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COMPOUND AUTHORIZATION FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE

Study Title: Reducing Adolescent Suicide Risk: Safety, Efficacy, and Connectome Phenotypes of Intravenous Ketamine
Principal Investigator (the person who is responsible for this research): Michael Bloch, MD, MS, 230 S. Frontage Rd., New Haven, CT 06519
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Research Study Summary:

- We are asking you to join a research study.
- The main purpose of the study is to find out if intravenous (IV) ketamine lowers suicidal thinking in teenagers who have hard to treat depression and a recent suicide event. A "suicide event" means either a suicide attempt, an emergency room visit for suicidal thinking, or moving to an inpatient unit for suicidality in the past 120 days.
- We compare ketamine to an "active placebo" called midazolam. Midazolam is a different kind of medicine than ketamine. From now on, when we say "placebo", we mean midazolam.
- We are also testing if certain brain-based measures, gotten by functional MRI neuroimaging, can tell us whose symptoms will get better with ketamine. This research also looks at how ketamine impacts the body's medical systems (liver function, kidney function, and bladder function) and how it impacts mental health symptoms in the 16 weeks after treatment.
- **Study procedures include:**
    - (1) clinical interviews and questionnaires,
    - (2) four intravenous (IV) medication treatments (you will get either ketamine or the active placebo medicine (midazolam); you have a 50/50 chance of getting ketamine. Neither you nor the doctor will know which medicine you get),
    - (3) if you get the active placebo medicine and you are still depressed or suicidal after the four treatments, you may get four IV ketamine treatments thereafter,
    - (4) three 1-hour visits where you will lay in an MRI while they rest or do some tasks, and
    - (5) after the IV treatments, we give standard of care adolescent depression treatment for 16 weeks. This means medication management by a Child and Adolescent Psychiatrist and an 8-week course of cognitive behavioral therapy (CBT) by a Child and Adolescent therapist. If feasible, we would prefer that you come in person for CBT sessions, if clinically appropriate these sessions may be offered remotely via telehealth assessment.
- **Number of Visits:** 24 visits are needed over 4 and a half months. If you get the placebo medicine first and want to get four ketamine treatments after that, the total number of visits goes up to 30 over 5 months.
- **Time per visit:** There are a few different kinds of visits, which take different amounts of time. The visits at the start of the study take the longest, and then tend to get shorter later in the study.

APPROVED BY THE YALE UNIVERSITY IRB 5/29/2024

- The first study day (the “baseline”) has lots of questions about mood and mental health, and an MRI. It happens on a day before the IV treatment starts and will take about 4 hours.
- The first and second IV treatment days will take about 5 hours each and are spaced two days apart. We do not schedule activities in between these days so that you can rest.
- The third and fourth IV treatment days are shorter, and take about 2.5 hours.
- During the 4-months after the four IV treatments (the “open phase”), weekly visits for CBT (8 weeks) and medication checks take about an hour.
- After the 8 weeks of CBT is over, weekly mood checks will take about 30 minutes and can happen over the phone. The monthly in-person mood and thinking/remembering questions will take about 1.5 - 2 hours.

- **Possible Risks:** There are some risks from being in in this study. Ketamine and the placebo medicine (midazolam) are FDA approved for anesthesia but they are not FDA approved for depression or suicidal thinking in adults. The FDA considers ketamine to be an Investigational New Drug in this study. The doses used in this study are lower than what someone would get for anesthesia and the study team has used them before in teenagers with depression. But they do still carry risks when they are given. Some risks are mild and common, such as nausea, feeling sleepy, feeling “out of it” or other psychological symptoms, and changes in blood pressure, heart rate, or breathing. Other risks are more rare but serious, such as changes in heart rhythm, severe slowing of breathing, big changes in blood or eye pressure, or psychological reactions that go on for a longer time. The level of risk of giving repeated doses of ketamine over time is not known. Rare, but serious possible longer-term risks implied from animal studies include brain toxicity, cognitive or thinking problems, liver and bladder inflammation (swelling), and substance abuse or dependence. Other study risks include discomfort from blood draws and getting an IV, discomfort from answering sensitive mental health questions, and feeling confined or having anxiety during an MRI. It is also possible that mental health symptoms could get worse during the study. Feeling worse could be due to the natural ups and downs of the illness, being assigned to placebo treatment (although we limit this risk by the option to get ketamine treatment after 2 weeks), or not having a therapeutic response to ketamine.

- **Possible Benefits:** The study might also directly help you. Studies with adults show that ketamine improves depressive symptoms and suicidal thinking in some patients, usually for a short time, or several days. The placebo (midazolam) is also used to help anxiety in children and adults, but often has shorter lasting effects than ketamine. If you get midazolam at first, you will be offered ketamine treatment after if you still feel depressed or have suicidal thinking. During all parts of the trial, the increased time spent with a child psychiatrist and research staff may be helpful to you.

- **Other options:** There are other choices available to you instead of this study. One other option is to continue your current mental health medications or therapy. Another option is to choose other depression treatments that are available from your doctor. There are multiple medicines and therapies that have been shown to help depression in teenagers. Another choice is to join a different pediatric depression study.

- **Safety:** Your safety is very important. If we think that you are in immediate danger ofhurting yourself or someone else, hospitalization is required. A hospitalization does not automatically mean that you cannot be in the study anymore. We will work with you, and your clinical teams to decide whether staying or leaving the study is in your best interest.

- Agreeing to take part in this study is your choice. You can choose to participate, or you can choose not to. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights orbenefits.

- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need beforeyou make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish agree to participate; if so, you will have to sign this form.

Why is this study being offered to me?
We are asking you to join a research study because you have hard to treat depression and recent suicidal thinking. Hard to treat depression means that you are still depressed after trying an antidepressant medicine. You also must have had serious suicidal thinking or action in the last 120 days. We are looking for 40-66 adolescents to be part of this research study.

Who is paying for the study?
The National Institutes of Mental Health (NIMH) is paying for this study. The NIMH research grant is R01MH125203.

Who is providing other support for the study?
None

What is the study about?
The main purpose of this research study is to find out if IV ketamine reduces suicidal thinking compared to an active placebo (a different medication, midazolam) in adolescents who have hard to treat depression and a recent “suicide event”. A “suicide event” can mean a suicide attempt. It can also mean an emergency room visit for suicidal thinking, or a move to an intensive outpatient or inpatient care for suicidality. “Recent” means within the last 120 days.

We are also testing whether certain brain-based measures, obtained by functional MRI brain imaging, can tell us who will feel better with ketamine. We also want to know how the brain changes with treatment. This research also looks at how ketamine impacts the body’s medical systems (liver function, kidney function, and bladder function) and how it impacts mental health symptoms in the 16 weeks after treatment. Ketamine has not been FDA approved for treating depression or suicidal thinking for patients of any age.

What are you asking me to do and how long will it take?
If you agree to join this study, this is what will happen:

Screening Visit:

The purpose of the screening visit is for us to tell you about the study. We will tell you about the risks, benefits, and other options. This visit is also for the research team to get to know you to see if the study might be an appropriate fit. After you give your consent, we begin the main study screening procedures to see if you can be in the study. The study screening usually happens in a single visit and takes between 2 and 3 hours. The visit includes a clinical evaluation, a review of past treatments, a medical assessment, and a urine test for drug use and pregnancy. We will ask you sign a release of information so that we may talk to your mental health providers. We will establish a connection with them so that we can talk to each other throughout the study. We will also give you a doctor's order to get lab tests after your visit.

Clinical Evaluation: This study is for adolescents (13 to 17 years old) who have hard to treat depression and recent suicidal thinking or action. Hard to treat depression means that you have a diagnosis of Major Depressive Disorder and are still depressed after trying an anti-depressant medicine. First, we will interview you to understand your mental health history. We will focus on depression and other disorders related to your condition. We will review your medical history, your current medications, and all other medication and behavioral treatments for depression that you have tried. If we find that you have hard to treat depression and had significant suicidal thinking or behavior within the last 120 days, we will go to the next step, which is the medical assessment.

Medical Assessment: The study doctor will perform a brief physical exam, including getting vital signs. We will give you a lab order to get an electrocardiogram (ECG) to trace the electrical activity of your heart. We will also give you a lab order for blood collection and urine collection, to check your health. Blood collection happens by venipuncture (entering a vein with a needle through the skin) and about 2 tablespoons of blood are needed. These are standard medical checks to make sure that you are healthy and eligible for the study. If any worrisome finding is seen in your blood work or ECG results, the primary study doctor or another doctor will contact you. They will tell you about the finding and discuss what they recommend from there. The decision to get additional medical exams or treatment would be completely up to you and your regular doctor. The investigators, the consulting doctor, and Yale University are not responsible for any exams or treatment that you get based on these findings.

Rating Scales: Trained research staff will ask you to complete rating scales about your feelings and behaviors. These rating scales are research-related. They will find out if you meet diagnosis and severity criteria for the study. To be eligible for this study, you must have had significant symptoms of depression and recent suicidal thinking. You will be asked to complete surveys which include questions about depression, thoughts of suicide, appetite and weight, quality of sleep, memory, energy level, and current feelings, etc. For some surveys the doctor will ask you the questions and for others you will use a tablet to read questions and give answers on your own. Study staff will be present at all times to assess safety.

Drug, Alcohol, and Pregnancy Testing: Female participants of childbearing potential will require pregnancy testing by a blood test before they can be in the study. Once you are in the study, you will have urine pregnancy tests during the treatment phase. Only you will be told the results. We will, of course, counsel you to seek appropriate healthcare and if you were found to be pregnant. A positive pregnancy test means that you cannot be in this study. If you are not comfortable with pregnancy testing, then we would recommend that you do not participate.

The medicines used in this study pose a risk to an unborn baby if they are taken while pregnant. For this reason, sexual abstinence is strongly recommended. Contraceptive use is required for any heterosexually active participants during the treatment phase and for a certain time after that. For females, that time is 30 days after the last dose of study medication. For males, that time is 90 days after the last dose. Forms of contraception that we accept include: hormonal birth control being taken for at least 1 month before screening, intrauterine device, condom with spermicide (cream, spray, foam, gel, suppository, or polymer film), diaphragm with spermicide (with or without condom), cervical cap with spermicide (with or without condom), or vaginal sponge impregnated with spermicide used with a condom. Not having sex at all (sexual abstinence) is strongly recommended. Participants who practice total abstinence from sexual intercourse as their preferred lifestyle are not required to use additional contraception. Male participants are also asked to use a condom if their partner is pregnant and agree not to donate sperm during the study. Please tell your study doctor right away if you think you might be pregnant or are planning a pregnancy.

We will also need to ask you about current or past use of alcohol and illicit "street" drugs. We will require a urine toxicology screen on the screening day and at other times during the study. If you decide not to join the study, this drug testing information will be destroyed. If you are using drugs now or have a history of drug dependence, you will not be able to participate in this study. However, if you choose not to share, we must keep this information confidential. If you are uncomfortable with drug testing or talking about drug use, then we would recommend that you do not join this study. Throughout the study, if you are in immediate danger of hurting yourself or someone else, we will refer you to get an emergency evaluation.

Baseline (Study Day 0, Visit 1)

Once screening is complete (including review of lab results), we will know if you are eligible for the study. If eligible, you will be enrolled in the study and we will schedule the baseline visit. We ask you, and your outpatient psychiatrist to avoid making any medication changes. This means not changing the medicine type or the dose until the follow-up phase of the study. The baseline visit occurs on a Monday and lasts about 4 hours.

Rating Scales and Questionnaires: You will come to the Child Study Center to complete the baseline clinical assessments. Questionnaires are about both mood and cognition, which refers to how someone thinks and remembers. We expect the questionnaires and cognitive testing to take about 2 hours.

Safety Planning: You will meet with the study therapist. You will work together to create your safety plan. This includes identifying triggers, coping skills, and people to call if there is a crisis. We will include phone numbers for the study staff, including a 24-hour phone number for a study clinician. We will ask you to keep copies of the plan in places that are easy to find in your home. We will review and update the plan throughout the study.

MRI neuroimaging: After the questions, a member of the research team will bring you to the Magnetic Resonance Research Center (MRRC). They will stay with you for the entire scan. There, you will review safety procedures with study staff, including walking through a metal

detector. Part of your body will be passed into a long, narrow tube – the MRI scanner – which is open at both ends. You will lie on your back in the scanner.

The MRI machine is very loud. You will be given ear plugs, and headphones will be placed over your ears to dampen out the sounds of the machine (the MR system). You may have a clip placed on your finger to monitor your pulse, and a belt placed across your abdomen to monitor breathing patterns. Your head will be cradled in pillows and a special holder before being moved into the MR magnet in order to help you keep still throughout the study. The researchers operating the MR system will be able to see you, and you will be able to talk with them while in the magnet. You will be able to see out into the room via a mirror prism. When the study starts, we will begin taking images of your brain. When an image is being taken, the machine will make a short burst of noise. You will be required to lie as still as possible. You will be inside the scanner for 1 hour. For some portion of this time, while we perform scans of the function of your brain, you will participate in computer tasks in which you will look at a screen inside the scanner, listen to information presented through headphones (loud enough to hear despite the earplugs), or both. For some tasks, you will press buttons in response to the task. For other portions of the time in the scanner, you will not need to do any task.

MRI tasks include:

1. Card guessing task: You will be shown a card on a screen and will have to guess whether the number on the other side of the card is less than or greater than five. The card will then be flipped over and you will be told if you guessed correctly via feedback on the screen.
2. N-back task: You will be asked to watch a set of pictures (or words) and push a button if a new picture (or word) is the same as the previous item (1-back condition) or as the item that came two items before (2-back condition).
3. Response inhibition task: You will see items on the screen and either respond (go trial) or not respond (no-go trial), depending on the presented item.
4. Understanding mental states task: You will be asked to infer the perspective of others, either by looking at photographs of their eyes and labeling the emotions of the person in the picture, or by responding to questions that require you to interpret social “hints” in vignettes.
5. Perception: You will be asked to passively watch images on a screen or listen to sounds through headphones, which could include flashing checkerboards, movie clips, beeps and tones, blank screens, etc.
6. Resting state run: You will be asked to stay still with his or her eyes open during the resting runs. There is no task involved.

<u>Phase A1: Double Blind Phase</u> (doctors and participants do not know which medicine you are assigned) (IV Treatments on Days 1, 3, 8, 10 Visits 2 – 6 and Post-Treatment (Day 11, Visit 7)

Once enrolled, you will be scheduled to receive four IV treatments over a 2-week period. You will get either ketamine (the study drug) or midazolam (the active placebo). IV treatments occur on Tuesdays and Thursdays. The first treatment will be on Visit 2 (Day 1). The Yale Investigational Drug Service will decide which medicine you get. Neither you nor the study doctors and nurses will know which treatment was assigned during these first 2 weeks. In an emergency, we can find out right away which medicine you got. All IV treatments will happen at the Interventional Psychiatry Service (IPS) at Yale Psychiatric Hospital.

We ask you to follow American Society of Anesthesiologists eating guidelines the night before the treatments. These rules allow milk or a “light meal” 6 hours before the treatment and clear liquids up to 2 hours before. One hour before the IV treatment, catheters (small plastic tubes) will be placed in your arm or hand. These are used to give the IV treatment and to collect samples of blood (approximately 2 tablespoons total). On the first treatment day (Day 1, Visit 2), two IV’s will be placed to make bloodwork collection easier. On the other IV treatment days only one IV will be placed. The blood samples are only used for research. They will be used to measure the way that ketamine is broken down in the body. Before each treatment, you will be asked a series of questions by a trained research staff member who is supervised by a licensed professional. The questions are about your depression symptoms, and other psychiatric conditions or physical symptoms. You will get an ECG before the first IV treatment, and a rapid urine drug screen and urine pregnancy test (if applicable) before the first and third treatments. Before the second IV treatment (Day 3, Visit 4), you will have your second brain imaging session. The brain imaging tasks are the same as the ones you did at baseline. The scanning session will take less than 1 hour. For the day in between the first and second treatments, we will not ask you to come in, but will check in with you by phone. On the phone, we will ask about mood and any physical symptoms (estimated phone time of 20 minutes).

Once questionnaires and medical checks are finished (estimated to take 30 minutes to 1 hour), we will start the IV treatment. The medication (ketamine or placebo) will be given through the IV catheter in your arm or hand, which takes 40 minutes. Afterward, the study doctor will ask you questions to check how you are feeling. Your vital signs will be monitored for two hours after the IV treatment. A doctor who has extra training to handle medical emergencies (Advanced Cardiovascular Life Support certification), a trained research nurse, and a psychiatrist will be present at all times during the treatment and recovery. You will come back on Day 11 (Visit 7), which is the day after the last IV treatment. This in-person visit includes an in depth assessment of mood, thinking, and remembering. It will take about 2 hours. After the rating scales are finished on Day 11, the study doctor will contact the pharmacy to ask which medicine you have been getting. If you were getting the active placebo (midazolam) and your mental health symptoms have not gotten significantly better, we will discuss with you the option for you to get four ketamine IV treatments, starting the next week.

The first IV treatment visit will take about 5 hours. It is longer than the others because of blood draws after the IV treatment. The second treatment visit will take about 4 hours. It is longer because of the brain imaging session. The treatment visits after that will take about 3 hours. Another responsible adult must be available to take you home from this visit. You should not drive for 24 hours following the procedure. The in-person follow-up visit on Day 11 will take about 2 hours.

<u>Phase A2: Open Phase IV Ketamine Treatments</u> (doctors and participants know that you are getting ketamine)—this phase is only available if you received the active placebo in the first phase (A1) and did not get significant symptom improvement. **(IV Treatment on Days 15, 17, 22, 24 Visits 8 – 12 and Post-Treatment Day 25, Visit 13).**

In the first phase of the study (A1), you will get either ketamine or the active placebo (midazolam). So that we can offer active ketamine treatment to all participants who still have severe symptoms, at the end of the first 2 weeks, we will find out which medicine you got. If you

got midazolam and still have severe symptoms, we will offer you the choice to now get 4 ketamine treatments. If you decide to do this, the study procedures are identical to the ones described in Phase A1. That includes additional blood tests on the first IV treatment day (Day 15) and a brain imaging session before the second IV treatment (Day 17). The four open IV ketamine treatments will be followed by an in-person assessment on Day 25 (Visit13).

If you got ketamine during the first 2 weeks, you will go directly to Phase B. If you got midazolam in the first 2 weeks and your symptoms got much better, you will also go directly to Phase B. There are no additional ketamine treatments for these groups.

Table 1. Study Outline for First Phases (A1 and A2)

	Screening	Baseline (D0)	D1	D3	D8	D10	D11
			(D15)	(D17)	(D22)	(D24)	(D25)
IV Treatment			X	X	X	X	
Physical Exam	X						
ECG	X		X				
Blood Draw	X		X				
Urine Tests	X		X		X		
Brain imaging		X		X			
Symptom Questionnaires	X	X	X	X	X	X	X
Cognitive Testing (assesses thinking and remembering)		X					X
Estimated Total time	2-3 hours	4 hours	5 hours	4 hours	3 hours	3 hours	2 hours

Phase B: Open Phase Follow-up and Standard of Care Depression Treatment

(Visits 8 – 24 for participants proceeding directly from Phase A1)

(Visits 14 – 30 for participants proceeding from Phase A2)

After finishing the IV treatments, we provide you with standard of care depression treatment through the study. We used the guidelines of the American Academy of Child and Adolescent Psychiatry to design the treatment. You will get medication management visits with a Child and Adolescent Psychiatrist. You will also get an 8-week course of CBT with a trained therapist. In this phase, you will have weekly mood check-ins and monthly in-depth mood and cognitive assessments with our research staff. If feasible, we would prefer that you come in person for CBT sessions, if clinically appropriate these sessions may be offered remotely via telehealth assessment.

The study team works to group study procedures with the standard of care depression treatment to make visits more convenient. In the first 8 weeks of follow-up, visits include about 30 minutes of symptom questionnaires, a 15-minute med management visit, and a 45-minute CBT session (total visit is about 1-1.5 hours). Every fourth week, there is a more in-depth assessment of mood, thinking, and remembering, that you must come in for. This is instead of the basic mood symptom questionnaires. These visits will take about 2.5 hours.

If there is a pandemic or public-health related reason that you can't come in person, we may have these visits by telehealth.

For the last 8 weeks of the follow-up phase, the course of CBT will have ended. Then, the brief mood questionnaires can happen over the phone (taking about 30 minutes). The only required in person visits will be for the last two monthly in-depth mood and cognitive assessments.

Table 2. Study Outline for Second Phase (Follow-up)

Study Day		CBT	Medication Management	Brief mood question-aires	Mood and Cognitive Testing	Blood and Urine Labs	Location	Estimated Time
D17	(D31)	X	X	X			In person/Telepsychiatry	1.5 hours
D24	(D38)	X	X	X			In person/Telepsychiatry	1.5 hours
D31	(D45)	X	X	X			In person/Telepsychiatry	1.5 hours
D38	(D52)	X	X		X		In person/Telepsychiatry	2.5 hours
D45	(D59)	X	X	X			In person/Telepsychiatry	1.5 hours
D52	(D66)	X	X	X			In person/Telepsychiatry	1.5 hours

D59	(D73)	X	X	X			In person/Telepsychiatry	1.5 hours
D66	(D80)	X	X		X	X	In person/Telepsychiatry	2.5 hours
D73	(D87)			X			Telepsychiatry	30 minutes
D80	(D94)			X			Telepsychiatry	30 minutes
D87	(D101)			X			Telepsychiatry	30 minutes
D94	(D108)		X		X		In person	2 hours
D101	(D115)			X			Telepsychiatry	30 minutes
D108	(D122)			X			Telepsychiatry	30 minutes
D115	(D129)			X			Telepsychiatry	30 minutes
D122	(D136)		X		X	X	In person	2 hours
D126	(D140)	Discharge Visit					In person	1 hour

Discharge from the study
If you are still very depressed or at increased suicide risk at the end of the study, the study will help make referrals. Referrals could include other outpatient mental health doctors, intensive outpatient programs, or inpatient psychiatric hospitals. The study staff may continue close monitoring of you if your symptoms put you at elevated risk until the referrals are in place.

What are the risks and discomforts of participating?

(A) Risks of Ketamine and Midazolam

The experimental (study) drug in this study, ketamine, is a medicine approved by the FDA to be used as an anesthetic in children and adults. An anesthetic is a medicine used to block

sensations or pain, and to make people drowsy or sedated during surgery. Ketamine is not FDA approved to treat depression or suicidal thinking in adults or children. All of the risks of ketamine are not fully known. The dose of ketamine used in this study is lower than the dose typically used for anesthesia. You will be told that it is possible for people to abuse ketamine. It is unclear whether exposure to ketamine in the laboratory can result in recreational ketamine use or abuse. If you are concerned about this possibility, you should not join this study.

The active placebo drug, midazolam, is a medication that is approved by the FDA as a sedative for both children and adults. It is a benzodiazepine used commonly in pediatric dentistry and conscious sedation. “Conscious sedation” means ways to use medicines to relax people or decrease pain without putting them fully to sleep. It is often given more quickly and at higher doses than in the current study. Midazolam is not FDA approved for depression treatment or suicidal thinking in adults or children. We do not expect it to improve depression symptoms or suicidality. If used often, midazolam also has the potential for physical dependence and abuse.

Now we will describe the potential effects of ketamine or midazolam that you may or may not experience. Both midazolam and ketamine are medicines that are broken down quickly by the body. Side effects are not typical after 30 to 60 minutes after getting the medicine. Our research group has significant experience giving ketamine and midazolam to adolescents with depression.

The most common short-term side effects of these medications are:

1. Elevated blood pressure, breathing rate, heart rate, and sweating
2. Local pain at injection site and temporary rash
3. A variety of temporary psychological symptoms including, but not limited to anxiety, sadness, disorientation or confusion, decreased concentration, decreased pain, feeling high, feeling detached from surroundings, flashbacks, hallucinations (hearing or seeing things that are not really there), dream-like sensations, changes in the way colors or sounds are perceived, changed bodily sensations (e.g. floating), and psychotic symptoms.
4. Many people also experience sleepiness, sedation, or blurred vision
5. Nausea, vomiting, hiccups: the risks of vomiting will be minimized if you do not eat anything on the morning of the IV treatments. If you still get nauseous, we can give an anti-nausea medicine called ondansetron. If given for nausea, 4mg of ondansetron is given by mouth. The dose can be repeated one more time for a total amount of 8mg. There may be side effects from taking ondansetron and we will tell you about those.
6. Headache

Less common short-term side effects of these medications are:

1. Respiratory depression or slowed breathing
2. Enhanced muscle tone causing shakiness and jerking movements

Rare but serious possible short-term risks or side effects of these medications are:

1. Changes in heart rhythm

2. Severe slowing down or stopping of breathing (apnea)
3. Elevations in intraocular pressure (eye pressure) that could lead to vision problems
4. Recurrences of psychological side effects such as hallucinations, disorientation, or anxiety up to 24 hours after the dose administration.
5. Allergic reactions are possible. Serious allergic reactions can be life-threatening
6. Elevation in blood pressure that could result in stroke, heart problems, and death
7. Drop in blood pressure

We believe that the risks of serious adverse heart or breathing events are low because we have chosen low doses for this study. In any case, airway equipment and qualified medical personnel will be readily available.

Rare but serious possible longer-term risks of these medications are:

1. Neurotoxicity: risk is larger in young children (less than 3 years old) and is thought to relate to high doses or long exposures. However, the exact dose or number of exposures that can cause these problems in humans is unknown. High amounts of ketamine given to rats caused damage to different parts of the brain. It is not known whether this finding in rats will happen in humans, but the ketamine doses given to you will be lower than the amounts given to the rats in the animal study.
2. Adverse effects on cognition (thinking and remembering): The added effect of repeated ketamine treatments is unknown. People who have taken ketamine many times (mostly people who are abusing ketamine for recreational purposes) have structural and functional brain changes that are associated with cognitive problems. We are uncertain if this will occur with the four ketamine doses proposed in this study. We will be carefully following your cognitive function during this study with monthly neurocognitive testing.
3. Liver and bladder inflammation: Bladder and liver inflammation have been related to the repeated use of ketamine (mostly in people who are abusing ketamine). We are uncertain if this will occur with the four ketamine doses proposed in this study, however we will be monitoring liver, kidney, and bladder health at 2 months and 4 months into the study.
4. Substance abuse/dependence: If at any point after completing this study you become aware that you are having a desire to use or abuse ketamine or midazolam, you should contact us right away. We will refer you to an appropriate treatment facility if necessary. In our experience doing research with these medicines, we are unaware of people abusing ketamine as a result of being in a study.

You will be evaluated by a clinical member of the research staff before leaving the IV treatment visits. This is to ensure that all clinically significant medication effects have gone away and that it is safe to leave the research site. Before arriving, please arrange how you will be transported back home. You should not drive to avoid any difficulties with lingering sleepiness. Some people have reported mildly decreased concentration or a ‘hangover’ on the day after receiving these medications, or more vivid dreams.

People with a history of mental health problems may be more likely to have an unpleasant experience when taking these medicines. So, please tell us as much as you can about your past and present mental health difficulties during screening.

We also take a number of precautions to help reduce the chance of having an unpleasant response to the study medications and to reduce the severity of any potential lingering effects. These precautions include:

1) A research clinician will be there throughout the study visit to offer support. They can also help spell out the progress of the treatment day in case the medicine makes you feel confused. A research doctor will also be available.
2) If you experience psychological distress, diazepam may be given. Diazepam is a medicine that helps to quickly reduce anxiety. If used for anxiety, 5mg of diazepam is given by mouth one time.
3) We will ask you to stay at the treatment site for at least two hours after the behavioral effects of the study medications are expected to wear off. Please see study schedule for the details of each IV treatment day.
4) We will review the treatment day with you to explore any feelings and reactions to the session before leaving.
5) We will ask you to contact us at any time if any unpleasant effects occur.
6) We will ask you not to engage in demanding work on the day after the treatment sessions.
7) If you have any medication effects that last longer than expected, such as drowsiness, we will terminate the remaining test days. We will work with you and you until these side effects have resolved.
8) If your mental health significantly worsens, you will be referred to the Yale-New Haven Hospital Psychiatric Emergency Room for further evaluation and treatment. No adult patients getting ketamine for depression in research studies have needed psychiatric hospitalization because of side-effects of ketamine or midazolam given during the study. If you are determined to be an acute danger to yourself or others, psychiatric hospitalization would be required.
9) This study is designed to evaluate the anti-depressant, anti-suicidal, and safety profile of the study medicines in the 16 weeks after the last dose. We will have frequent contact with you over those 16 weeks post-treatment. Please see Table 1 for the contact schedule during the treatment phase. See Table 2 for the contact schedule during the 16-week post-treatment phase.

(B) Risks of Neuroimaging (MRI) studies

Magnetic resonance imaging (MRI) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The FDA has set guidelines for magnet strength and exposure to radio waves. We carefully observe those guidelines.

You will be watched closely throughout the MRI study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time, and we will take you out of the MRI scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste, or feel tingling sensations or muscle twitches. These sensations usually go away quickly, but you should tell the research staff if you have them.

There are some risks with an MRI study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this portion of the study because the strong magnets in the MRI scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk, we require that all people

involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. It is also necessary to know whether you have a tattoo or a self-tattoo, and where the tattoo is located. You will be instructed to inform the research team if you feel pain, burning, or an uncomfortable sensation at the tattoo site.

We want you to read and answer very carefully the questions on the MRI Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MRI Safety Questionnaire. Please be sure to tell us any information you think might be important.

This MRI study is for research purposes only and is not in any way a healthcare exam. The scans performed in this study are not designed to find abnormalities. The principal investigator, the lab, the MRI technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MRI scans and are not responsible for providing a healthcare evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact you. They will inform you of the finding regarding your exam, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie only with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any exam or treatment that you gets based on these findings. The images collected in this study are not a healthcare MRI exam and, for that reason, they will not be made available for healthcare purposes.

If you are unable to get an MRI or feel very uncomfortable getting an MRI, please let us know. You may still be able to do the treatment parts of the study if you meet all of the other study criteria.

(C) Risk of Blood Drawing/IV placement: This study requires drawing blood and the placement of an IV needle into your arm in order to deliver the study medicines. These procedures may cause pain, bruising, lightheadedness, fainting, and, on rare occasions, infection. These risks will be minimized by using trained personnel who will draw blood and insert IV needles under sterile conditions. A total of 5 tablespoons of blood be drawn over the first 2 weeks. That includes 2tbsp at baseline and 3tbsp on the first IV treatment day (Day 1). If you go on to get ketamine treatment after at first being assigned to placebo, another 3tbsp will be drawn on the first day of the ketamine series (Day 15). We collect labs two more times during the 4-month open phase (Phase B). We collect 2tbsp at the half-way point and 2tbsp at the end.

(D) Risk of Questionnaires: As part of the study, you will be asked to complete questionnaires about your feelings and behaviors. It is possible that you may find these questionnaires to be upsetting. However, these questions have been used in research before and a negative reaction has been uncommon. A trained researcher will be asking these questions under the supervision of a study doctor. You do not have to answer any questions that make you feel uncomfortable.

(E) Risk of Worsening Symptoms: There is a risk that you may experience an increase in depression symptoms or suicidal thinking. This could be due to the natural course of the illness or being given the placebo during the first 2 weeks. It could also be because of a poor response to ketamine treatment. You will be asked not to change any of your medicines during the first 2 weeks of the study, there will be frequent follow-up by the study team. Additionally, the standard of care treatment for a child or adolescent who insufficiently responds to initial antidepressant therapy is to try another antidepressant or add an additional medication. By participating in this trial, you would be delaying the standard of care change in your medication by 2-4 weeks. If you feel that your symptoms are getting worse, you will be evaluated by a clinic psychiatrist. You will be provided treatment if appropriate, in collaboration with your outpatient mental health provider(s). Referrals may be given if a higher level of care (such as an intensive outpatient program) is recommended. If you are in immediate danger of hurting yourself or someone else, hospitalization is required. Being hospitalized does not automatically mean that you must leave the study. We will work with you and the hospital team to decide whether staying or leaving the study is in your best interest. If new medicines are needed to treat the worsening symptoms, you should know that this decision will not affect your eligibility to participate in future studies. It also will not affect your chance to get treatment at the Yale Child Study Center or Yale New Haven Hospital, or to get treatment on a private basis from a referring doctor. Everyone in the study will be given wallet-sized cards, which provide contact information. The cards will identify the HIC number of the study, the study PI (Michael Bloch, MD, MS 203-745-9921), and the Yale Investigational Drug service phone number (203-688-4872). They will also have telephone contact numbers for research support staff.

(F) Risk of time commitment: The first two weeks of the study are busy. It is likely that it will be hard to be at school full-time while getting the experimental treatments. If you get placebo at first, then ketamine after, the next two weeks are busy also. Not being at school full-time everyday can impact school performance. The study team can provide doctor's notes for school or another commitment to explain why you were absent. We can also suggest that your school allow re-arranging assignments or modifying the workload during this part of the study.

(G) Risk of Remote Assessments: Like online shopping, videoconferencing technology has some privacy and security risks. It is possible that information could be intercepted by unauthorized people (hacked) or otherwise shared by accident. This risk can't be completely eliminated, however Yale has approved the use of an encrypted version of zoom for videoconferencing sessions because the appointments take place over a secure encrypted network. We want to make sure you are aware of this.

Video sessions can be conducted using a smart phone, tablet or personal computer enabled with a camera/microphone and internet connection. You should use your home computer or personal device, and not a shared or work device, and use a home (private) Wi-Fi network, and not free (public) Wi-Fi for your internet connection. To use zoom, an e-mail will be sent to you including the instructions for how to log-in. When meeting with the team remotely for study-related activities, you should be in a private space.

There is limited experience with ketamine in the treatment of teenage depression. Therefore, the study may involve risks and side effects that we cannot predict or foresee.

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about you taking part in this study.

How can the study possibly benefit me?

The study has the potential to directly benefit you. Studies with adults show that ketamine improves depressive symptoms and suicidal thinking in some patients. This is usually for a short time, or several days. Midazolam (the placebo) is used to reduce anxiety in children and adults. Midazolam typically has shorter lasting effects than ketamine (lasts for minutes to hours). Even if you get midazolam in the first phase, you will have the option to get open ketamine treatment afterward if you still have significant depression or suicidal thinking. During all parts of the trial, you may get some benefit from increased contact with a child psychiatrist and research staff. Through this study you will also receive a thorough medical and mental health evaluation.

How can the study possibly benefit other people?

The benefits to science and other people may include a better understanding and treatment of depression and suicidality in teenagers. Your involvement may also help us better understand how brain function links to treatment outcomes with these medications.

Are there any costs to participation?

If you join this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only. “Research only” means that it is NOT part of your routine medical care. However, there may be additional costs to you. These can include costs of transportation and the time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance.

Will I be paid for participation?

To try to offset costs related to your travel and time, you will be paid in the following way:

Completing the 2-week double-blind phase: $40
If applicable: completing the 2-week open ketamine phase: $40

Open Phase:
Completing all 4 visits and rating scales in Month 1: $80
Completing all 4 visits and ratings scales in Month 2: $80
Completing all 4 visits and rating scales in Month 3: $80
Completing all 5 visits and rating scales in Month 4: $80

You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

We will use a Bank of America pre-paid debit card to provide the payment for taking part in the study. We will have to share your name, address, and telephone number with Bank of America for ePayments. You will receive a card in the mail with the first payment. You will need to activate the card over the phone. Each additional payment will be automatically added to your card.

What are my choices if I decide not to take part in this study?

Instead of joining this study, you have some other choices.
You could:

- Get treatment without being in a study. Other options involve continuing your current medicines or therapy. The study doctor will discuss these with you. You do not have to join this study to be treated for depression. There are multiple medicines and behavioral therapies that have been shown to be effective for pediatric depression. Examples of medicines include fluoxetine, sertraline and other selective-serotonin reuptake inhibitors. Examples of psychotherapy include cognitive behavior therapy. Electroconvulsive therapy is FDA approved for severe adolescent depression and can beappropriate.
- Take part in another study.
- Receive comfort care only, without any treatment for your disease.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if we learn that someone is hurting a child or an older person.

Any study records that identify you and the study parental permission form and assent form signed by you will be locked in a file cabinet in the Yale Child Study Center. They will be made available only to the researchers on this study. Any electronic study information will be stored on a password-protected computer. When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We understand that information about you obtained in connection with your health is personal. We are committed to protecting the privacy of that information. If you decide to be in this study, we will obtain information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, date of birth, address, and telephone number. This information will be de-identified at the earliest reasonable time after we receive it. That means that we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information. This link will be kept secure and available only to the members of the research team that need it. Any information that can identify you will remain confidential. All study materials will be kept in locked storage cabinets and password protected computers in

locked rooms. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 2 years after the study is over. After the that time, the link will be destroyed, and the data will become anonymous. The data will be kept in this anonymous form for 7 years after completion of the study and then will be destroyed.

What information will you collect about me in this study?

The information we are asking to use and share is called "Protected Health Information (PHI)." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records.
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by Yale New Haven Hospital or Yale Medicine created between the date of signed consent and the end of your participation in the research study.
- Records about phone calls made as part of this research
- Records about your study visits.
- Information obtained during this research regarding
    - Physical exams.
    - Laboratory, x-ray, neuroimaging results, and other test results.
    - Diaries and questionnaires.
    - The diagnosis and treatment of a mental health condition.
    - Use of illegal drugs or the study of illegal behavior.
    - Records about any study drug you received.

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies (for example, NIMH).
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board, who are responsible for ensuring research compliance. The Institutional Review Board is the committee that reviews, approves, and monitors research on human participants. These individuals are required to keep all information confidential.
- The FDA. This is done so that the FDA can review information about ketamine for use in adolescents with depression and suicidality, which is not currently an FDA-approved use of this medicine. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Health care providers who provide services to you in connection with this study.

- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- The study's Principal Investigator.
- Co-Investigators and other investigators.
- Study Coordinator and Members of the Research Team.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct ofthe Study.

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

If you decide to join this research study and you are a female, you will be asked to have a pregnancy test before starting this study. Only you will be told the results. If you are pregnant, we will advise you to get care for your pregnancy and to get the support of a medical professional. Females under the age of 13 with a positive pregnancy test require a report to the Department of Children and Families, however this study only includes adolescents 13 or older.

Certification of Confidentiality (CoC)
We will also be asking you for urine samples, which we will test for drugs of abuse. This research is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. The CoC protects the researchers from being forced, even under a court order or subpoena, to release research information that could identify you.

Information protected by this CoC cannot be shared with anyone else who is not connected with the research except in the cases below.

- One exception is if there is a federal, state, or local law that requires us to disclose information. Examples include reporting child or elder abuse, certain communicable diseases, or when we believe you may harm yourself or someone else. If we find that you are experiencing abuse, we will give you a list of additional resources and referral options for trauma treatment.
- Another exception is if you have consented to us sharing the information. Signing this permission form means that you agree to the information sharing we describe. This includes releasing data to a clinician involved in your medical or mental health treatment. It also includes the release of your de-identified data to a public data repository. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.
- A third exception is if it is used for other scientific research, as allowed by federal regulations that protect research participants.

This research is sponsored by the Department of Health and Human Services (DHHS) through the NIMH. The CoC cannot be used to refuse a request for information from staff from the NIMH and other DHHS agencies that is needed for auditing or program evaluation. Researchers must also submit any information that must be disclosed to meet FDA requirements.

Even with the CoC, you and your family members must still continue to actively protect your own privacy. If you voluntarily give your written consent for anyone to receive information about your participation, then we may not use the CoC to withhold this information.

Data Sharing for Future Research

We may also share de-identified information about you with other researchers for future research. “De-identified information” means that all personal information about research participants such as name, address, and phone number is removed. It is replaced with a code number so that there is no information that can directly identify you. We will not ask you for any additional permission. Once de-identified information or biospecimens could be used for future research studies or given to another investigator for future research studies, we will not need additional informed consent from you.

De-identified data from this study will be submitted to the NIMH Data Archive (NDA) at the NIH. The NDA is a large data repository that allows researchers studying mental illness and healthy cognition to collect and share de-identified information with each other. A data repository is a large database where information from many studies is stored and managed. During and after the study, the researchers will send de-identified information about your health and behavior to the NDA. Other researchers across the world may then obtain access to your de-identified study data for research purposes. Sharing de-identified study data helps researchers learn new and important things about mental health more quickly than before.

Every researcher (and the institutions where they work) who requests the deidentified study data must promise to keep the data safe. They also must promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce privacy risks. Sharing your study data does have some risks, although these risks are rare. The study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and how to help others with mental health disorders. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to the NDA, call or email the study staff, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to be sure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

However, the first part of this study is a double blind treatment study. That means that you, and the study staff are not supposed to know which medicine you are getting. If you sign this permission form, you will not be allowed to look at or copy your study related information until after we see which medicine you got. This will happen at the end of the first two weeks of the study (i.e. after the four IV treatments are completed).

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Michael Bloch, MD, MS, 230 S. Frontage Rd at the Yale University, New Haven, CT 06519.

If you withdraw your permission, you will not be able to stay in this study. But, the care you get from your doctor outside of this study will not change. No new health information identifying you will be gathered after the date you withdraw your permission. Information that has already been collected may still be used and given to others until the end of the research study. This policy is to ensure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while enrolled in the study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research- related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

What if I want to refuse or end my participation before the study is over?

Taking part in this study is your choice. You can choose to give permission, or you can choose not to give permission. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want you to take part.

The researchers may withdraw you from participating in the research if necessary. There are several reasons that a researcher may need to withdrawal you from the study. You could have a poor response to treatment or develop a serious side effect(s). You could be withdrawn if you do not follow study instructions or if you change doses of the other medicines that you are taking. You would also be withdrawn if the study is closed for safety reasons.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you choose not to participate or withdraws it will not harm your relationship with your doctors, Yale Child Study Center, or Yale New Haven Hospital. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

What will happen with my data if I stop participating?

You may withdraw or take away permission to use and disclose your health information at any time. You do this by telling the study staff or by writing to the study doctor Michael Bloch, MD, MS at Yale University 230 South Frontage Rd. New Haven, CT 06519. If you withdraw your permission, you will not be able to stay enrolled in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study. This policy is to insure the integrity of the study and/or study oversight.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator, Michael Bloch, MD, MS, at 203-745-9921

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

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

Permission Quiz:

1. In the first 2 weeks of the study, I will get…

☐ 1 IV treatment ☐ 4 IV treatments ☐ 100 IV treatments

2. Is ketamine approved by the FDA to treat depression or suicidal thinking?

☐ Yes ☐ No

3. In the first two weeks of the study, who will know if I am getting ketamine or the active placebo (midazolam)?

☐ The Study Doctor (Dr. Bloch)
☐ Me
☐ None of the above

4. I may experience some side effects from the study medicines, such as:

☐ Nausea
☐ Increased heart rate
☐ Sweating
☐ Feeling sleepy
☐ All of the above

5. If I get the active placebo medicine (midazolam) in the first 2 weeks of the trial, but am still very depressed I will:

☐ Get more midazolam treatments
☐ Be offered ketamine treatment
☐ Be asked to leave the study

6. I can stop participating in this trial…

☐ Only if Dr. Bloch says it's OK ☐ Anytime I wish to stop

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name		
Participant Signature		
Person Obtaining Permission Printed Name	Person Obtaining Permission Signature	Date

Opt-Out: Please write your initials if you are unable or feel uncomfortable doing these parts of the study.

_____Brain imaging parts of the study.

_____ De-identified data shared in the NIMH Data Archive