Protocol Title:
Ketamine Treatment for Pediatric-Refractory Obsessive-Compulsive Disorder (OCD)

Version Date:
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Protocol Number:
7023

Clinic:
Children's Day Unit

First Approval:
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01/25/2019

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Co-Investigator(s):
Helen Simpson, MD
Moira Rynn, 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?
Child Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
Pediatric Anxiety and Mood Research Clinic (PAMRC) / Children's Day Unit (CDU)

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.

Evelyn Berger-Jenkins, MD, MPH (Assistant Professor of Pediatrics, Columbia University Medical Center)

Moira Rynn, MD (Consulting Professor and Chair, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center)

Application for Continuation of Research

Status

Current Status of Study:
Subject enrollment 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.
We have enrolled 5 participants to date. We have not had any serious events related to the ketamine infusion. The participants and their families have reported satisfaction with their participation in the study. We have provided case reports to the IRB highlighting participants' experience.

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
10
Total number of participants enrolled to date
5
Number of participants who have completed the study to date
4
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Adolescents and young adults with OCD
Total number of participants enrolled from this population to date
5
Gender, Racial and Ethnic Breakdown

We have screened a total of 9 participants and completed the study with 4 participants. 1 participant is currently in the 3-month follow-up period.

Gender:
- Male:1
- Female: 4

Race/Ethnicity:
- White: 4
- Mixed race: 1

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
3
Number of participants currently enrolled
1
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
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Medication-Free Period or Treatment Washout
✓ Off-label Use of Drug or Device

Population

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

✓ Children (ages 13-17)
✓ Adults

Research Support/Funding

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

PC002246 YAC Columbia account

903-4081A RFMH account

903-4132A RFMH account

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
Other
Sponsor

NYPH YAC (Youth Anxiety Center)
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

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This pilot study is proposed to determine the acceptability, feasibility and potential efficacy of ketamine, a medication that modulates glutamate in the brain, as a rapid treatment for obsessive-compulsive disorder (OCD) symptoms in adolescents and young adults with OCD. This study will recruit 10 youth (ages 14-22) who are diagnosed with clinically significant OCD and have failed at least one adequate trial of a Serotonin Reuptake Inhibitor (SRI) medication and a course of Cognitive-Behavioral Therapy (CBT) for OCD in the past. Participants will receive a single infusion of intravenous ketamine and be assessed at regular intervals post-infusion for up to 14 days. At the end of the 14-day treatment phase, all participants will be offered three months of open treatment for OCD with medication and/or CBT. The study will be conducted at NYSPI and will follow similar methodology to the approved protocol that studied the effects of ketamine in adults with OCD (IRB#5833, PI: Dr. Carolyn Rodriguez, now being analyzed under IRB#7219, PI: Dr. Helen Blair Simpson). Promising data will lead to a grant application to the National Institutes of Mental Health for a full-scale randomized controlled trial.

Background, Significance and Rationale

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Overview:

Obsessive-compulsive disorder (OCD) is a disabling illness that usually begins by adolescence, persists for life, and impairs function. There have been no new classes of Food and Drug Administration (FDA)-approved medications to treat children and adolescents with OCD since the development of serotonin reuptake inhibitors (SRIs) over 30 years ago. SRIs provide only limited symptom relief and typically have a 2-3 month lag time before clinically meaningful improvement. Thus, there is a compelling need for alternative pharmacological treatments in adolescents with OCD. At the same time, there has been a surge in our understanding of the pathophysiology of OCD: it is associated with abnormal functioning of a corticostriatal circuit, and there are known abnormalities within the glutamate neurotransmitter system (e.g. glutamate is the main excitatory chemical that helps nerve cells communicate). These basic science findings have recently prompted excitement in testing medications that target glutamate to decrease OCD symptoms.

Background & Rationale:

In this study, we will evaluate the feasibility, tolerability, and preliminary efficacy of ketamine, a medication that modulates glutamate in the brain, as a rapid treatment for OCD symptoms in adolescents and young adults with OCD. Our rationale for using ketamine is threefold. First, glutamatergic abnormalities in corticostriatal circuits may underlie OCD symptoms based on human imaging, genetic, and animal studies; [1-3] striatal glutamatergic levels have been associated with OCD severity. [4, 5] Thus, medications that modulate glutamatergic neurotransmission (e.g., riluzole, memantine, minocycline) may be effective.[5, 6] Second, riluzole and memantine have shown promise for OCD in case reports or open trials, [7-9] but neither is FDA-approved for use in children; riluzole also has significant liabilities in terms of adverse events and cost. [10] In contrast, ketamine is FDA-approved for anesthesia and chronic pain in children, adolescents and adults, and is routinely used at higher doses than proposed in this study. [11] It is also used as adjunctive pain management for children and adolescents suffering from end stage medical illness.[12-13] Third, we found in a small randomized controlled trial that unmedicated OCD adults had a near cessation of obsessional thoughts during an intravenous ketamine infusion; these effects were maintained in half of the patients for up to one week.[14] These exciting findings lead to two questions: 1) is this type of study acceptable and feasible in youth; 2) are ketamine's effects similar in adolescents and young adults? This proof-of-concept study has the potential to pave the way to rapid-acting treatment strategies for adolescents and young adults with OCD.

Our decision to allow participants to remain on their prescribed SRI medications during the study is based on a review of the literature. There are no known interactions between these medications. Additionally, three published psychiatric studies have allowed patients to concurrently take antidepressant medications and ketamine.[15-17] These studies have a combined sample size of 92 participants, and there were no related adverse events. Refer to the uploaded chart titled "SRI - Ketamine Literature Summary" for more information.

Specific Aims and Hypotheses

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Specific Aims:

The goal of this proof-of-concept study is to investigate the effect of ketamine on the symptoms of OCD in adolescents and young adults ages 14-22. The symptoms of OCD are evaluated using a number of validated scales designed to measure their clinical status. The specific aims of the study are as follows:

Aim 1. To assess the acceptability, feasibility and tolerability of a single ketamine infusion in adolescents and young adults with OCD.
Aim 2. To assess the effects of ketamine on OCD severity.

Primary Hypothesis:
Adolescent and young adult OCD patients will have a reduction in OCD symptoms immediately following the ketamine infusion.

Description of Subject Population

Sample #1

Specify subject population
Individuals with obsessive-compulsive disorder
Number of completers required to accomplish study aims
10
Projected number of subjects who will be enrolled to obtain required number of completers
20
Age range of subject population
14-22 inclusive

Gender, Racial and Ethnic Breakdown
Based on our experience and the demographics of the catchment area served by our institution, we expect the subject racial distribution to be approximately 73% White, 18% Black, 9% Asian, and for the ethnic distribution to be approximately 22% Hispanic. We expect the sample to be 50% female.
Description of subject population
We will recruit 10 adolescents and young adults (post-pubertal, ages 14-22) with OCD using similar criteria as in the prior study in adults [14] with the modification that participants have had at least one adequate trial of an SRI medication and a course of CBT for OCD. They will be free of medication or on a stable dose of an SRI medication, score ≥ 16 on the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) prior to entering the study and report at least moderate severity of obsessions and/or compulsions.

Recruitment Procedures

Describe settings where recruitment will occur
The study will recruit participants from the Anxiety Disorders Clinic (ADC), directed by Dr. Simpson, as

well as the CAPES Evaluation Service and the Children's Day Unit (CDU), which are directed by Dr. Laura Mufson. The ADC screens over 200 adults (≥ 18) with OCD a year. The CAPES/CDU provides free expert consultation, evaluation, and treatment referrals for children and adolescents suffering from mood and anxiety disorders. OCD self-help organizations such as the International OCD Foundation will be contacted to further publicize the existence of this study.

Participants (ages 14-22) and their parent/caregiver will be assessed by an IRB-approved phone screen (IRB# 7058R (formally 6019R), IRB# 6574). For participants ages 18-22, the research team will obtain permission from the participant before speaking to his/her parent/caregiver. We do not communicate to families that we will destroy their screening information if they do not come in for a study visit. Regardless of study participation, we enter the information from the phone screens into a deindentifed and password protected database.

How and by whom will subjects be approached and/or recruited?

Research staff on the CDU and ADC may approach and discuss the research study with potential participants who have given permission to be contacted about research. Drs. Goldberg and Simpson will be responsible for fully explaining the details of the study, answering any questions, and consenting the participants if they are interested in the study.

How will the study be advertised/publicized?
IRB-approved radio/newspaper/web advertisements, flyers and RecruitMe will be used to recruit participants.

Do you have ads/recruitment material requiring review at this time?
No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02422290

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Participants may be recruited from the following ongoing studies:

- "Evaluation at the NYSPI Child Psychiatry Research Clinic." (IRB# 7058R)
- "MRS Glutamate Measurement in Healthy Controls and People with OCD." (IRB #6218)
- "Novel Medication Strategies Targeting Brain Mechanisms in Pediatric OCD." (IRB #6574)

- "Attaining and Maintaining Wellness in OCD." (IRB #6628)

Inclusion/Exclusion Criteria

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

CRITERION	METHOD OF ASCERTAINMENT
1) Participant must be 14-22 years of age at the time of consent (post-pubertal)	Phone screen, inquiry at time of consent by trained research staff
2) Participant and a parent/guardian must be able to read and understand English	Phone screen, inquiry at time of consent by trained research staff
3) Participant must be physically healthy and weigh at least 25kg. If female, must not be pregnant.	Clinical interview by trained MD or PhD, physical examination, EKG, and blood tests
4) Participant must fulfill DSM-V criteria for OCD, OCD being the principal disorder (i.e., currently the most severe and in need of treatment) and have had OCD for at least six months.	Clinical interview and results of ADIS-C/P
5) Participant must score ≥ 16 on the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) prior to entering the study, report at least moderate severity of obsessions and/or compulsions.	CYBOCS administration by trained rater, OCD-VAS
6) Participant must have tried and failed at least one adequate trial of an SSRI medication or clomipramine and a course of CBT unless the participant is unable (or unwilling) to access or tolerate CBT treatment. **a.** In order to meet criteria for having had at least one adequate trial of an SRI medication, participants must have been on a stable and minimal adequate dose of at least one SSRI medication or clomipramine as defined by the literature for at least 12 weeks, and have a documented history of intolerable adverse effects at a higher dose as evaluated by the study psychiatrist and are therefore unable to increase the dose or complete the full 12	Phone screen, clinical interview, consultation with referring physician

weeks, or have refused further SRI trials. Congruent with the literature, the range of minimally adequate doses to treat OCD are as follows: Clomipramine (Anafranil) 75-100 mg/day; Fluoxetine (Prozac) 20-60 mg/day; Paroxetine or Paroxetine CR (Paxil) 20-40 mg/day; Sertraline (Zoloft) 50-100 mg/day; Fluvoxamine (Luvox) 100-200 mg/day; Citalopram (Celexa) 20-40 mg; Escitalopram (Lexapro) 10-20 mg/day for a minimum of 12 weeks. b. In order to meet criteria for having had an adequate course of CBT for OCD, patients should have received at least 8 sessions of Exposure and Response Prevention Therapy (EX/RP) by a licensed clinician trained in doing CBT for OCD. A CBT expert on our team will ensure that the clinician administering these exposures has had adequate training and experience in providing this treatment. Participants may also be considered if they are unable to access or unwilling to pursue CBT treatment.		Create or insert table to describe the exclusion criteria and methods to ascertain them
7) Participant is off all psychotropic and other types of drugs likely to interact with glutamate for at least 14 days before starting the study. The exceptions are SRI medications and short acting benzodiazepines for distressing anxiety or insomnia (which can be taken up to 24 hours prior to ketamine infusion). Participants will be off neuroleptics for 1 month and off fluoxetine for 6 weeks prior to the study.	Phone screen, clinical interview, consultation with referring physician	
8) For participants younger than 18, written informed assent by the participant and consent by the parent. For participants 18 and older, written consent by the participant and permission for legal guardian/parent to provide information.	Consent interview by study psychiatrist	

CRITERION	METHOD OF ASCERTAINMENT
1) Family history of a first degree relative with psychosis or substance abuse/dependence.	Clinical interview
2) History of violence	Clinical interview
3) Presence of psychotic symptoms or lifetime diagnosis of schizophrenia including any auditory or visual hallucinations or presence of delusional thinking, bipolar disorder, substance-induced psychotic disorder, psychosis due to general medical condition.	Clinical interview, ADIS-C/P
4) Severely depressed patients with the Children's Depression Rating Scale (CDRS) ≥ 60 or judged clinically to be at risk of suicide.	Clinical interview, ADIS-C/P and CDRS
5) Current diagnosis of an eating disorder.	Clinical interview, ADIS-C/P
6) Current or past history of PTSD or significant trauma.	Clinical interview, ADIS-C/P
7) Current or past diagnosis of substance abuse/dependence.	Clinical interview, ADIS-C/P
8) Current or past diagnosis of autism or a related disorder.	Clinical interview
9) Current or past diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS). This will be defined by the following criteria: abrupt onset of OCD symptoms (often with comorbid tics) with a relapsing–remitting symptom course, a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal (GAS) infection, association with neurological abnormalities during exacerbations (adventitious movements, motoric hyperactivity, urinary hesitancy), and prepubertal age of onset.	Clinical interview
10) Participants planning to commence cognitive-behavioral therapy during the period of the study or those who have begun CBT within 8 weeks prior to enrollment.	Phone screen, clinical interview, consultation with current provider
11) Documented history of hypersensitivity or intolerance to ketamine.	Clinical interview
12) Female participants who are either pregnant or nursing or female participants of child bearing age who are sexually active and not taking hormonal birth control.	Medication evaluation
13) History of significant medical condition that might increase the risk of participation. This would include hypertension (BP > 140/90), chronic congestive heart failure, tachyarrhythmias, myocardial ischemia, intracranial mass lesions, head injury, globe injuries, hydrocephalus or a thyroid disorder.	Clinical interview and medical examination
14) Concurrent use of any medications that might increase	Clinical interview

the risk of participation. This would include: St. John's Wort, Tramadol, atracurium or thyroid medication, due to potential adverse drug-drug interactions.	
15) Positive urine screen for illicit drugs	Urine toxicology assessment
16) Inability of participant or parent/guardian to read or understand English.	Phone screen, inquiry at time of consent by trained research staff.
17) Documented history of adverse reaction to anesthesia.	Clinical interview

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
Yes
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?
No
Describe procedures used to obtain consent during the screening process
Prior to initiating screening procedures, Drs. Goldberg or Simpson will obtain consent from the participant (if 18 or older) or participant's parent/legal guardian by describing the purpose and nature of this research study. Families will have a chance to review the consent form thoroughly and ask any questions prior to signing.
Describe Study Consent Procedures
Drs. Goldberg or Simpson will answer any questions the participant or participant's parent/legal guardian may have and will obtain written consent. The participant/participant's parent/legal guardian will receive a copy of the signed consent.
Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following

The waiver was requested to allow us to obtain information on participants' family history. The Family history screen (FHS) form was previously uploaded for IRB review. As per Federal Regulation 45CFR46. 116(d), (1) The research involves no more than minimal risk to the subjects; (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) The research could not practicably be carried out without the waiver or alteration; and (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Explain why your research can not be practicably carried out without the waiver or alteration
The FHS is a standardized questionnaire that will be used to screen for the presence of 15 psychiatric disorders among the participant's biological relatives and patients with a family history of psychosis or substance use/dependence will be excluded from participating in this study. It would not be feasible to contact all of the patient's biological relatives to complete this form. Consent will be obtained from the parents of patients under 18 years to be able to collect this information via the FHS form.
Describe whether and how subjects will be provided with additional pertinent information after participation
The participants and their families will be not be provided with any additional information after participation in the study.

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded
Drs. Goldberg or Simpson will describe the purpose and nature of the research study. The participant will have a chance to review the assent form thoroughly and ask any questions prior to signing. If they decide to participate in the study, they will also receive a copy of the signed assent form.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Goldberg, Pablo, MD
Simpson, Helen, MD
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study
Overview:

The current plan is for the study to be conducted at the Children's Day Unit (CDU) at NYPSI and the Irving Institute for Clinical and Translational Research at CUMC. The CDU is an outpatient clinic and a research day treatment program that provides services for the psychiatric and educational needs of children and adolescents participating in research protocols at NYSPI. Most of the children have either failed or not completely responded to first line treatments for mood, OCD, or other anxiety disorders. School services are provided by PS186X, a New York City public school located on the unit during the academic year from September through June. In addition, during the 6 week summer program in July and August, the CDU provides educational tutoring. This unit provides continued clinical care for children and adolescents after their participation in an IRB approved protocol at no cost. Led by Dr. Mufson, the staff consists of a research medical director, Dr. Pablo Goldberg, a research nurse, a social worker, psychologists, and trainees. Although this protocol is primarily conducted as an outpatient study, we reserve the opportunity to offer admission to 4 Center (the 4th floor inpatient unit) for those adolescents in need of a higher level of care. If an adolescent requires additional support, the adolescent may be admitted to the CDU partial day program that runs Monday through Friday from 8:30 AM to 3:30 PM where the adolescent can be closely monitored, receive educational credit, and additional supportive services.

Screening:

Upon consenting, participants will complete all screening procedures at the CDU. Screening may last from 1 to 6 weeks to allow sufficient time to obtain thorough medical and psychiatric history to ensure the patient's safety and eligibility/ineligibility in the study. Screening procedures include:

- *Diagnostic Assessment:* Anxiety Disorders Interview Schedule - Child/Parent version (The child version will be administered to all participants. The parent version will be administered to parents of all participants ages 14-17 and to parents of participants ages 18-22 with their permission).

- *Efficacy Assessments:* Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), Children's Depression Rating Scale-Revised (CDRS-R).

Note: Diagnostic and Efficacy Assessments will be be administered by one of the study's Independent Evaluators (Dr. Paula Yanes-Lukin, Dr. Chiaying Wei, Juliet Jenkelowitz or Kristin Toffey).

- *Feasibility and Safety Assessment*: Columbia-Suicide Severity Rating Scale (C-SSRS)

- Clinical Global Impressions Scale (CGI), Medical History, Treatment History, Family History, OCD Onset form.

- *Medical Assessment:* Physical examination, EKG, Tanner Scale, Safety Labs, Vital Signs and Pregnancy Test (serum)

- If clinically indicated, study clinicians may administer the Social Communication Questionnaire (SCQ) and/or an OCPD assessment based on DSM criteria (uploaded).

Note: If the subject has been screened under IRB protocol #6019R "Evaluation at the NYSPI Child Psychiatry Research Clinic" or IRB protocol #6574 "Novel Medication Strategies Targeting Brain Mechanisms in Pediatric OCD" within 1 month of screening for this study, and do not have any new

medical or psychiatric diagnoses that would prevent study entry, they do not need a repeat ADIS or intake in order to reduce patient burden and promote data sharing.

Co-Morbid Depression: Patients with co-morbid depression will be allowed in the study as long as OCD is primary, the Children's Depression Rating Scale-Revised (CDRS-R) is <60, and patient is not currently suicidal. We would like to include patients with co-morbid MDD since ketamine has been shown to have rapid anti-depressant effects [15, 16]; thus, assessing the response of these patients to ketamine would allow us to understand the impact of co-morbid MDD on OCD symptoms (in addition to our main goal of understanding ketamine's effects on OCD patients without co-morbidities).

Washout:

In order to be eligible for this study, participants must be off all psychotropic medications aside from SRIs and other types of drugs likely to interact with glutamate for at least 14 days prior to starting the study. After consent is signed, if a medication washout is necessary, it can either be performed by a psychiatrist at the Pediatric Anxiety & Mood Research Clinic (PAMRC) or by the participant's own physician. During this washout period, patients will be monitored at least weekly in person and by phone more frequently if needed. Weekly assessments during the washout period will include the Clinical Global Impressions Scale (CGI-S). If a patient's score on the Global Improvement section of the CGI is a 6 ("much worse") or 7 ("very much worse") during the washout period, the clinician will take the patient off the protocol washout and initiate the 3-month open clinical treatment offered to all patients at the end of the study. Patients may independently elect to withdraw from standardized treatment at any time for any reason, independent of their CGI Global Improvement score. Physical exam, vital signs and adverse events will also be carefully assessed during the washout period.

Day 1: Baseline Evaluation & Ketamine Infusion

Baseline Evaluation

After completing the screening procedures and medication washout if applicable, participants will proceed to the baseline evaluation. Baseline evaluation procedures include:

- *Efficacy Assessments:* Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), Children's Depression Rating Scale-Revised (CDRS-R), Young Mania Rating Scale (YMRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), OCD Visual Analogue Scale (OCD-VAS), Yale-Brown Obsessive Compulsive Challenge Scale (YBOCCS), Child Obsessive-Compulsive Impact Scale-Revised (COIS-R)

- *Feasibility and Safety Assessment*: Columbia-Suicide Severity Rating Scale (C-SSRS)

- Clinical Global Impressions Scale (CGI)

- *Medical Assessment:* Vital Signs and Pregnancy Test (urine) for female participants

Test Day Procedures

It is planned that the ketamine infusion take place on an inpatient unit at the Irving Institute for Clinical & Translation Research at CUMC. After completing the baseline evaluation, if a participant is eligible for the study, they will be escorted to the Irving Institute by PAMRC staff. For the infusion, the participant's treatment team will comprise of a nurse, a Pediatric Advanced Life Support (PALS) certified pediatrician Dr. Evelyn Berger-Jenkins and the study MD (Dr. Pablo Goldberg). At the site of the infusion, a nurse will repeat the participant's vital signs, place the IV, and set up the IV infusion pump. The ketamine infusion can begin as soon as PALS-certified pediatrician is present. After the infusion, the study MD and PALS certified pediatrician will remain present to monitor the participant throughout the 2-hour post-infusion observation period.

Ketamine Infusion

Each participant will receive one slow intravenous infusion of 0.5mg/kg ketamine hydrocholoride. The infusion will be given over a course of 40 minutes. The study PI will meet with the research pharmacist and technician responsible for the preparation of infusions several days prior to the subject's first test day. EKG will constantly be monitored prior to, during, and after the ketamine infusion. Blood pressure, heart rate and oxygen saturation will be monitored and recorded at 5-minute intervals at baseline and throughout the ketamine infusion.

In addition to these medical assessments, after 20 minutes from the start of the infusion, the study MD will monitor participants closely using the Clinician Administered Dissociative States Scale (CADSS) and Clinical Global Impressions Scale (CGI). Participants will also be asked to complete the 1-item OCD Visual Analogue Scale (OCD-VAS) to monitor OCD symptoms over a rapid time frame.

Safety and Termination of Ketamine Infusion

In case of nausea or anxiety, patients can be administered anti-nausea medications, such as Zofran 0.15mg/kg/dose (a medication that helps to decrease nausea), or anxiolytics such as Ativan (a medication that helps to decrease nervousness) from the pharmacy formulary. In the case of excessive saliva production, Glycopyrrolate, 0.0025-0.005 mg/kg, (a medication that helps treat hypersalivation) can be administered. In the rare event of severe agitation, Haldol 0.1mg/kg/day in divided doses (an antipsychotic medication that helps decrease severe impulsive behaviors and uncontrolled movements), Ativan and Cogentin 0.02-0.05 mg/kg (a medication that helps with the side effects of Haldol) can be administered as well. The most common and severe adverse effects of these medication are described in the "Risks/ Discomforts/ Inconveniences" section of this protocol.

In case of very high blood pressure during the ketamine infusion, the infusion will be stopped; patients blood pressure will be monitored and if there is no decrease after 5 minutes, then either Clonidine, 0.05-0.1mg x 1, or one dose of sublingual nitroglycerin, 0.4 mg, will be administered. If patients experience blurred vision, headache or chest pain as a result of high blood pressure or any other medical complications, urgent care will be provided. The ketamine infusion will be terminated if the patient complains of any uncomfortable symptoms of rising anxiety and agitation, or any other uncomfortable symptoms. The most common and severe adverse effects of nitroglycerin is described in the "Risks/ Discomforts/ Inconveniences" section of this protocol.

Post-Infusion

Immediately after the infusion is complete, vital signs, EKG and responses on the Clinician Administered Dissociative States Scale (CADSS), Clinical Global Impressions Scale (CGI) and OCD Visual Analogue Scale (OCD-VAS) will be recorded by the study MD.

Infusions will be started in the morning and patients will be observed for 2 hours after the infusion (ketamine has a half-life of 10-15 minutes; 2 hours is 8 half lives); the entire visit will last approximately 3 hours. MD ratings will be administered at 60 minutes and 120 minutes post-infusion as per the attached study flowchart.

At the conclusion of each test day (after the 2-hour observation period), the study MD will evaluate the patient to determine if the effects of the study drug infusion have resolved to the point that subjects are safe to return home. These evaluation criteria will consist of absence of significant deviations from baseline in vital signs, gait, mental status exam, and assessments listed in the study flowchart including BPRS and CADSS scales. In the case of an adverse psychiatric event, patients will be admitted either to the Pediatric Emergency Department at New York Presbyterian Hospital or directly to the fourth floor inpatient unit (4 Center) at the New York State Psychiatric Institute, if clinically appropriate. The PALS-certified pediatrician will be available for the duration of the post-infusion 2-hour observation period. Once patients have been cleared by the MD to go home, adolescents will be required to leave the Irving Center with a parent or guardian and young adults will be required to leave the Irving Center with a parent or guardian or support person identified by the young adult.

Day 2 – 14: Post-Infusion Monitoring & Assessments

After the ketamine infusion, participants will be monitored closely for a 2-week period. The primary measure of change in OCD symptoms will be the Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS). This, along with additional measures will be administered during this 2-week period as follows:

- *Days 2-6 post-infusion:* OCD-VAS and YBOCCS are administered during optional daily phone calls (except when they have an in-person visit on day 3 or 4, during which these will be administered in person).

The in-person visit between day 2-6 post infusion is not a required study visit and will be offered on a case-by-case basis. During this period, if the study MD determines that an in-person visit is needed or if the participant requests an in-person appointment, they will be asked to come to the clinic and will complete the following assessments. Otherwise these assessments will be completed over the phone.

- *Day 3 or 4:* Participants come to the CDU to complete the following assessments:
    - MD ratings: Columbia-Suicide Severity Rating Scale (C-SSRS), Young Mania Rating Scale (YMRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions Scale (CGI).
    - Medical assessment: Vital Signs and Pregnancy Test (urine) for female participants

  Note: If a patient's score on the Global Improvement section of the CGI is a 6 ("much worse") or 7 ("very much worse") compared to baseline at the day 3 or 4 study visit, the clinician will take the

patient off the protocol and initiate the 3-month open clinical treatment offered to all patients at the end of the study.

- *Day 7 post-infusion:* Participants complete the following assessments at the CDU or over the phone (if participants live far away):

    - IE ratings: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), Children's Depression Rating Scale-Revised (CDRS-R), Clinical Global Impressions Scale (CGI).

    - MD ratings: Columbia-Suicide Severity Rating Scale (C-SSRS), Young Mania Rating Scale (YMRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions Scale (CGI).

    - Self-report forms: OCD Visual Analogue Scale (OCD-VAS), Yale-Brown Obsessive Compulsive Challenge Scale (YBOCCS), Child Obsessive-Compulsive Impact Scale-Revised (COIS-R).

    - Medical assessment: Vital Signs and Pregnancy Test (urine) for female participants

  Note: If a patient's score on the Global Improvement section of the CGI is a 6 ("much worse") or 7 ("very much worse") compared to baseline at the day 7 study visit, the clinician will take the patient off the protocol and initiate the 3-month open clinical treatment offered to all patients at the end of the study.

- *Day 8-13 post infusion:* OCD-VAS and YBOCCS are administered daily during optional phone calls.

- *Day 14 post-infusion:* Participants come to the CDU to complete the following assessments:

    - IE ratings: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), Children's Depression Rating Scale-Revised (CDRS-R), Clinical Global Impressions Scale (CGI).

    - MD ratings: Columbia-Suicide Severity Rating Scale (C-SSRS), Young Mania Rating Scale (YMRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions Scale (CGI).

    - Self-report forms: OCD Visual Analogue Scale (OCD-VAS), Yale-Brown Obsessive Compulsive Challenge Scale (YBOCCS), Child Obsessive-Compulsive Impact Scale-Revised (COIS-R).

    - Medical assessments: Safety labs, vital signs, pregnancy test (urine) for female participants.

Follow-up Treatment

Upon completion of the 14-day study period, participants will be offered an additional 3 months of open treatment for OCD (medication management and/or CBT) as clinically indicated based on their treatment

history. If a participant has not yet had a trial of Clomipramine, we will offer that medication to the participant following the 14 day period. In the event that they prefer to be treated elsewhere, they will also be provided with referrals to community providers. With their permission, all participants will be assessed at a 3-month follow-up visit. Participants will be asked to return to the CDU to complete the following assessments: Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), Clinical Global Impressions Scale (CGI), OCD Visual Analogue Scale (OCD-VAS), Yale-Brown Obsessive Compulsive Challenge Scale (YBOCCS), and vital signs. This will be pilot data to help us evaluate patient satisfaction, ongoing safety, and maintenance of response.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

Participants are free to withdraw from the study at any time for any reason. Study doctors are to discontinue participants from the study if participants:

- Request early discontinuation or withdraw consent.
- Experience a serious or intolerable adverse event that prevents the participant from continuing.
- In the study clinician's opinion are evaluated to be much worse (CGI-I score of 6) for two consecutive visits. If the participant begins to show clinical deterioration during the 14-day treatment phase and further continuation under such circumstances would be detrimental to the participant, a referral will be made for a clinical evaluation by an independent evaluator to determine whether the participant should be withdrawn from the study.
- In the study clinician's opinion are experiencing clinically significant deterioration in a comorbid condition such as major depression. For example, if a participant became suicidal or their symptoms of depression increased such that the depressive symptoms were much or very much worse relative to baseline and the CDRS is no longer <60, they would be discontinued from the study.
- Are lost to follow-up.
- Encounter other conditions (such as administrative issues or pregnancy).

If the participant discontinues from the study at any time at his/her own request or at the study doctor's request, the reason(s) for discontinuation will be recorded by the study. Participants who have received ketamine and withdraw during the 14-day treatment phase will be asked to return to the study site for final safety assessments and scheduled for the final study visit. Participants withdrawing from the study for reasons related to the study medication (usually adverse events) will be followed until the event(s) have resolved or no further action is required.

If a participant is withdrawn from the protocol, they will be eligible for up to three months of no cost treatment on the Children's Day Unit. They will also have the option to attend the school program on the CDU. If the participant or the participant's parent/guardian would prefer outside referrals, arrangements will

be made by the research staff. The psychiatrist has full responsibility and authority to refer the participant for this clinical evaluation at any time regarding the participant's suitability for remaining in the study.

Blood and other Biological Samples

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

A blood sample, approximately one tablespoon (15 cc's) of blood, will be taken at screening and at study completion (or withdrawal, if earlier) for a total of two tablespoons (30 cc). These samples will be used for safety monitoring, including Chemistry Screen and CBC. The samples will be forwarded to a centralized laboratory for analysis. Participants may experience a bruise at the site of venipuncture. EMLA cream may be used to minimize the discomfort of venipuncture.

Assessment Instruments

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

Anxiety Disorders Interview Schedule for Children for DSM-IV (ADIS-C/P Revised): This will be administered to the subject (and parent/caretaker for those <18 and those 18-22 with permission) by the independent evaluator (IE) at screening to confirm the diagnosis of OCD and its age of onset.

Yale-Brown Obsessive Compulsive Scale, Child version (CYBOCS): The CYBOCS is a semi-structured measure of OCD severity with excellent inter-rater reliability, internal consistency, and test-retest reliability. It is validated in those starting at age 7 and used in studies up to age 20. The CYBOCS differs from the adult YBOCS only in its use of simpler language. The CYBOCS will be administered by IE at screening and 120 minutes post-infusion to determine OCD severity. The CYBOCS will also be administered by IE at baseline, day 7, and day 14 and will be the primary outcome measure. As secondary outcomes, response will be defined as a CYBOCS decrease of ≥ 30% and excellent response as a CYBOCS of ≤ 10 following the Pediatric OCD Treatment Study (2004). The CYBOCS checklist will be used to determine symptom dimensions.

Children's Depression Rating Scale-Revised (CDRS-R): The CDRS-R is a 17-item clinician-administered semi-structured interview with good inter-rater reliability and validity that assesses 17 symptom areas related to depression, including those that serve as criteria in the DSM-IV. It provides an overall index of severity of depression. This assessment will be administered by IE at screening and 120 minutes post-infusion and by IE at baseline, day 7 and day 14.

Clinical Global Impressions Scale (CGI): This is a clinician rated instrument providing a single score for severity and improvement (from a 7-point scale) comparing the patient's condition during each visit on treatment to the condition at baseline (before treatment). The CGI will be administered by both IE and the study MD as per the study flow chart.

Columbia-Suicide Severity Rating Scale (C-SSRS): This is a semi-structured clinician rating of suicidal behavior, suicide attempts, and presence and intensity of suicidal ideation. The assessment will be administered by study MDs at screening, baseline, day 3 or 4, day 7, and day 14.

Young Mania Rating Scale (YMRS): YMRS is an 11- item clinician administered scale for rating manic symptoms. It will be administered by the study MD at baseline, 120 minutes post-infusion, day 3 or 4, day 7, and day 14.

Clinician Administered Dissociative States Scale (CADSS): This is a clinician rated instrument for rating degree of dissociation. A severity scale will be added: mild, moderate, severe for those items endorsed on interview. It will be administered by the study MD at baseline, 20 minutes from the start of the infusion, immediately post-infusion, 60 and 120 minutes post-infusion, day 3 or 4, day 7, and day 14.

Brief Psychiatric Rating Scale (BPRS): The BPRS is an 18-item observer-scale designed to assess patients with major psychiatric disorders, particularly schizophrenia. The BPRS measures positive symptoms, general psychopathology and affective symptoms. Some items (e.g. mannerisms and posturing) can be rated simply on observation of the patient; other items (e.g. anxiety) involve an element of self-report by the patient. The BPRS is administered by a trained clinician via a semi-structured interview at baseline, 120 minutes post-infusion, day 3 or 4, day 7, and day 14.

OCD Visual Analogue Scale (OCD-VAS): A one-item scale to assess OCD symptoms over a rapid time frame. Patients will be asked to report their rating on this scale prior to, during and after the infusion as per the study flowchart.

Child Obsessive-Compulsive Impact Scale-Revised (COIS-R): This 27-item self-report questionnaire measures OCD-specific functional impairment. The COIS-R-C is a 3-factor structure youth-report form. The COIS-R-P is a 4-factor structure parent-report measure (completed by the parent/caretaker for those <18 and those 18-22 with permission). Participants and their parents will be asked to complete the COIS-R at baseline, day 7, and day 14.

Yale-Brown Obsessive Compulsive Challenge Scale (YBOCCS): A brief self-report scale to assess rapid changes in OCD symptoms. Patients will be asked to report their rating on this scale prior to, during and after the infusion as per the study flowchart.

Family History Screen (FHS): This screens for the presence of 15 psychiatric disorders among the participant's biological relatives. It is administered to a family informant (for those ages 8-17) or to the subject (ages 18-22), who reports on himself/herself and on other biological relatives. It will be administered by the MD at screening.

Social Communication Questionnaire (SCQ): This is a 40 item yes-or-no parent questionnaire to screen for autism spectrum disorders.

DSM-IV OCPD Assessment: This is a semi-structured interview that assesses for symptoms of Obsessive Compulsive Personality Disorder.

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
Ketamine
Approval Status
No IND is required
Choose one of the following options
FDA conditions are met (see 'Rules')
Explain
We completed the IND Decision Worksheet and it appears that we do not need to apply for an IND exception. The IND Decision Worksheet was previously uploaded for review.

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment
For enrolled participants that do not require a medication washout, there will be no delay to receiving treatment. For enrolled participants that require a medication washout, the maximum delay in initiating study treatment will be two weeks.
Maximum duration of delay to standard care or treatment of known efficacy

For all enrolled participants, the maximum delay to standard care or treatment of known efficacy will be 14 days.
Treatment to be provided at the end of the study
Upon completion of the acute 14-day treatment period, participants will be offered three additional months of open treatment for OCD (medication management and/or CBT) at no cost. This treatment will be offered to all participants regardless of response during the acute study treatment period. For participants requiring continued OCD treatment following this three-month follow-up period, the research staff will refer the patient to his or her previous providers or will assist the participant and his/her family in identifying new treatment providers.

Clinical Treatment Alternatives

Clinical treatment alternatives
Currently cognitive-behavioral treatment involving exposure and response prevention (CBT/ERP) and serotonin reuptake inhibitor (SRI) medication are considered the first line treatments for OCD. However, pharmacotherapies have relatively modest effects in OCD. CBT/ERP treatment is the mainstay of the treatment for OCD. CBT/ERP alone results in response rates of anywhere between 60% and 80%, but fear of and non-adherence to CBT/ERP are hypothesized to serve as barriers to the treatment's efficacy. Subjects will have these treatments explained to them by the study doctor, and they will be offered the option to receive referrals for one or both of these treatments rather than participating in the study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period
Risks associated with participation are: 1) distress from discussion about emotional symptoms; 2) blood sampling; 3) clinical deterioration due to being off medication; and 4) medication-related adverse events and side effects from ketamine infusion; 5) medication-related adverse events and side effects from Zofran, Ativan, Haldol, Cogentin and Nitroglycerin.

1) Distress from thoughts or discussion about emotional symptoms: Some participants may experience distress or anxiety related to participating in these procedures. Participants will be monitored throughout the procedures, and they will be encouraged to report any concerns. A psychiatrist will be available to assist the participant if needed, and participants will be removed from the protocol if their distress or anxiety becomes intolerable. Participants and their legal guardians will be informed that their continued treatment at NYSPI will not be impacted if at any point they choose to no longer participate.

2) Risks of blood sampling: A blood sample, approximately one tablespoon (15 cc's) of blood, will be taken at screening and at study completion (or withdrawal, if earlier) for a total of two tablespoons (30 cc). These samples will be used for safety monitoring, including Chemistry Screen and CBC. The samples will be forwarded to a centralized laboratory for analysis. Participants may experience a bruise at the site of venipuncture. EMLA cream may be used to minimize the discomfort of venipuncture.

3) Risks of being off medication: In order to participate in this study, participants need to be off all psychotropic medications other than SRI medications for two weeks prior to study procedures. This carries the risk of the participant's OCD symptoms worsening, becoming more depressed, and worsening of other symptoms including feeling suicidal or risk of suicide. Medications will be slowly stopped in a safe manner as directed by the study doctor, who will work with the participant's present treating doctor. Participants will closely be monitored during this medication washout period and they will be offered other medications for relief from sleeplessness and anxiety as needed. If the participant or study doctor feel that he or she cannot tolerate further delay in treatment, they will be withdrawn from the study and treated with known OCD medications.

4) Ketamine risks: Ketamine is FDA approved as an anesthetic in surgical procedures at higher doses (6 mg/kg for induction in children and adolescents) than the doses being used in this study [11] and has also been used safely in the management of chronic pain in the pediatric population [12, 13]. In this study, ketamine will be carefully administered through an infusion and patients will be continuously monitored by a study physician. The dose of 0.5mg/kg has been safely administered to children and adolescents without adverse side effects in multiple prior studies of ketamine.[17,18]

The following risks might be associated with ketamine:

- Based on data from the study conducted by Rodriguez and colleagues [14] on ketamine for the treatment of adult OCD, there is a chance that the participant might experience some distress if his/her OCD symptoms begin to return after the infusion. To minimize this distress, study staff will check in with the participant and their family daily and all participants will be offered up to three months of front-line treatment for OCD at no cost after the study.
- Ketamine may produce temporary symptoms, including vivid dreams, feeling like you are floating above your own body, that your surroundings are strange, or seeing/hearing things that are not there (illusions/hallucinations). For this reason, any patients with current or past symptoms of psychosis will not be permitted to enroll in this study. Ketamine may also cause temporary (lasting at most 1-2 hours after being given ketamine) increased libido (sex drive), euphoria (happy mood), increased thirst, metallic taste, upset stomach, or heachache. Participants will be monitored closely for side effects during and after the infusion.
- Ketamine may produce hypersalivation, nausea and in some cases vomiting. Experienced study doctors will be on site to take care of the participant in the rare case that this should happen.
- Ketamine can cause mild increases in your heart rate or blood pressure. Study doctors will closely monitor the participant's heart rate and blood pressure during the ketamine administration.
- There is a theoretical risk that exposure to ketamine may predispose susceptible subjects to subsequent abuse of this drug. For this reason, participants with a history or substance abuse or dependence will be asked not to participate.
- Participants should not drive a car or engage in hazardous activities for at least 24 hours after the ketamine dose. Research staff will regularly contact the participant (and parent, if applicable) by telephone during the week to check on any possible consequences of having participated in the study.

Should uncomfortable feelings or thoughts occur, the ketamine infusion can be stopped, and the study discontinued. We will also stop the study for any reason at the parent or participant's request, or if we observe that the participant is experiencing bad effects from ketamine.

Safety and Termination of Ketamine Infusion:

In case of nausea or anxiety, patients can be administered anti-nausea medications, such as Zofran (a medication that helps to decrease nausea), or anxiolytics such as Ativan (a medication that helps to decrease nervousness) from the pharmacy formulary. In the rare event of severe agitation, Haldol (an antipsychotic medication that helps decrease severe impulsive behaviors and uncontrolled movements), Ativan and Cogentin (a medication that helps with the side effects of Haldol) can be administered as well. The common and severe side effects of Zofran, Ativan, Haldol and Cogentin are described below:

Zofran- Most common side effects: Constipation, diarrhea, increased liver enzymes, headache, fatigue and malaise. Severe side effects: Serious arrhythmia such as Torsades de pointes and prolonged QT interval (changes in heart rhythm).

Ativan- Most common side effects: Asthenia (weakness), dizziness, sedation, unsteadiness and depression. Severe side effect: Delirium.

Glycopryolate- Most common side effects: Flushing, constipation, vomiting, xerostomia, headache, urinary tract infectious disease, nasel congestion, and nasopharyngitis. Serious side effects: Bradyarrhythmia, cardiac arrest, cardiac dysrhythmia, tachycardia, ventricular fibrillation, malignant hyperthermia, nystagmus, seizure, respiratory arrest.

Haldol- Most common side effects: Constipation, xerostomia (dry mouth), dystonia (abnormal movements), extrapyramidal disease (neurological symptoms such as: abnormal mood, stiffness, and tic like behaviors), somnolence and blurred vision. Severe side effects: Serious arrhythmia such as Torsades de pointes and prolonged QT interval (changes in heart rhythm), agranulocytosis (significant decrease in white blood cells), seizure, tardive dyskinesia (abnormal neural movements), priapism (abnormal erection), and pulmonary embolism (blood clot in lungs).

Cogentin- Most common side effects: Tachycardia (heart racing), constipation, nausea, xerostomia (dry mouth), blurred vision, dysuria (painful urination), urinary retention (difficulty urinating). Severe side effects: Anhidrosis (dryness in the skin), heat stroke (increased body temperature), paralytic ileus (bowel dysfunction), confusion, disorientation, drug-induced psychosis and visual hallucinations.

In case of very high blood pressure during the ketamine infusion, the infusion will be stopped; patients blood pressure will be monitored and if there is no decrease after 5 minutes, then either Clonidine, 0.05-0.1mg x 1 or one dose of sublingual nitroglycerin, 0.3 mg, will be administered. If patients experience blurred vision, headache or chest pain as a result of high blood pressure or any other medical complications, urgent care will be provided. The ketamine infusion will be terminated if patients complain of any uncomfortable symptoms of rising anxiety and agitation, or any other uncomfortable symptoms. The common and severe side effects of nitroglycerin are described below:

Clonidine- Most common side effects: Contact dermatitis, erythema, pruritus, xerostomia, dizziness, headache, sedation, somnolence and fatigue. Severe side effects: Atrioventricular block.

Nitroglycerin- Most common side effects: Hypotension (low blood pressure), flushing (redness in the face), headache and lightheadedness. Severe side effects: Anaphylactoid reaction (allergic reactions), methemoglobinemia (changes in the structure of hemoglobin), raised intracranial pressure (increased pressure in the fluid of the central nervous system).

Describe procedures for minimizing risks

All efforts will be made to minimize risks and to ensure participant safety. Participants will be encouraged to relay the emergence of any adverse events to the study team, who will attend to it appropriately. We have taken steps to ensure the safety of subject from these safety issues in the following ways:

a) Patients will be assessed and monitored frequently during and immediately after the infusion, as well as for two hours post-infusion with assessments by study physicians (i.e. vital signs, scales of psychosis and dissociation)

b) Patients with medical and psychiatric co-morbidity that makes participation unsafe or vulnerability to psychosis (past history of psychosis or family member with schizophrenia) will not be eligible.

c) Patients with history of substance dependence or history of substance abuse in the prior year will be excluded.

d) Patients with any adverse events associated with the infusion will be hospitalized, if needed.

e) Since relief from OCD symptoms is expected to be temporary for some participants after the ketamine infusion, all participants will be offered up to three months of front-line treatment for OCD with medications and/or CBT at no cost, regardless of their response to the ketamine infusion.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

Confidentiality will be maintained by assigning unique identifying code numbers to each participant and his/her family. Code numbers, rather than names, will be used on all documents pertaining to the participants. All data will be kept in locked files or on Windows 2003 servers or XP workstations with password access, to which only researchers will have access. These operating systems provide multi-level security restrictions and privileges will only be granted by Drs. Rynn, Simpson and to others working on the project. All individuals granted access to the database will be issued a password. The portion of the database that connects a person's identifying information and the code numbers will be maintained separately and

require a higher level of security clearance on the system. No individual will be named or described with information that could allow him/her to be identified in published reports.

Clinical data will be entered into a Microsoft Access relational database, checked for consistency. This database is stored on a network server securely located behind the NYSPI firewall; a username and password are required to access the server and a separate password to access this database. Subjects are identified by numeric codes consistent with HIPAA guidelines; hard copies of data are stored in locked rooms with restricted access. The data manager will perform random data audits to further ensure the integrity of the data. Server backups of study databases are performed nightly; database copies on CD-ROM archive disks are stored separately for safety. Drs. Simpson and Rynn will oversee the operation and scientific integrity of the clinical trial and ensure that the protocol design, instrumentation, patient recruitment, data collection and analysis yield information that achieves the major objectives of the study.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects

The potential benefit of this study is that the participant may respond to this novel treatment strategy for OCD. In a recent study of adults with OCD, ketamine was associated with an immediate remission of clinical symptoms, and this improvement was maintained in some adults for up to 1 week. [14] In addition, each participant will be receiving a thorough psychiatric evaluation and will be carefully followed in the study. After completion of the study, participants will receive up to 3 months of no-cost OCD treatment (medication management and/or CBT) from the study team.

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.
Participants will be compensated $75 for the evaluations done at the time of the infusion, and $50 for assessments completed at each of the three subsequent in-person visits, for a total compensation of up to $225. The compensation takes into account the time involved, travel costs and parking in New York City, and meals or snacks.

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