OPEN-LABEL INTRAVENOUS SUBANESTHETIC KETAMINE FOR ADOLESCENTS WITH TREATMENT-RESISTANT DEPRESSION

Regulatory Sponsor:	Kathryn R. Cullen, MD Department of Psychiatry University of Minnesota
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Study Product:	Ketamine hydrochloride
Protocol Number:	CTSI 22225
IND Number:	IND exemption
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CONFIDENTIAL

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List of Abbreviations

3T	3 Tesla
AE	Adverse Event
ATHF	Antidepressant Treatment History Form
BDI-II	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinician-Administered Dissociative States Scale
CC	Cubic Centimeters
CDRS-R	Children's Depression Rating Scale - Revised
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions
CMRR	Center for Magnetic Resonance Research
CRF	Case Report Form
CSSRS	Columbia Suicide Severity Rating Scale
CSSRS-SLV	Columbia Suicide Severity Rating Scale – Since Last Visit
CTSI	Clinical and Translational Science Institute
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DPX	Dot Pattern Expectancy task
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IDS	Investigational Drug Services
IRB	Institutional Review Board
IV	Intravenous
KG	Kilogram
K-SADS-PL	Kiddie Schedule of Affective Disorders and Schizophrenia -Present and Lifetime
LPS	Lipopolysaccharide
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major-Depressive Disorder
MEG	Magnetoencephalography
MG	Milligram
ML	Milliliter
MMC	Mayo Mail Code
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NOS	Not Otherwise Specified
PBS	Phosphate Buffered Saline
PET	Positron Emission Tomography
PHA	Phytohemagglutinin
PHI	Protected Health Information
PI	Principal Investigator
POMS-A	Profile of Mood States – Adolescent
REPA	Report of External Professional Activities

SAE	Serious Adverse Event
SHAPS	Snaith-Hamilton Pleasure Scale
TRD	Treatment-Resistant Depression
TEPS	Temporal Experience of Pleasure Scale
UTox	Urine Toxicology Screen
VA	Veterans' Affairs
WASI	Weschler Abbreviated Scale of Intelligence

Study Summary

Title	Open-label intravenous subanesthetic ketamine for adolescents with treatment-resistant depression
Protocol Number	CTSI 22225
Phase	2
Methodology	Single group open-label pilot study
Study Duration	2 years
Study Center(s)	University of Minnesota
Objectives	To determine the efficacy of repeated-dose subanesthetic IV ketamine among adolescent patients with treatment resistant depression.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Male and female adolescents aged 12 to 18 with the presence of recurrent major depressive disorder without psychotic features.
Study Product, Dose, Route, Regimen	IV infusions of 0.5mg/kg of Ketamine hydrochloride over a 40-minute infusion period. Participants will receive a total of 6 doses over a 2-week period.
Duration of administration	2 weeks
Reference therapy	Not applicable.
Statistical Methodology	The maximum effect of the ketamine infusions on symptoms for each participant will be assessed by conducting paired t tests between the lowest score from the post-treatment assessments and the baseline symptoms levels. The time to relapse for each participant will be calculated and an average relapse time for the group will be reported. Exploratory analysis will be done on changes in brain function, connectivity and chemistry, as well as in peripheral blood biomarkers.

1 Introduction

This document is a protocol for a human research study. This study will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonisation guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Depression frequently emerges during adolescence and is associated with severe outcomes. Current interventions do not lead to remission for many adolescents. Treatment-resistant depression (TRD) in adolescence is an ominous prognostic indicator for a lifetime of suffering and increased risk for suicide. Efforts should be directed toward novel interventions that could alter this perilous course. Theoretically, restoration of healthy development during this critical window would substantially improve outcomes over the lifespan.

Ketamine is a noncompetitive, high-affinity antagonist of the *N*-methyl-D-aspartate type glutamate receptor that has long been used for induction and maintenance of anesthesia in children and adults, and recently has been investigated for its rapid antidepressant effects.

No results from any studies examining effectiveness of either single-dose or serial-dose ketamine have yet been published in adolescents with TRD. Because of the ongoing neurodevelopment in adolescence, which is thought to confer enhanced neuroplasticity, it is possible that adolescents with TRD could show greater responses and more sustained remission than adults with TRD. The biological mechanisms of depression impacted by ketamine are only now being uncovered in adults (Zarate et al., 2013). Characterization of the neural mechanisms underlying ketamine response or non-response in adolescents with TRD will represent a significant advance.

1.2 Investigational Agent

The effects of ketamine are mediated by N-methyl-D-aspartate, opioid, muscarinic and different voltage-gated receptors. It has hypnotic, analgesic and amnesic effects (Sinner & Graf, 2008). Ketamine is water and lipid soluble, which allows it to be administered in different ways (intramuscularly, intravenously, intranasally, rectally and orally) and distributes widely throughout the body including crossing the blood brain barrier. It has a molecular weight of 274.4M, its chemical formula is C13H16ClNO, and its melting point is between 258°C and 261°C (Sinner & Graf, 2008). The IV dose used for anesthesia ranges between 1 to 4.5 mg/kg (Elia & Tramer, 2005; Sinner & Graf, 2008). The median dose for analgesia is 0.4 mg/kg (Elia & Tramer, 2005), similar to that used for depression. Dose reported in the drug abuse literature is typically 1/8 g usually taken intranasally. Metabolism of ketamine is primary hepatic and it is excreted in the urine; metabolism half-life is 2.5-3 hours (Sinner & Graf, 2008).

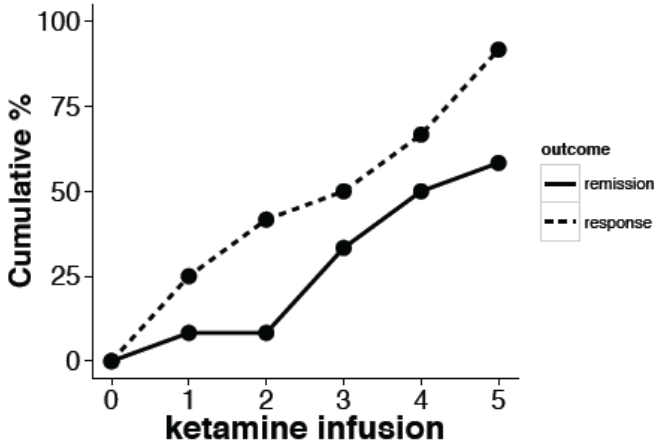
1.3 Preclinical Data

Despite the fact that depression frequently emerges during adolescence (Kessler & Walters, 1998) and that many adolescents do not respond to treatment (March et al., 2004), ketamine has not yet been tested in adolescents. However, recent research using animal models of depression has suggested that repeated doses of ketamine alleviated depressive behaviors in both adolescent and adult rats (Parise et al., 2013). Due to the enhanced neuroplasticity associated with the developing brain, adolescents with TRD may show greater and more sustained response to ketamine than adults with TRD.

1.4 Clinical Data to Date

Randomized, double-blind, saline-controlled trials in adults with TRD have demonstrated that a single, subanesthetic infusion of intravenous (IV) ketamine at 0.5 mg/kg over 40 minutes can produce a rapid (within 2 hours) antidepressant response (Ibrahim et al., 2011; Zarate et al., 2006). Recent evidence suggests that serial doses of ketamine may be even more effective and may lead to more prolonged remission (aan het Rot et al., 2010; Murrough et al., 2012). Our current research with using serial dosing of IV ketamine among adult veterans with TRD over a 2-week period has shown promising results, with a response rate of 92% among the 12 participants to date.

Our motivation to test the efficacy of IV ketamine in adolescents with TRD stems in part from our encouraging experience testing repeated-dose IV ketamine in adult veterans with TRD (PI Lim) at the Veterans' Affairs (VA) Medical Center in Minneapolis (Shiroma, Journal of Affective Disorders 2013, *in press*). Patients receive 6 infusions of IV ketamine 0.5mg.kg over 60 minutes, with infusion visits occurring 3 times weekly for 2 weeks with no "wash-out" period. So far, as indicated below, a 90% cumulative response rate has been observed. The duration of response (i.e. time to relapse) has been considerably longer than other studies (i.e. 2-3 weeks (Murrough et al., 2013)). At 4 weeks, 50% of the patients in our study have still not relapsed. Ten adults have completed treatment to date.



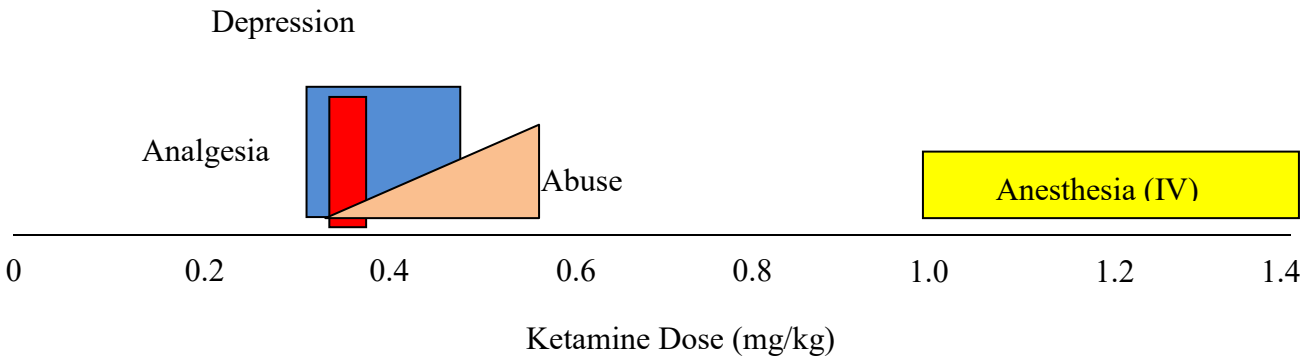
With its rapid onset of action, ketamine provides an ideal tool for the study of biomarkers in major depressive disorder (MDD). Prior studies have used neuroimaging, including functional magnetic resonance imaging (fMRI) (Scheidegger et al., 2012), positron emission tomography (PET) (Carlson et al., 2013), and magnetoencephalography (MEG) (Salvadore et al., 2009; Salvadore et al., 2010), and proton magnetic resonance spectroscopy (proton MRS) (Salvadore et al., 2012) in ketamine trials to further elucidate the underlying biological mechanisms of MDD. We have been developing tools for examining neural circuitry in adolescents with MDD (Cullen et al., 2009; Cullen et al., 2010) which we plan to apply in the proposed study to examine neural mechanisms of ketamine action.

Another avenue for understanding the mechanisms of response to ketamine in TRD is to examine the cellular mechanisms associated with stress and resilience. MDD and other mental illnesses provide significant stress on an individual, and research has shown that there are deleterious neurobiological effects that result from chronic stress. Allostatic overload occurs in certain chronic medical disorders that are associated with chronic stress such as mood disorders (Brietzke et al., 2011). Allostatic overload leads to compromised resilience, rendering the organism more vulnerable to disease (Karatsoreos & McEwen, 2011). Evidence suggests that there is a correlation between enhanced cellular aging, as seen by reduced telomerase activity and telomerase length, and TRD (Wolkowitz et al., 2012) and it is hypothesized that allostatic overload is the driving factor. Insulin signaling and cytokine responses are two key cellular pathways that are chronically altered through the process of allostatic overload over time (Tanti et al., 2013). We hypothesize that the rapid effects of ketamine to reverse depression symptoms may occur via reversal of these systems. Through experimental procedures including white blood cell challenge, we hope to identify how these key cellular adaptations are associated with disease severity and treatment response to ketamine.

1.5 Dose Rationale and Risk/Benefits

Subjects will receive an IV infusion of 0.5 mg/Kg of ketamine hydrochloride over 40 minutes. The dose is based on antidepressant effects of patients with major depression reported in previous studies (Ibrahim et al., 2011; Zarate et al., 2006). The dose of ketamine will be determined by actual body weight.

The IV dose used for anesthesia ranges between 1 to 4.5 mg/kg (Elia & Tramer, 2005; Sinner & Graf, 2008). The median dose for analgesia is 0.4 mg/kg (Elia & Tramer, 2005), similar to that used for depression. The dose reported in the drug abuse literature is typically 1/8 g usually taken intranasally (see graphic below).



As a laboratory agent, ketamine has several desirable qualities. It has a short-half life; it is relatively easy to administer; it does not usually cause cardiovascular or respiratory depression and it has been well-studied in clinical settings (Reich & Silvay, 1989). Recent literature supports the safety of using ketamine as an ideal anesthetic for children emergency room settings because of its positive safety profile including lack of respiratory suppression (Dolansky et al., 2008). In the lower doses used for antidepressant treatment reported in the literature, short-term side effects are very infrequent, mild, and transient (Carpenter, 1999; Lahti et al., 2001). These side effects include perceptual and mood changes and impairment in memory, attention and abstract reasoning, euphoria, elevations in blood pressure, dizziness, and increased libido, as well as gastrointestinal distress, increased thirst, headache, metallic taste, and constipation (Reich & Silvay, 1989). In the long-term, subanesthetic doses yielded no reports of emotional or psychological problems, cognitive deficits, medical or neurological problems, cravings for ketamine, use outside the research setting, unusual perceptions, sluggishness, flashbacks or paranoid thoughts (Perry et al., 2007). These findings further document the lack of long-term effects previously reported with anesthetic doses of ketamine (Moretti et al., 1984) and support the FDA-approved drug insert about the safety of ketamine:

"Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of ketamine (up to ten times that usually required) have been followed by prolonged but complete recovery".

2 Study Objectives

Primary Objective:

To determine the efficacy of repeated-dose subanesthetic IV ketamine among adolescent patients with treatment resistant depression (TRD). *Hypothesis:* Based on previous results in adults with TRD, we predict that response rates will improve over the course of six treatments of ketamine.

Secondary Objectives:

To explore the durability of antidepressant response to repeated dose of IV ketamine in a 6-week observational period. *Hypothesis:* Based on the inherent neuroplasticity in adolescence due to ongoing neurodevelopment, adolescents may show a more durable clinical response than has been seen in adults.

To study the neurobiological mechanisms of response to ketamine. We will explore how clinical improvement relates to change in brain function, brain connectivity, brain chemistry, and in peripheral blood biomarkers of neuroplasticity and cellular resilience.

3 Study Design

3.1 General Design

This is a single-group (n=20) open-label pilot study of 6 doses of IV ketamine, 3 doses per week over a 2-week period, followed by a 4-week post-treatment observational period. Symptom levels will be assessed prior to infusion, directly after infusion, 1 and 2 hours after infusion. We will also assess symptoms weekly for 6 weeks after the last ketamine infusion. A study goal is to identify neurobiological biomarkers of treatment response using neuroimaging and blood studies.

3.2 Primary Study Endpoints

The primary outcome measure is response status as defined by Children's Depression Rating Scale (CDRS) (Poznanski, 1985)Responders will be defined as having a significant reduction in their CDRS score (≥50%) whereas non-responders will be defined as subjects whose scores do not show such a significant reduction or whose score increase. The percent change will be calculated by the formula below (Tao, 2009):

(Baseline CDRS – Exit CDRS) / (Baseline CDRS – 17)

Baseline CDRS: CDRS score obtained on Visit 1 – Baseline Assessment (Section 6.1)
Exit CDRS: the latest CDRS score obtained on Visit 10 - Clinical Assessment (Section 6.6) or Visit 11-16 – Follow-up Period (Section 6.7)

3.3 Secondary Study Endpoints

1. Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) score of ≥50%. The MADRS has been used in most previous ketamine studies in adults and is designed to be sensitive to change. Although it has not been validated in adolescents, it has been used in several previous treatment studies of adolescent depression (Berard et al., 2006; von Knorring et al., 2006).
2. The Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al., 1998)
3. The Profile of Mood States-Adolescent Version (POMS-A) (Terry et al., 1999)
4. The Beck Depression Inventory-II (Beck, 1988) which has been validated for adolescents (Osman et al., 2004)
5. The four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall, 1962) consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization.
6. Relapse will be defined as a CDRS score ≥50% of the pre-ketamine baseline. The onset of relapse will be calculated as the day halfway between the date of relapse and the previous date of response.
7. Biological endpoints will include MRI-based measures and blood-based measures of neuroplasticity.
8. The Clinical Global Impressions Scale (CGI) (Guy, 1976)
9. The Dot Pattern Expectancy task (2017) The DPX-task is a neurocognitive task that measures an aspect of goal representation known as context processing using pairs of simple dot patterns. In this task, there are four types of trials, and we refer to the trial type using letters: A means valid target, B means invalid target; X means valid cue, Y means invalid cue. Most of the trials are "target trials" (AX); in these types of trials a valid cue (A versus B) is followed by a valid probe (X versus Y). The 3 other trial types are "Non-target trials" in which either a valid cue is followed by an invalid probe (AY) or an invalid cue is followed by either a valid probe (BX) or invalid probe (BY). Participants are required to make one response for target trials, and another response for non-target trials. The nature of the cue (valid or invalid) provides the "context" for responding on a given trial. The intent of having the majority of trials as "target trials" (AX) is to encourage participants to "expect" a valid probe to follow a valid cue. A consequence of this manipulation is that participants develop a prepotency to respond with "target" responses on trials for which valid cues are presented, regardless of whether the trials were of the target (AX) or non-target (AY) type. Non-target cues provide the context that a non-target response will be required, regardless of the nature of the probe (valid or invalid). The expectancy manipulation is designed to increase AY error rates. On BX trials, participants with normal context processing must maintain the cue in order to inhibit the prepotency to respond to valid probes with a target response. Compared with controls, persons with impaired context processing may be expected to make more BX errors, whereas the AY condition is more difficult for people with intact context processing. (Jones, Sponheim & MacDonald 2010; MacDonald, III, Carter, Flory, Ferrel & Manuch, 2007; MacDonald et al, 2005).

3.4 Primary Safety Endpoints

Primary safety endpoints will consist of vital signs (blood pressure, pulse, oxygen saturation, and respiratory rate), measured every 15 minutes during the administration of ketamine and every 30 minutes in the ensuing 2 hours, and the Clinician-Administered Dissociative States Scale (CADSS) (Bremner et al., 1998).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Patients will be eligible to participate in the study if all of the following conditions exist:

1) Willing and able to provide informed consent and assent.

2) Male and female adolescents aged 12 to 18 years.

3) Presence of recurrent MDD confirmed by the K-SADS-PL (Kaufman et al., 1997).

4) Current depression severity measured by the Children's Depression Rating Scale (CDRS) (Poznanski, 1985) raw score greater than or equal to 36 at screening and the day ketamine is due to be received for the first time.

5) Current depressive episode resistant to treatment, defined as failure to achieve remission (elimination of symptoms and restoration of pre-morbid psychosocial functioning) from at least 2 antidepressant trials. Systematic evaluation of previous antidepressant trials will be assessed by using the Antidepressant Treatment History Form (Sackeim, 2001).

6) If present, current antidepressant medication treatment must be dose stable for at least 2 months prior to beginning the study*

7) Participants should have a medical history and physical examination in the 30 days prior to initiating the ketamine infusions.

4.2 Exclusion Criteria

Patients will be excluded from participation in the study if any of the following conditions exist:

1. Inability to speak English

2. A history of Mental Retardation or Autism Spectrum Disorder

3. Current or lifetime diagnosis of schizophrenia, schizoaffective disorder, psychosis not otherwise specified (NOS).

4. Diagnosis of seizures or other neurological disorders.

5. Comorbid diagnosis of substance abuse or dependence within 6 months of assessment.

6. Clinically unstable medical illness.

7. Current use of barbiturates, narcotics, or non-benzodiazepine hypnotics at doses higher than Zolpidem 10 mg or equivalent for insomnia.

8. For females: pregnancy.

9. Inability to undergo an MRI scan.

10. A Family History notable for having at least one first-degree relative with schizophrenia, schizoaffective disorder, psychosis not otherwise specified (NOS).

* If there has been a recent discontinuation of a medication, we will require lapses of time before study entry as follows: Antidepressants (excluding Fluoxetine) – 2 weeks; Fluoxetine – 4 weeks; Mood Stabilizers – 2 weeks; Antipsychotics – 2 weeks; Stimulants – 1 week.

4.3 Subject Recruitment and Screening

Adolescents with treatment resistant depression who have been admitted to the adolescent mental health inpatient unit, who present to the University of Minnesota Psychiatry Adolescent Mood Clinic, or who are referred from outside clinicians, and who meet inclusion and exclusion criteria for the study, will be invited to participate.

Prior to enrollment, project staff selected to recruit for this study will screen review records from the hospital and clinical services noted above to determine potentially eligible adolescent participants. If an adolescent appears to meet basic criteria for the study (appropriate age and diagnosis), staff will then check the consent for treatment form in the patient's chart. If parents indicated on that form their willingness to have their child's medical records used in research, study staff will then contact the current treating provider to determine whether the provider feels it would be appropriate to invite this participant into the study. If so, the provider will request written permission of the adolescent and/or the parent for the study staff to contact them regarding the study. The study staff will then contact the parents by phone or in person to inform them about the purpose and activities of the current study.

We anticipate that some families will hear about our study through word of mouth or by searching on ClinicalTrials.gov. We will post information about the study in the community using flyers and online posting boards.

If after hearing about the study from study staff patients/families are interested in participating, the study staff will then conduct a screening form to ensure eligibility. If parents are interested and the adolescent is eligible, the first study visit will be scheduled. Informed consent will be obtained at the time of the first study visit.

4.4 Early Withdrawal of Subjects

When and How to Withdraw Subjects
A subject may be withdrawn from the study prior to expected completion for the following reasons:

- Participant experiences adverse side effects to the ketamine treatments that are intolerable to the adolescent or the parent.
- Participant fails to adhere to protocol requirements
- Participant or participant's parent(s) withdraw consent

If a subject exits the study for any reason (withdrawal, non-response, or relapse), he or she will continue his or her pre-study regimens and consult with his or her psychiatrist about the next step in treatment.

Data Collection and Follow-up for Withdrawn Subjects
For all participants, we will request permission during the consent process to collect naturalistic follow-up data through in person visit to clinic or video conference 6 months after the 6-week study period.

The naturalistic follow-up encounter will be as follows:

We will ask permission to contact the family to inquire about the participant. Subjects will be determined lost to follow-up if they do not respond to 4 e-mails to the primary e-mail address of parent(s) or 4 phone calls to their primary number or to their next-of-kin, or to a certified letter.

During the follow up in person visit to clinic or video conference subject will be asked to provide:

a) A narrative interval history including following elements
    a. Changes in medications and their effects
    b. Therapies or other treatments they have undergone and their effects
    c. Evolution of their symptoms during the interval
    d. Any hospitalizations including cause and outcome
    e. Any suicide attempts including precipitating factor (if any) and outcome

b) Participate in a clinical interview in order for clinician to complete an assessment using CDRS-R, CADSS, CGI, and MADRS.
c) Complete the BDI-II, Profile of Mood States – Adolescent, SHAPS and TEPS

5 Study Drug

5.1 Description

Study solutions of ketamine will be prepared as a liquid in 50mL IV bag, with 0.9% saline and a dose of ketamine that equal 0.5mg/kg of the subject's actual body weight, dissolved into the saline.

5.2 Treatment Regimen

At each of the ketamine treatment visits, subjects will receive an IV infusion of 0.5mg/Kg of ketamine hydrochloride over 40 minutes. To ease IV placement, we will use emla cream, or if necessary, J tip (a needle-free injector that uses compressed air to propel lidocaine beneath the skin's surface, numbing the area). The dose of ketamine will be determined by body weight.

Each participant will undergo a total of 6 ketamine infusions over a 2-week period (on a Monday, Wednesday, Friday schedule).

For this pilot study we do not include a placebo in the design. After confirming the feasibility of recruiting adolescents with TRD to a ketamine study and showing preliminary evidence of efficacy and mechanism, a future step will be to conduct a randomized placebo controlled trial.

Patients will continue with current antidepressant treatment throughout the study. Based on our experience in current research at the VA Medical Center using serial ketamine dosing, patients have shown positive results while continuing their current antidepressant treatment.

5.3 Method for Assigning Subjects to Treatment Groups

Not applicable. There is only one treatment group.

5.4 Preparation and Administration of Study Drug

The IV ketamine study medication will be prepared in the Investigational Pharmacy and administered by the nursing staff in the Journey Clinic.

5.5 Subject Compliance Monitoring

Since the study medication is administered in an infusion unit, compliance with study medication will be measured by whether participants present to infusion visits and cooperate with all procedures of IV ketamine administration. To be compliant with other aspects of the study, participants will be required to attend two MRI scans, six ketamine treatment visits and six weekly follow-up visits. The follow up visits may take place in person or, for subjects who do not reside within convenient travel distance to Minneapolis, via phone or video conference. Study staff will monitor whether the participant is attending these visits. If a participant is not compliant with study procedures, his/her participation in the study will be terminated.

5.6 Prior and Concomitant Therapy

If present, current antidepressant treatment (pharmacological, augmenting agents, and non-pharmacological) must be dose stable for at least 2 months prior to beginning the study. Patients will continue with current antidepressant treatment throughout the study. Based on our experience in current research at the VA Medical Center using serial ketamine dosing (Shiroma 2013), patients have shown positive results while continuing their current antidepressant treatment.

5.7 Packaging

Commercially available ketamine hydrochloride will be purchased 10 mL vials of 50mg/mL ketamine. Cartons of study drug vials will be purchased to ensure sufficient drug is available for at least five subjects at a time.

5.8 Blinding of Study Drug

Not applicable.

5.9 Receiving, Storage, Dispensing and Return

Receipt and Storage of Drug Supplies

The local site pharmacist will purchase and store the commercially available study drug. Ketamine must be stored between 20 and 25 degrees Celsius, and protected from light. Ketamine vials will be stored in carton until time of use.

Dispensing of Study Drug

The local site pharmacist will dispense the study drug, which will be openly labeled for investigational use only. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Visit 1 – Baseline assessment

As a first step, informed consent will be obtained from the parents/guardians of the adolescent and assent will be obtained from the adolescent by authorized members of the study team. If the adolescent is able to provide consent legally, such consent will be obtained from him/her. We will attempt to obtain consent from both parents except where it is not possible (e.g. death of a parent, parent does not have custody) or it is prohibitive to do so (e.g. parent lives in another state, parent is unavailable during reasonable business hours).

Demographic information will be obtained from the adolescent and the parent(s)/guardian(s) using “Ketamine Demographics Form”.

The adolescent and the parent(s)/guardian(s) will participate in a semi-structured diagnostic interview (the Kiddie Schedule for Affective Disorders and Schizophrenia, parent and lifetime version – K-SADS-PL). During this interview, a complete psychiatric history will be obtained for each participant. We will systematically evaluate the history of previous antidepressant trials using the Antidepressant Treatment History Form (Sackeim, 2001). Adolescent participants will complete a self-report Beck-Depression Inventory-II to assess depression severity as well as Snait-Hamilton Pleasure Scale (SHAPS) and Temporal Experience of Pleasure Scale (TEPS) to assess anhedonia severity. The clinician will complete a Children’s Depression Rating Scale-Revised, a clinical interview with both adolescent and parent/guardian (separately), to assess depression severity. Clinicians will also complete the Columbia Suicide Severity Rating Scale (CSSRS), Brief Psychiatric Rating Scale (BPRS) and Montgomery-Åsberg Depression Rating Scale (MADRS). Additionally, the clinician will also administer the two subset version of the WASI to estimate intelligence. Finally, the participant will be asked to complete DPX-task. If participants meet inclusion criteria they will be scheduled for the subsequent procedures. For participants that have not had a medical history and physical examination completed within the past 30 days, this will be completed at the end of the baseline visit by one of the medical doctors on the research team.

6.2 Visit 2 – MRI scan

Participants will be undergo an MRI scan before the first ketamine treatment and after the last ketamine treatment using a Siemens Prisma 3 Tesla scanner located in the University of Minnesota Center for Magnetic Resonance Research (CMRR). Before the scan, the parent/guardian will be asked to complete an MRI safety screening form for their child and the adolescent will be asked to provide a urine sample, which will be used to test for the presence of illicit drugs and (for females) pregnancy. If either result is positive, the participant will not be able to continue with the study. The scanning protocol will consist of two functional MRI scans (one during rest and one during an emotion task), a high-resolution T1-weighted anatomical image, and a diffusion tensor imaging sequence. Participants will be transported to the CMRR by their parents. If the participant is on the inpatient service, the treating physician will write a pass to allow the

family to take the patient for several hours to complete the scanning. If the study physician and/or the family do not feel that a pass would be appropriate due to safety concerns, the MRI visit will be waived.

6.3 Visit 3 – First ketamine infusion

On the day of each infusion, participants will arrive at the University of Minnesota Masonic Children's Hospital - Journey Clinic infusion center. Adolescent participants who are currently inpatient on the adolescent psychiatric ward will be escorted to the Journey clinic by hospital staff (four floors up the elevator). Adolescent participants who are outpatient will arrive at the Journey Clinic with their parent or guardian. An indwelling catheter will be placed in the non-dominant arm for ketamine administration and for two blood draws at the first infusion visit.

At this visit, directly before the ketamine infusion, participants will have 20 cc of blood drawn into heparinized tubes. They will have a second blood draw two hours after the infusion is complete. The blood samples will be sent to Dr. Susannah Tye at the Mayo Clinic for analysis.

Subjects will receive IV infusion of 0.5 mg/Kg of ketamine hydrochloride over 40 minutes. Digital pulse oximetry, respiratory rate, heart rate and blood pressure will be recorded every 15 minutes throughout the infusion, beginning 15 minutes before infusion. Vital signs will be monitored for at least 2 hours post infusion, to be assured there are no lingering side effects before leaving the unit.

Prior to infusion, participants will be asked to complete the BDI-II, SHAPS, TEPS and POMS-A, and a trained member of research staff will complete the Clinical Global Impressions Scale (CGI) (Guy, 1976), BPRS+, MADRS, CADSS. At the end of the infusion and 1 hour post infusion, participants will be asked to complete SHAPS, TEPS and POMS-A, and a trained member of research staff will complete BPRS+ and CADSS. At 2 hours post infusion, participants will be asked to complete the BDI-II, MADRS, SHAPS, TEPS and POMS-A, and a trained member of research staff will complete the Clinical Global Impressions Scale (CGI) (Guy, 1976), BPRS+, MADRS, CADSS.

If adolescent reports experiencing nausea or vomits during the infusion or the subsequent 2-hour observation period, the PI will evaluate the adolescent's reported symptoms and determine if (a) P.R.N. Ondansetron is indicated at that time (0.15mg/kg, up to 8mg), and (b) pre-treatment with IV Ondansetron for control of nausea is warranted for the subsequent infusions.

Participants will be asked about any adverse events (AE) and concomitant medications at each visit.

To be discharged from the infusion unit, the adolescent must meet the following discharge criteria:

1) Stable vital signs
2) Pain is under control
3) A return to the level of consciousness that is similar to the baseline for that patient
4) Adequate head control and muscle strength to maintain a patent airway
5) Nausea and/or vomiting is not present
6) The patient is adequately hydrated.

After each infusion, adolescents will either return to the inpatient unit escorted by hospital staff, or if they are outpatient, will return home escorted by their parent(s). Participants (and parents if outpatient, or hospital staff if inpatient) will receive written discharge instructions regarding rare but serious side effects from ketamine and several measures to improve recovery at home.

6.4 Visits 4-8 – 5 subsequent ketamine infusions

Participants will undergo a total of six ketamine infusions within a 2-week period (on a Monday-Wednesday-Friday schedule). The 5 subsequent treatments will be conducted in the same way the first treatment was conducted (please see section 6.3 for details), except the blood draw only occurs before the first and after the last infusion.

After the conclusion of the 6th ketamine infusion (after participants has past the "2 hour post infusion" time point during the 6th clinic visit). Participants will again have 20cc of blood drawn by venipuncture, which will be handled in the same way as other blood draws (see section 6.3 for further details).

If adolescent has experienced nausea or vomited during any prior infusion and PI has determined that pre-treatment with IV Ondansetron is appropriate for management of adolescent's nausea symptoms, adolescent will receive IV Ondansetron at a dose of 0.15 mg /kg (up to 8 mg) via the same IV port established for infusion of ketamine immediately before the administration of ketamine.

6.5 Visit 9 – Second brain MRI

Within 1 week of the last ketamine infusion, participants will undergo another brain MRI identical to the previous one (please see section 6.2 for more details).

6.6 Visit 10 – Clinical assessment and blood draw

Also within one week of the last ketamine infusion, participants will come to the Ambulatory Research Center or participate in a phone or video conference for clinical evaluation to assess their clinical response to the ketamine infusions. At this visit, the following assessments will be completed to determine response to treatment: Columbia Suicide Severity Rating Scale – Since Last Visit (CSSRS-SLV), Montgomery-Asberg Depression Rating Scale (MADRS), Clinician-Administered Dissociative States Scale (CADSS), Profile of Mood States-Adolescent Version (POMS-A), Snaith-Hamilton Pleasure Scale (SHAPS), Temporal Experience of Pleasure Scale (TEPS), Beck Depression Inventory-II (BDI-II), Clinical Global Impression (CGI), and Brief Psychiatric Rating Scale (BPRS). Also, the clinician will complete a Children's Depression Rating

Scale-Revised, a clinical interview with both adolescent and parent/guardian (separately), to assess depression severity. The participant will also be asked to perform the DPX-task.

6.7 Visits 11-16 – Follow-up period

All participants will be asked to speak with the research team for weekly follow-up visits for 6 weeks. Participants will continue to take medications as prescribed by their doctor. At each of these visits, participants will be asked about any medication changes and will complete the same assessments as administered in visit 10 (MADRS, CADSS, POMS-A, SHAPS, TEPS, BDI-II, CGI, CDRS and BPRS).

All participants will be asked to participate in the 6 weekly follow-up visits, regardless of response.

6.8 Schedule of Events Table

	Consent	Interview	Questionnaires in-person	MRI	Blood draw	Ketamine infusion
Initial visit	X	X	X			
Within a week from first visit				X	X	
Week 1 *Monday						X
Week 1 Wednesday						X
Week 1 Friday						X
Week 2 Monday						X
Week 2 Wednesday						X
Week 2 Friday						X
Within a week from last infusion		X	X	X	X	
Follow-Up Week 1			X			
Follow-Up Week 2			X			
Follow-Up Week 3			X			
Follow-Up Week 4			X			
Follow-Up Week 5			X			
Follow-Up Week 6			X			

*The Monday, Wednesday, Friday schedule does not have to start on a Monday, it can start on a Wednesday or Friday, but treatments will always occur on these days and the total time will always be 2 weeks.

7 Statistical Plan

7.1 Sample Size Determination

In view of the lack of any reports on ketamine in adolescent depression, the study sample was based on published studies in adult depression.

7.2 Subject Population(s) for Analysis

Data from each participant who completes the six ketamine treatments will be subjected to the primary study analysis. We will conduct secondary analyses on all participants who received at least one dose of treatment.

7.3 Statistical Methods

In the following analyses, primary outcome measures will include the “per protocol” population. The secondary measures will include the “intent to treat” population.

Primary analysis: Paired t tests will be conducted between the lowest score from the post-treatment assessments and the baseline symptom levels to assess the maximum effect of ketamine infusion on symptoms for each person.

Secondary Analyses:

1. We will calculate the time to relapse for each participant.
2. Biological Mechanisms:
    a. Neuroimaging data: Paired t tests will be conducted to evaluate pre- and post ketamine treatment changes in measures of brain functional activation, connectivity, white matter microstructure and brain metabolite concentrations. These preliminary data will be used to identify responsive measures and estimate sample sizes that would be needed to use these measures as endpoints in future studies.
    b. Bimolecular studies to examine mechanisms of cellular resilience (insulin challenge, cytokine testing, gene expression) will be conducted to evaluate change in these pathways before and after ketamine. Analyses will be conducted by Dr. Susannah Tye at Mayo Clinic. Peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood and divided into two groups. The first group will not receive any treatment. RNA will be extracted and whole genome microarray will be performed using illumina's genome-wide gene expression arrays. Differential pre- versus post-ketamine mRNA levels will be quantified and bioinformatics pathway analysis will be used to identify key differences in molecular responses to ketamine. A second subset of PBMCs will be cultured and cryopreserved. Once all samples are collected cells will be immortalized to ensure sufficient tissue availability. The following two separate analyses will then be performed:

i. Group 1 PBMCs will be stimulated with insulin and intracellular Akt, mTOR, and GSK3 gene and protein levels will be quantified following 0, 5, 15, and 30 minutes of stimulation. This signaling pathway is implicated in mediating the antidepressant response to ketamine. Western blot and rtPCR techniques will be used to quantify protein and gene expression, respectively;
ii. Group 2 PBMCs will be immortalized and undergo inflammatory challenge via stimulation with phytohemagglutinin. Levels of cytokines and kynurenines will be measured in the culture medium 1, 3 and 24 hours post-stimulation. ELISA kits will be used to quantify proinflammatory cytokine levels.

Outcomes of each assay will be correlated with patient response profile. All tissue will be destroyed upon completion of the study.

Interim Analysis: The above analyses will be conducted on data from the first ten subjects to ensure that there is preliminary support for the proposed hypotheses.

8 Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs a hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-

patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as *non-serious adverse events*.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Post-Study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be

reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

Adverse Event Recording
At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

SAE Recording
A Serious Adverse Event (SAE) form must be completed by the investigator or study team member within 24 hours of finding out about the event. The investigator must determine causality and confirm the severity of the event in the SAE form. The sponsor-investigator will keep a copy of this SAE form on file at the study site.

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that

will assist the understanding of the event. Significant new information of ongoing serious adverse events should be provided promptly to the sponsor-investigator.

8.3 Reporting of Serious Adverse Events

IRB Notification by Investigator
Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the regulatory binder.

Any other event not defined as an SAE, yet unanticipated, related and increases risk to subjects must be reported to the IRB within 10 working days, as defined in the IRB's UPIRTSO guidelines.

FDA Notification by Sponsor
The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

Summary Table of Reporting Requirements

Agency	Criteria for Reporting	Timeframe	Form to Use	Submission address/fax numbers
U of MN IRB	SAE: fatal, life-threatening or serious, unexpected, at least possibly related	10 working days	UMCC SAE	
	UPIRTSO For all unanticipated events that	10 working days	IRB's UPIRTSO form	MMC 820

	increase risk to subjects or others			
FDA	SAE: fatal, life-threatening, unexpected, at least possible related	7 calendar days	FDA prefers MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter)	Fax: 1 (800) FDA - 0178
	SAE: serious, unexpected, at least possibly related	15 calendar days		

8.4 Unblinding Procedures

Not applicable.

8.5 Stopping Rules

The study will be stopped if new results either from our study or from other studies arise suggesting that the risks of the study medication significantly outweigh the benefit.

8.6 Data and Safety Monitoring / Auditing

Medical Monitoring
The Principal Investigator will oversee the safety of the study at the University of Minnesota site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Study Monitoring Plan

Independent monitoring of the clinical protocol will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the UMN CTSI in accordance with the monitoring plan.

This study will be monitored according to FDA/GCP guidelines. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Internal Data and Safety Monitoring Board

An internal independent, 3-person panel of physicians and researchers will conduct a reassessment of the risks and benefits to study participants. This panel will review all adverse events for severity and frequency. Dr. Gail Bernstein, M.D., Dr. Jeff Wozniak, Ph.D., and Dr. Sanjiv Kurma, M.D. will review the safety of the study after the first five participants have completed at least the first infusion. The results of their review will be submitted to the IRB. Subsequent reviews will occur annually.

Auditing and Inspecting
The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after

verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, “N/D” will be written. If the item is not applicable to the individual case, “N/A” will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line through the incorrect entry will be drawn and the correct data will be entered above it. All such changes will be initialed and dated. Errors will never be erased or whited out. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

9.4 Records Retention

As applicable the Investigator-Sponsor will retain the specified records and reports until 2 years after investigations under the IND have been discontinued and the FDA so notified. In addition, University policy states in part that researchers should maintain a file of all documents concerning the use of human subjects in research for 3 years from completion of IRB related work and 6 years for HIPAA.

10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided an assent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. Parents and/or guardians of the subject will be given a parent/guardian consent form that describes the study. The consent and assent forms

will be submitted with the protocol for review and approval by the IRB for the study. The formal assent of a subject and consent of the parent/guardian, using the IRB-approved consent and assent forms, must be obtained before that subject is submitted to any study procedure. The assent and consent forms must be signed by the subject and parent/guardian, respectively, and the investigator-designated research professional obtaining the consent. Although only one signature of one parent/guardian is required for this treatment study, the study team will attempt to obtain the signatures of both parents.

11 Study Finances

11.1 Funding Source

The study is funded by the Clinical Science Translational Institute at the University of Minnesota, under the K to R Transition to Independence Award Program.

11.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must refer to the Regents Policies on Individual Conflict of Interest Policy or Institutional Conflict of Interest Policy. These policies require University Faculty and staff to report external professional activities and business and significant financial interests related to his or her University activities by submitting a REPA (Report of External Professional Activities) at least once per year. Faculty and staff should also file a REPA when substantial changes in business or financial interests occur, when an activity that presents a potential conflict of interest is anticipated, or when submitting an application for research support or technology transfer, submitting research protocols to the IRB, or receiving financial contributions. All University of Minnesota investigators will follow the University conflict of interest policy.

11.3 Subject Stipends or Payments

Each child participant will be compensated up to $220 for completing the entire study: $40 for the baseline assessment, $20 for the clinical assessment after 6 infusions, $40 for each MRI assessment (total of 2), $20 for the naturalistic follow up visit at 6 months and $10 for each of the weekly follow-up visits (up to 6). Participants will not be reimbursed for ketamine treatment visits. For participants who start but do not finish the study, monetary compensation will be pro-rated according to each completed visit. Parking will be reimbursed for each of the visits.

12 Publication Plan

Upon completion of the data collection, data analysis and interpretation of the results, the results of the study will be published in one or more peer-reviewed Psychiatry journal(s) by the investigators.

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14 List of Reference Documents

The following study related documents will be maintained in the regulatory binder.

- Parental consent form
- Child assent
- Consent form for adult participants (over age 18)
- Addendum assent for female minors
- Phone screen
- Questionnaires/Rating Scales
    - ATHF Antidepressant Treatment History Form
    - BDI-II Beck Depression Inventory-II
    - BPRS Brief Psychiatric Rating Scale
    - CADSS Clinician-Administered Dissociative States Scale
    - CDRS Children's Depression Rating Scale
    - CGI Clinical Global Impressions
    - CSSRS Columbia Suicide Severity Rating Scale
    - K-SADS-PL and Lifetime Kiddie-Schedule of Affective Disorders and Schizophrenia-Present
    - MADRS Montgomery-Asberg Depression Rating Scale
    - POMS-A Profile of Mood States – Adolescent
    - SHAPS Snaith-Hamilton Pleasure Scale
    - TEPS Temporal Experience of Pleasure Scale
    - WASI Weschler Abbreviated Scale of Intelligence
    - DPX task Dot Pattern Expectancy task

- Data Monitoring Plan
- Ketamine hydrochloride package insert