TITLE OF RESEARCH: A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy of Ketamine for the Treatment of Concurrent Opioid Use Disorder and Major Depressive Disorder

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Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

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Concise Summary

Your consent is being sought for a research study. Participation is voluntary. The purpose of the study is to examine whether an investigational medication called ketamine is able to improve treatment outcomes for opioid addiction and depression when used in combination with a standard of care medication for opioid addiction. Buprenorphine, methadone, and naltrexone are the currently approved medication treatments for opioid addiction. If you are eligible and you decide to participate in the study, your participation will last approximately 8-16 weeks, or 2-4 months.

The study will involve an initial screening visit, which may be conducted by telehealth. You will complete questionnaires and interviews in a private room, and some tests to measure drug use and pregnancy. The questionnaires and interviews will be related to your physical and mental health. The initial phase of the study will involve 8 clinic visits (two per week). At each of these visits, you will be asked to answer several questionnaires and provide a urine sample to check for pregnancy and drug testing. You will be guided through a short, breathing-based relaxation exercise to help reduce any anxiety you may have about the treatment. You will then be administered the study medication by intramuscular injection or the non-active placebo treatment (a saline intramuscular injection) and will be monitored by a study clinician for a minimum of two hours. You will also complete follow-up visits one week, two weeks, and four weeks after the initial phase is complete. These visits will include questionnaires and urine drug testing and may be conducted by telehealth. There are risks of participating in the study that are described in this document. The most significant risks include temporary high blood pressure, anxiety, and having the sensation that you are detached from your body or having an altered perception of time or your body. There is also a risk of loss of confidentiality, although steps will be taken to minimize this risk. Because it is not known if the study medication is safe in pregnancy, if you are a woman, you will complete a pregnancy test at each visit when medication is to be taken to be sure that you are not pregnant.

If you are in the group that receives placebo, your condition will go without active treatment for 4 weeks. However, everyone who participates will continue with their standard of care medication (buprenorphine, methadone or naltrexone). After you complete the initial 8 medication visits, you have the option to find out whether you received ketamine or the placebo. If you received the placebo, you may elect to complete an additional 8 visits during which you would receive ketamine. Your potential benefits from participating include having a lower desire to use opioids, feeling like it is easier to remain abstinent from opioids, or having less severe symptoms of depression. Your alternative is not to participate in the study.

A. PURPOSE OF THE RESEARCH

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making you decision. As the study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand.

The purpose of this study is to examine the ability of a medication called ketamine to reduce the severity of depression and opioid addiction (also called opioid use disorder). Ketamine is currently approved by the Food and Drug Administration (FDA) to reduce pain during some surgeries. However, ketamine is considered "investigational use" in this study, meaning that the FDA has not approved it for the treatment of either opioid addiction or depression. This is a Phase II study of ketamine, meaning that it has established use for other purposes and researchers are now testing this medication in larger populations. The purpose of this study is to evaluate the safety and effectiveness of ketamine in the treatment of opioid addiction and depression. You are being asked to participate because you are over 18 years of age, you have symptoms of depression, and you have opioid use disorder.

The investigator in charge of the study is Dr. Jennifer Jones at the Medical University of South Carolina (MUSC). This study is being conducted with funding from a grant from the National Institute on Drug Abuse (NIDA). Portions of Dr. Jones' and her research team's salaries will be paid by this grant. This study is being conducted at MUSC in Charleston, SC and will involve approximately 30 participants.

B. PROCEDURES

If you agree to be in this research study, the following will happen:

1. Screening and Baseline Visit (approximately 2-3 hours in length, may be conducted by telehealth):
   - The initial visit will involve the following:
     - Completion of written questionnaires related to your mental and physical health. Questionnaires will also be related your previous use of alcohol and other drugs, your craving levels for opioids, ways in which opioids has impacted your life (such as legal trouble or relationship conflicts) and your personal goals regarding your opioid use and depression.
     - An interview with a clinician about questions related to your physical and mental health.
     - A basic physical exam similar to what you would get at a checkup. Your blood pressure, pulse, and temperature may be checked at a local pharmacy or by a home measurement device.
     - If you have a history of heart problems or are taking methadone, you will be asked to complete an electrocardiogram (EKG). This is a test of the function of your heart and involves placing small adhesive pads with wires attached on your chest. After the adhesive pads are placed, a monitor shows a picture of the electrical activity of your heart, which is printed out on paper. This test usually takes less than 10 minutes to

complete. If you have had this test done within the previous sixty days at MUSC, your medical record will be reviewed. If this test was normal, you will not have to complete the electrocardiogram test.

- If you have a history of liver, kidney, or blood cell-related problems, you will be asked to have your blood drawn. Approximately 1 teaspoon of blood will be drawn for these tests to evaluate whether your liver or kidneys are working well. The tests will also check whether you have any electrolyte imbalances such as abnormal sodium or potassium levels. The tests will also measure the levels of your blood cells, which are responsible for fighting infection, carrying oxygen, and forming clots when you are bleeding. If you have had these blood tests done within the previous sixty days at MUSC, your medical record will be reviewed. If they were normal, you will not have to complete the blood tests.

- After staff has reviewed all the information collected, you will be contacted to inform you of your eligibility status. If you are eligible to enroll and choose to continue participation, a randomization visit will be scheduled. If you are not found eligible and/or do not choose to continue in the study, additional community resources can be made available to you upon request.

- If you are a woman of childbearing potential and/or a man capable of fathering a child, precautions should be taken throughout the course of the medication phase of the study. Examples of acceptable methods of birth control for participants involved in the study includes: birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant.

- If the physical examination and test results show that you are eligible for the study, you will be randomly assigned to one of two groups. This means that you have a 50/50 chance (like flipping a coin) of being in either group. Neither the researchers nor you will make the choice to which group you are assigned. The two groups are Group A (ketamine) and Group B (placebo, an inactive substance). If you are assigned to Group B, you have the option of completing 8 ketamine medication visits after completion of your first 8 visits when you received placebo.

2. Medication Visits (approximately 3 hours each in length):

- If you enroll in the study, over the next 4-8 weeks you will come to the study center twice per week to complete the medication visits. You will be encouraged to come well hydrated, but in a fasting state (i.e. not having eaten on the morning of the treatment visit). At these visits, you will complete questionnaires and urine testing much like the ones completed at the screening visit. These tasks will take about 30 minutes.

- You will complete a urine pregnancy test (only if you are a woman). The urine pregnancy test must be negative in order to participate.
- If your pregnancy test is negative, or if you are male, your urine or a saliva sample will be tested for drug use. Testing positive for drugs (except ketamine) will not prohibit you from participating in the research study.
- Prior to taking the medication, you will sit in a chair and be coached by the study doctor through a basic relaxation exercise. This exercise will help you to focus on your breathing

and is designed to help reduce any anxiety you may feel related to the medication sessions. The relaxation exercise will last about 10 minutes.

- After you complete the relaxation exercise, you will have your blood pressure and heart rate checked, and you will have a small, painless monitoring device placed on your finger which will measure the oxygen levels in your blood throughout the medication session.
- As long as your blood pressure is not too high, you will be instructed on how to take the study medication. Both the ketamine and the placebo medications will be given in the form of an intramuscular injection.
- After receiving the injection, you will be instructed to rest in a chair, and you will have your blood pressure monitored every forty-five minutes. After approximately 90 minutes, you will take complete several short questionnaires.
- Your blood pressure will be checked again, and if it is normal, the blood oxygen finger device will be removed and the visit will be completed. If your blood pressure is too high, you are feeling anxious, or you are not feeling like yourself, you will continue to be monitored by the study doctor until these symptoms return to normal.
- After completing the visit, you will be asked to have someone drive you home. If you do not have someone that can drive you home, transportation (such as a taxi) will be provided for you at no cost to you.

3. Follow-Up Visits (approximately 30 minutes each in length):
   - Over the next 4 weeks, you will complete three additional follow-up visits, which may be conducted by telehealth (one time during your fifth, sixth, and eighth weeks after starting the study). At these visits, you will complete questionnaires much like the ones completed at the screening visit and drug testing (either by saliva or urine).

C. DURATION

Participation in the study will take about 12-20 visits over a period of approximately 2-4 months. There will be an initial screening visit (approximately 2-3 hours), 8-16 study medication visits (approximately 3 hours each), and 3 follow-up visits (approximately 30 minutes).

D. RISKS AND DISCOMFORTS

There are risks involved with participating in this study, including risks associated with ketamine, study procedures, and loss of confidentiality.

Ketamine Risks:
Ketamine may cause some, all or none of the side-effects listed below. These effects are generally temporary and resolve within one hour, although they may last up to six hours. A study physician will monitor you until these symptoms resolve.

More Likely (10 percent to 50 percent):

- Perceptual changes (e.g. distortion of time and space, sense of illusions) and dissociation (including a sense of detachment or altered sense of reality)
- Feeling abnormal or drunk
- Elevated blood pressure
- Elevated heart rate
- Anxiety
- Sedation (sleepiness)
- Vertigo or dizziness
- Nausea
- Decreased pain threshold

Less Likely (5 percent to 10 percent):

- Injection site swelling, pain, redness, or discomfort

Rare (less than or equal to 5 percent):

- Bladder discomfort or increased frequency of urination (also called cystitis)
- Anaphylaxis

Unknown risks:

- 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. The amount of ketamine given to the rats was higher than what you will receive in this study.
- The added effect of repeated ketamine infusions is unknown. Chronic ketamine users (mostly ketamine abusers) may have structural and functional brain changes with associated memory problems. We are uncertain if this will occur at the frequency and duration proposed in this study.
- Bladder irritation and liver problems have been related to the repeated use of ketamine. We are uncertain if this will occur at the frequency and duration proposed in this study.
- The study treatment may also involve other risks, which are currently unforeseeable.
- If you become pregnant, the study treatment might involve risks to the embryo or fetus, which are currently unforeseeable.

Placebo Risk: If you are in the group that receives placebo (saline), you may still experience anxiety, Injection site swelling, pain, redness, or discomfort. These symptoms are anticipated to occur at a similar frequency compared to if you were given the active treatment. Regardless of which treatment group you are assigned to, throughout the study you will continue taking buprenorphine for opioid addiction. If you have previously been on an antidepressant, you will continue taking that as well. If you are in the placebo group, you have the option of completing 8 ketamine medication visits after completion of your first 8 visits during which you received placebo.

Interviews and Surveys: The questions that will be asked may be sensitive in nature and may make you feel uncomfortable. You may be asked personal questions that you find distressing. You may refuse to answer any question(s) that you do not wish to answer.

Risks from Blood Draws: Risks associated with drawing blood from your arm include brief discomfort, anxiety, and/or bruising. Infection, excess bleeding, clotting, or fainting is possible, although unlikely.

Electrocardiogram (ECG): The ECG procedure may cause some mild discomfort during the placement and removal of the leads to and from the skin. You may also experience some local irritation, redness, or burning in the areas where the leads are attached.

Risk of Loss of Confidentiality
There is a risk of a loss of confidentiality of your personal information as a result of participation in this study. Some answers you give during the research visits (like whether you use illegal drugs) may put you at risk if other people find out. To keep what you say private, your study records will use a code number instead of your name. We will protect your records to the extent allowed by law by keeping all your materials in locked file cabinets only accessible by research staff and all computer files will be secure password-protected files only accessed by research staff. Your research records are kept separate from your other medical records. Only research staff will have access to your private information.

Limits of Confidentiality:
Suspected or known abuse or neglect of a child, disabled or elder abuse, or threatened violence to self or others may be reported to appropriate authorities.

If you are or become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

Unknown Risks: The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything during the course of the study that might make you change your mind about participating in the study.

E. MEDICAL RECORDS AND/OR CERTIFICATE OF CONFIDENTIALITY

If you have a medical record at MUSC, it may be reviewed to determine your study eligibility. Results from blood and electrocardiogram testing that you may be asked to complete for the study will be included in your medical record. Other information about your study participation will not be in your medical record. This means that your research participation, drug and pregnancy testing, and responses to questionnaires will not be included in your MUSC medical record.

F. BENEFITS

If you receive ketamine, and it is more successful in treating your conditions compared to your current standard therapy with buprenorphine, you may benefit from participating in the study. However, given the investigational nature of this study, benefit cannot be guaranteed or promised. Information gained

from this study may help other investigators have a better understanding of the treatment of opioid use disorder and depression.

G. COSTS

There will be no cost to you as a result of participation in this study. If you choose to receive text message study reminders, normal data and usage rates will apply.

H. PAYMENT TO PARTICIPANTS

In return for your time and effort, you will be paid for every visit you complete. Maximum payment is received if study visit is completed in full and as scheduled. For each of the 12 visits, you will be paid $40 in the form of a pre-paid debit card (also called a ClinCard). The maximum amount that you would be paid is $480 if you are in Group A, or $800 if you are in Group B and you choose to complete the additional 8 ketamine medication visits.

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

I. ALTERNATIVES

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapies for your opioid addiction include both medications (such as buprenorphine, methadone, and naltrexone) and counseling-based treatments (including group sessions such as Alcoholics Anonymous/Narcotics Anonymous and individual counseling sessions). There are many standard treatments for depression including medications and therapy (both group-based therapies and individual therapy or counseling).

Withdrawal from the Study

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should talk with the investigator in charge of this study (Dr. Jones) if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled. The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions, or if the study is stopped by the study sponsor, the institutional review board (IRB), or by a regulatory agency (such as the FDA). If your participation is ended for medical reasons, you will be referred to a doctor or other health professional for care. You will be responsible for the cost of these services.

J. DATA SHARING

Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

K. DISCLOSURE OF RESULTS

Study data will not be shared with participants to maintain confidentiality.

L. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the course of the study, you will be notified.

M. STUDENT PARTICIPATION

Your participation or discontinuance will not constitute an element of your academic performance, nor will it be a part of your academic record at this Institution.

N. EMPLOYEE PARTICIPATION

Your participation or discontinuance will not constitute an element of your job performance or evaluation, nor will it be a part of your personnel record at this Institution.

O. CLINICAL TRIALS.GOV

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.

P. COLLECTION OF SPECIMENS

Blood and urine specimens will be collected in this study. Blood samples will be taken as part of the initial visit, and will not be stored. Results of the blood test will be made a part of your MUSC medical record. All participants will provide a urine sample during the screening phase and at each subsequent visit. Samples from females will first be checked for pregnancy at the baseline visit and every medication visit. Samples that are negative for pregnancy or that are not checked for pregnancy will be tested for drugs at every visit. Results of urine testing (pregnancy or drug testing) will not be made a part of your medical record. These specimens will be used solely as part of this research study and will not be shared with other investigators or used for commercial profit. All specimens will be coded with your numeric study code to protect your confidentiality.

Q. OPTIONAL KETAMINE MEDICATION VISITS FOR PLACEBO GROUP

If you complete the initial 8 medication visits, and you were assigned to Group B (the placebo group), you have the option of completing 8 medication visits during which you will receive ketamine at the same dose and frequency as Group A. This portion of the study is optional, and you will not be informed which group you were in until you complete the initial 8 medication visits. If you were in Group A (the group that received ketamine), you will not be eligible to participate in this optional portion of the study. Please initial by your choice below for paper consents, or scroll down to the bottom of the screen and select your choice electronically:

____Yes, I agree to participate in this optional portion of the study if I am assigned to the placebo group.

____No, I do not agree to participate in this optional portion of the study if I am assigned to the placebo group.

Q. FUTURE CONTACT

The researcher in charge of this study might like to contact you in the future about other research opportunities. Please initial by your choice below for paper consents, or scroll down to the bottom of the screen and select your choice electronically:

____Yes, I agree to be contacted

____No, I do not agree to be contacted

You have the option of receiving appointment reminders and link to study surveys through text messages. Should you elect to receive text messages, normal cellular data usage and rates will apply. Please initial by your choice below for paper consents, or scroll down to the bottom of the screen and select your choice electronically:

____Yes, I agree to be contacted via text message

____No, I do not agree to be contacted via text message

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical

University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement
I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Dr. Jennifer Jones at (843) 792-5594. I may contact the Medical University of SC Patient and Family Care Liaison (843) 792-5555 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records. Please sign below for paper consents or scroll to the bottom of the screen to provide an electronic signature.

_____
Signature of Participant Date

_____
Printed Name of Participant Date

_____

Signature of Person Obtaining Consent Date