to be safe even in the elderly (15) Paradoxical excitation has approximately a 10% incidence after midazolam doses twice as high as the dose we will use, is more common among older patients, and is reversible within 30 seconds with administration of flumazenil (16).

iv) Specific measures and precautions

The experiment will be carried out in the presence of at least one psychiatrist. In case of severe agitation or hyperarousal, the blind will be broken and if the patient received midazolam, then they will be treated with neuroleptics and or flumazenil. 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.

2.A.3. Side Effects of Other Medications

Zolpidem: The potential side effects are diarrhea, dizziness, drowsiness, a drugged feeling, and dry mouth.

Lorazepam: The potential side effects are dizziness, drowsiness, a drugged feeling, and some potential for tolerance and withdrawal symptoms.

Diphenhydramine, hydroxyzine: The potential side effects are dizziness, drowsiness, a drugged

feeling, and dry mouth.

2.B. Other medication related risks:

Delay to Infusion: We will schedule the infusion as soon as possible. Patients on psychotropic medications may continue them. 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.

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, they 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 participants 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. **Subjects will not receive payment for research assessments or procedures during the inpatient stay.**

References

References

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- (3) Grunebaum MF, Ellis SP, Duan N, Burke AK, Oquendo MA, Mann JJ. Pilot randomized clinical trial of an SSRI vs bupropion: effects on suicidal behavior, ideation, and mood in major depression. Neuropsychopharmacology 2012 February;37(3):697-706.
- (4) Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: The scale for suicide

ideation. J Consult Clin Psychol 1979;47(2):343-52.

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(7) Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002;95:114-8.

(8) Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009;66(5):522-6.

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(10) Krystal JH, Karper LP, Seibyl JP et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51(3):199-214.

(11) Brunton LL, Lazo JS, Parker KL. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York: McGraw-Hill; 2006.

(12) Evers AS, Maze M, Kharasch ED. Anesthetic Pharmacology: basic principles and clinical practice. Cambridge: Cambridge University Press; 2011.

(13) Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and Uses.

Anesthesiology 1985;62:310-24.

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(15) Christe C, Janssens JP, Armenian B, Herrmann F, Vogt N. Midazolam sedation for upper gastrointestinal endoscopy in older persons: a randomized, double-blind, placebo-controlled study. J Am Geriatr Soc 2000;48(11):1398-403.

(16) Weinbroum AA, Szold O, Ogorek D, Flaishon R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. Eur J Anaesthesiol 2001;18(12):789-97.

(17) Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects

in clinical trials. Psychopharmacol Bull 1986;22:343-81.

Uploads

Upload the entire grant application(s)

Upload copy(ies) of unbolded Consent Form(s)

CF_Bipolar ket_mid un-bolded_5-6-15.pdf

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

Advertisements 5-6-15.pdf

Upload copy(ies) of the HIPAA form

IRB HIPAA Form_6785_6-17-15.pdf

Upload any additional documents that may be related to this study

Fig-2 Assessment Sched_ 3-10-15.pdf

IRB# 6785

Ketamine research study for bipolar depression
with suicidal thoughts.

Persons suffering from bipolar depression with suicidal thoughts
may be eligible for a research study with ketamine
at Columbia University Medical Center/New York State Psychiatric Institute.
A brief inpatient stay is required. This NIH-funded study is testing the potential
rapid relief of suicidal thoughts using the experimental antidepressant ketamine.
Participants receive 6-months treatment (inpatient/outpatient) at no cost.

For further information please call _____ at 646-774-_____.

Columbia University Medical Center

Do You Have Bipolar Depression with Suicidal Thoughts?

Are you between the ages of 18 and 65?

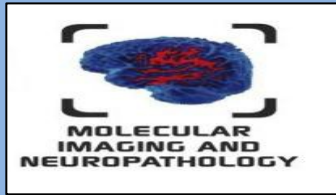
If you are **medically stable** you may be eligible to participate in a
ketamine research study
for bipolar depression with suicidal thoughts.

This NIH-funded research study is testing the potential rapid relief of suicidal thoughts
in bipolar depression using the experimental antidepressant ketamine.

Participants are offered 6-months treatment (inpatient/outpatient) at no cost.

A brief inpatient stay is required.

For further information please call _____ at 646-774-_____



Columbia University Medical Center

Depressed with Suicidal Thoughts?

If you have bipolar depression, suicidal thoughts, are between ages 18-65 and medically stable, you may be eligible for a research study of a potentially fast-acting experimental treatment for suicidal depression.

Study participation may help improve suicide prevention in bipolar depression.

A brief inpatient hospital stay is required.

www.columbiapsychiatry.org

For more information please call:

_____ at
(646) 774-_____

New York State
Psychiatric Institute

Participants are offered 6 months of treatment in/outpatient at no cost

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (774) 646-_____

Call: _____
Phone: (646) 774-_____

Call: _____
Phone: (646) 774-_____

NYSPI IRB Approved

6785

07/08/2015 -> 07/07/2016

Figure 2. Schedule of Research Procedures and Assessments

^aStaff: MD = Physician; CR = Clinical Rater; RA = Research Assistant; RT = Research Technician; SR = Self-Rating by patient.

^bPhysical exam performed by MD; other tests administered by RA and results interpreted by MD.

^cPerformed under 4815.

^dBlood 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.

^eTwo samples, one upon waking and the other 30 minutes later.

^fSSI administered pre-infusion by either MD or CR depending on availability.

^gThe second optional infusion of 0.5 mg/kg of ketamine will only be offered to patients who are non-responders to a first infusion of midazolam; Vital signs monitoring during the 2nd/optional infusion will follow the same protocol as for the first infusion.

^hPost-infusion neuropsychological testing may be done up to 72hrs after infusion.

ⁱThe final pre-infusion SSI will be done after subject admitted to hospital and within 24hrs pre-infusion if the "time-sensitive" SSI assessment for randomization does not already meet these criteria.

^jDay 03 post-infusion SSI only for ketamine Day 01 non-responders.

**INFORMATION SHEET – OUTLINE OF STUDY PROCEDURES FOR
Protocol #6785**

Ketamine vs. Midazolam in Bipolar Depression

Principal Investigator: Michael Grunebaum, MD (646-774-7573)

Overview:

This outline is meant as an overview to help you decide whether to participate in this study. The consent form contains detailed information about potential risks. The study is designed to compare the effectiveness of two medications, given by infusion in a vein, for rapidly reducing suicidal thoughts in people with bipolar depression.

One drug, ketamine, is an experimental antidepressant that early studies have shown may quickly reduce depression and suicidal thoughts. Ketamine is a marketed drug, but not an approved treatment for bipolar depression and we are not sure how well it may work. The comparison drug, midazolam, is not thought to reduce depression or suicidal thoughts. Both drugs are used for anesthesia, but in this study will be used at lower doses that should not cause sleep. The study results may help find new and faster treatments for depression and suicidal thoughts.

Procedures:

- If you are taking psychiatric medications, you may continue them.
- Certain medications for anxiety or sleep will not be permitted during the 24 hours pre-infusion. If you are taking this type of medication, the dose may need to be reduced so that you can do without it the pre-infusion day.
- The study infusion requires a brief inpatient admission to New York State Psychiatric Institute.
- You will have research interviews, psychological testing, and will be asked to provide saliva samples for stress hormone tests in the several days before the infusion.
- You will be randomly assigned to receive ketamine or midazolam in a single dose, once through a vein in your arm, over about 40 minutes. We will take blood samples before the infusion through the iv site and after the infusion by a separate blood test.
- Interviews will be conducted during study visits to ask about side effects and to see how you respond to the study medication.
- Cognitive and saliva stress hormone tests will be repeated after the infusion.
- If you do not respond to the infusion and you received midazolam, you will be offered an optional second infusion with ketamine. You will then start open clinical treatment.
- After the infusion(s) you will have weekly research interviews for 6 weeks to monitor your response.
- We will try to keep your inpatient hospitalization as short as possible. You will be discharged from hospital according to usual practice when your doctors agree it is safe for you to continue with outpatient treatment.
- You will be offered treatment at no cost for a total of up to 6 months from the date of enrollment, combining inpatient and outpatient treatment.

Alternative to Participating:

The alternative to participating in this study is to seek regular clinical treatment.

Risks:

There are risks and discomforts associated with participating (refer to the consent form for details). These include:

- Ketamine and/or midazolam may produce a feeling of being unreal, hallucinations, relaxation or stimulation, nausea, vomiting, mild increase or decrease in heart rate or blood pressure, or mild decrease in breathing rate. Immediate effects of the infusion may be unpleasant and some subjects may feel worse. If you have ever had bad side effects with ketamine or midazolam for anesthesia or used them as a street drug, you should not participate in this study.
- Ketamine and midazolam are used in combination with other medications you may be taking, and there may be unknown risks. We will monitor you and your vital signs carefully throughout the infusion.

Costs and Compensation: The inpatient stay, infusion, all doctor and clinic visits associated with this study, and lorazepam or zolpidem, if needed, are at no cost. You will be responsible for the cost of other medications. After the screening day, if you participate, you will receive \$20 for each study visit where you complete research measures, but not for purely clinical visits.

Questions: Contact the study doctor, Michael Grunebaum, MD (646) 774-7573 with any questions.

Other Information: This is a voluntary study. You do not have to participate, and you may stop at any time.

**NEW YORK STATE PSYCHIATRIC INSTITUTE
CLINICAL INVESTIGATION CONSENT FORM**

Ketamine vs. Midazolam for Suicide Risk in Bipolar Depression

**Contact for Questions and Emergency Contact Information:
Michael Grunebaum, MD (646-774-7573)**

Subject Name: _____

PURPOSE OF STUDY

The goal of this study is to test the effectiveness of an experimental antidepressant drug, ketamine, for rapidly reducing suicidal thoughts in people with bipolar depression. Two small studies found ketamine reduced depression and/or suicidal thoughts in bipolar depression within hours and lasting several days. Other studies have shown similar effects in non-bipolar depression. Ketamine is a commonly used anesthetic, but is not proven or approved as an antidepressant. We will use the same ketamine dose as those studies and will compare it to another common anesthetic drug, midazolam. Both drugs may cause "spacey" or relaxed feelings. Midazolam is not thought to reduce depression or suicidal thoughts. Both drugs are widely used in anesthesia at much higher doses than in this study. Since ketamine is a new experimental treatment there is no guarantee that it will work for your depression.

STUDY DESIGN

You may continue your current medications. However, if you are taking a benzodiazepine (such as Ativan, Klonopin, or Xanax), you will be able to take up to 2 mg per day of lorazepam during the week before the infusion (or the equivalent of other medication), but none will be permitted in the 24 hours pre-infusion. Also, zolpidem (Ambien) will not be permitted in the 24 hours pre-infusion. If you choose to participate, your dose of these medications may need to be reduced so that you can do without it during the 24 hours pre-infusion.

You will be randomly assigned (by chance) to receive a ketamine or midazolam infusion in a vein over about 40 minutes. You will be admitted to hospital for the infusion. You cannot choose which medication you receive. You will have an equal chance of getting ketamine or midazolam. If the ketamine works, benefit may appear within a few hours and may last for several days. After the infusion you will receive open clinical treatment. If you respond to the infusion, you will learn which infusion you received at the end of your 6-month treatment in our clinic or when you leave our clinic, whichever is first.

If you do not respond to the infusion according to research ratings the day after, then we will tell you which infusion you received. If it was midazolam, then you will be offered an optional ketamine infusion.

There is no guarantee the standard medication will maintain any benefits of ketamine. We will try to keep your inpatient hospitalization as short as possible. You will be discharged from hospital according to usual practice when your doctors agree it is safe for you to continue with outpatient treatment.

A total of 30 patients will participate in this study. You have been asked to participate because you could benefit from medication treatment for bipolar depression. For safety reasons, you may only participate in this study if you are willing to be admitted into the hospital at New York State Psychiatric Institute for the infusion. We estimate the inpatient stay will be approximately 5-7 days, though this may vary due to scheduling and/or clinical issues.

ALTERNATIVES TO STUDY PARTICIPATION

You do not need to participate in this research study to receive treatment. The alternative to participating is to seek standard psychiatric treatment without research procedures. Approved treatments, including medication and psychotherapy, are available in the community. To get treatment you can speak to your own local doctor or you can ask us for a referral. The interviews, cognitive testing, and saliva testing are not part of routine psychiatric treatment and are tests to learn more about bipolar depression and how ketamine works and not about you or your diagnosis.

STUDY PROCEDURES

Evaluation Day: You have already received a psychiatric and medical evaluation. You will also have an electrocardiogram (ECG) that checks out your heart. Based on these evaluations and lab results, we will be able to tell if you are eligible for this study.

Pre-Infusion: During the several days before the ketamine/midazolam infusion, you will complete research interviews, cognitive testing, and a morning saliva stress hormone test. High levels of the stress hormone cortisol have been reported to be associated with depression and suicidal risk. We will test the level of this hormone in saliva samples collected before and after the infusion to investigate relationships to clinical symptoms.

Ketamine/Midazolam Infusion: You should eat no food and drink no liquids after midnight before the infusion. An intravenous (IV) tube will be placed in one arm before the infusion. Ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg) will be given via this tube over 40 minutes. Before, during, and after the infusion, we will monitor your blood pressure, pulse, and breathing, and will evaluate how you are feeling with brief questionnaires. To measure ketamine, norketamine (a breakdown product) and BDNF (a nerve growth factor), we will take blood samples before the infusion through the iv site and after the infusion by a separate blood test.

Post-Infusion: On the day after the infusion, you will repeat the same research interviews and a morning saliva stress hormone test as you did pre-infusion. Cognitive testing will be repeated within 3 days after the infusion. After the infusion you will receive open clinical treatment.

If the ratings show you have not had a good enough response to the infusion, then we will determine which medication you received and if it was midazolam, you will be offered an optional second infusion with ketamine, following the same procedure (Note: This could delay your starting standard treatment by a few days). You will be offered open clinical treatment for up to 6 months including inpatient and outpatient treatment.

The six weeks after the infusion will include weekly follow-up meetings with a study psychiatrist and research interviews to measure your symptoms. After that, psychiatrist appointments will be as clinically necessary, but at least monthly.

Discharge from Hospital: To participate in this study you must be willing to stay in the hospital at least until the second post-infusion day. We will make every effort to keep your hospital stay as brief as possible. For you to be discharged from the hospital, the research team and separate inpatient unit staff must agree that it is safe for you to change to outpatient treatment.

Clinical Research Interviews and Follow-up: Each follow-up interview will take about 20 minutes and we will ask about how you are doing and any side effects you might have noticed. At this visit you will also meet with a study psychiatrist who will monitor how the standard medication is working for you. During follow-up treatment, if indicated, such as for clinical worsening, you may be admitted to hospital for more supervised care.

Follow up Contact: At 3 and 6 months post-infusion, we will contact you to check how you are doing and to confirm that you have not taken ketamine without a prescription since the study.

RISKS

Some risk and inconvenience are associated with this study. We cannot predict whether ketamine will improve your depression. In terms of risks, throughout all these procedures, experienced staff will be present and a physician will be available.

Delay to start of treatment: There may be up to a 2-week delay from when you enroll in the study until the inpatient admission, for obtaining lab results, baseline interviews, and scheduling the admission and infusion. Your symptoms may worsen during this time, particularly if your anxiety or sleep medication needs to be reduced, and you will be monitored by a study psychiatrist. If you or your physician feels that you cannot tolerate further delay in treatment, you will be withdrawn from the study and given clinical treatment.

Ketamine/Midazolam: Ketamine and midazolam are drugs that are used for anesthesia. In this study, they are used at low doses, which should not make you sleep. However, they may produce temporary symptoms, lasting a couple of hours, including: relaxation, confusion, feeling unreal, hallucinations, nausea, less often vomiting, faster heart rate, and slower breathing. Other side effects may include modest and transient increases or decreases in blood pressure. Immediate effects of the infusion may be unpleasant and some subjects may feel worse. If you have heart disease or uncontrolled high blood pressure you should not participate in this study. Ketamine and midazolam will be used in this study in combination with other medications you may be taking, and there may be unknown risks. We will monitor you and your vital signs carefully throughout the infusion: we will monitor your heart rate, blood pressure, breathing, and blood oxygen. Should uncomfortable feelings or thoughts occur, the infusion can be stopped. We will also stop the infusion for any reason at your request, or if we observe that you are experiencing any severe reaction.

Ketamine is also a street drug of abuse, sometimes called 'special k', and midazolam is also a type of medication that some people abuse. We are concerned about the risk that if you feel good after the infusion it may encourage you to try either drug on your own after this study, without medical supervision, and even risk addiction or other harm. For this reason, it is important for you to be honest with us about any problems with substance abuse you may have experienced in the past or after starting this study.

You will be checked by a physician during and after the infusion and before you return to the inpatient unit. You should not drive a car or engage in hazardous activities for at least 24 hours after receiving the infusion. Our research staff will be available during this time and will check with you to evaluate any concerns.

Risks Associated with Mood Stabilizing Medications: There are numerous medications used to stabilize mood in bipolar disorder, such as lithium, anticonvulsants (valproate, lamotrigine, etc.), and neuroleptics (quetiapine, olanzapine, etc.). Each medication may have specific side effects, which could include the following: fatigue or drowsiness, urinary changes, stomach upset or diarrhea, muscle stiffness or tremor, rash or allergic reaction. You will be monitored regularly by a physician for adverse effects and medications will be changed if side effects are intolerable or dangerous.

Risks Associated with Antidepressant Use: Open clinical treatment may include antidepressant in addition to mood stabilizing medication.

The Food and Drug Administration (FDA) has concluded that antidepressants may increase the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults up to age 25 years with Major Depressive Disorder (MDD) and other psychiatric disorders. It is unknown whether the suicidality risk extends to longer-term use, that is, beyond several months.

The FDA has directed the manufacturers of all antidepressant medications to add a "black box" warning that describes the increased risk of suicidality related to antidepressant use in children, adolescents, and young adults. The warning urges that adults with MDD being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

We do not believe that this information warrants a change in your treatment. It is very important that you do not abruptly stop taking the medication without first discussing this with the doctor who prescribed the medication. Suddenly stopping these medications may be followed by withdrawal symptoms or by a return of the depressive feelings.

Zolpidem: Potential common side effects are diarrhea, dizziness, drowsiness, a drugged feeling, and dry mouth.

Lorazepam: Potential common side effects are dizziness, drowsiness, a drugged feeling, and some potential for tolerance and withdrawal symptoms.

Diphenhydramine, Hydroxyzine: Potential common side effects are dizziness, drowsiness, a drugged feeling, and

dry mouth.

Non-Response: There is a chance that the medications and/or dosages used in this study will not be helpful for your depression or that you may feel worse during the study. If you feel worse, we want you to tell us so that we may do our best to help.

Blood Drawing: The risks associated with drawing blood are slight discomfort and occasional bruising.

Venous Catheter Placement: Mild discomfort can be expected from placement of a catheter or plastic tube in a vein. Sometimes a bruise will occur at the puncture site and on rare occasions a blood clot or infection.

Saliva sample: This procedure has no significant risks other than minor inconvenience.

Interviews: Psychiatric interviews can sometimes be upsetting, but many people find talking to a physician or psychologist helpful. The interviewers will all be experienced personnel.

Electrocardiogram (ECG): An ECG has no serious risks. On rare occasions a rash may develop where the electrode patches are placed on the skin. This usually goes away without treatment.

Pregnancy: The study medications should not be used during pregnancy because of possible risk to the fetus. Women of child-bearing age will be required to have a urine pregnancy test at the time of medical screening and again within 24 hours of the infusion. You will not be charged for the pregnancy tests.

BENEFITS

Participation in this study may be of no benefit to you if you do not respond to this experimental treatment. You will get a thorough evaluation. Study results may increase knowledge about the effects of ketamine on bipolar depression and suicidal thoughts.

COSTS

You will be offered up to 6 months of a combination of inpatient and outpatient treatment. Doctor visits, inpatient treatment, and study medications (ketamine, midazolam, lorazepam, zolpidem) are free of charge. You will be responsible for costs of other medications.

If for some reason you are unable to complete the infusion, you will be eligible to receive up to 6 months of open, clinical outpatient treatment with your study psychiatrist. You will be responsible for the cost of medications, but not for the doctor visits.

COMPENSATION

Not including the screening day, if you participate in the study, you will receive \$20 for each outpatient visit at which research ratings are completed, but not for purely clinical visits, such as during open clinical treatment.

CONFIDENTIALITY

If you consent to participate in this research, your personal information will be kept confidential and will not be released without your written permission except as described in this section or as required by law. Your name or other identifying information will not be made known if the results of this study are published for scientific purposes.

Clinical records, including your name and other personal identifying information, and research data will be kept in secure storage at the New York State Psychiatric Institute. Information in paper format will be kept in locked files. Electronic data will be protected by a firewall (programming that makes it virtually impossible to access the data from outside the New York State Psychiatric Institute) and by restricting access within the New York State Psychiatric Institute through use of a password known only to authorized personnel. If information is transmitted electronically, it will be encrypted so that your identifying information remains confidential.

Your information will only be available to study research staff and other authorized individuals, including those at the New York State Psychiatric Institute, New York State and federal regulatory agencies such as the Food and Drug Administration who may review records as part of routine audits. There are also legal advocacy organizations that have the authority under New York State law to have access to otherwise confidential subject records, although they cannot disclose this information without your consent.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

RESEARCH STANDARDS AND RIGHTS OF PARTICIPANT

Voluntary Participation: Participation in this study is voluntary and you may decide not to participate. If you agree to start, you may stop at any time. You are free to agree to participate in portions of the study without agreeing to all procedures. You may refuse to participate or withdraw from the study without any loss of benefits to which you are otherwise entitled. You also have the right to have any research material and/or data destroyed or made anonymous. The doctors conducting this research study are also responsible for your clinical care if you are being treated as an outpatient in our clinic. You will also be informed of significant new information that may relate to your willingness to continue to participate in this study. A decision not to participate will not affect your treatment at the New York Psychiatric Institute or at the Columbia Presbyterian Medical Center.

Termination: The investigator may terminate your participation without your consent, for example, if a test indicates that you are pregnant or because of some other medical, or laboratory finding.

In Case of Injury: Federal regulations require that the investigators inform you about this institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Michael Grunebaum, at (646) 774-7573 so that you can review the matter and identify the medical resources that may be available to you. The New York State Psychiatric Institute, Columbia University and New York Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital. In addition, the investigators will be of assistance in arranging follow-up care in such instances. You will be responsible for the cost of such care, either personally or through your medical insurance or other form of medical coverage. No monetary compensation for wages lost as a result of injury will be paid to you by the New York State Psychiatric Institute, Columbia University or by New York Presbyterian Hospital. By signing this consent form, you are not waiving any of your legal rights to seek compensation through the courts.

Questions: If you have any question about your rights as a research participant or any complaints, you can call the Administrative Director of the NYSPI IRB at 646-774-7161 during office hours. You are free to ask any questions of Dr. Michael Grunebaum at 646-774-7573.

You will be given a copy of this signed consent form to keep.

Documentation of Consent:

I voluntarily agree to participate in this study understanding that I may discontinue participation at any time.

Date

Patient Signature

Patient Printed Name

Physician Statement of Consent:

I have discussed the proposed research with this subject, and, in my opinion, this subject understands the benefits, risks and alternatives (including non-participation) and is capable of freely consenting to participate in this research.

Date

Physician Signature

Physician Printed Name

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 vs. midazolam 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

