RUSH

CONSENT/AUTHORIZATION FOR PARTICIPATION IN A RESEARCH STUDY

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Protocol Title: **(2R,6R)-Hydroxynorketamine a Novel therapeutic Analgesic for the Treatment of Neuropathic Pain**

Sponsor(s): **Department of Anesthesiology**

Funder(s): **Department of Defense**

Name of Participant: _____

Key Information:

You are being invited to participate in a research study. Research studies answer important questions that might help change or improve the way we do things in the future.

This consent (permission) form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Taking part in this research study is voluntary. You do not have to participate in this study and may choose to leave the study at any time. If you decide not to participate in this study or leave the study at a later time, your health care, benefits, or relationship with Rush University Medical Center will not change or be affected.

The purpose of this study is to show if the investigational drug (2R-6R)- Hydroxynorketamine (HNK), can be used to effectively and safely treat chronic neuropathic pain. The National Institute of Mental Health developed (2R-6R)- Hydroxynorketamine for depression. Neuropathic pain is nerve pain that can happen if your nervous system malfunctions or gets damaged. Chronic neuropathic pain can be mild or severe. It might come and go, or it might linger. Diseases like diabetes, shingles and central nervous system disorders can cause it. An "investigational drug" is a drug that has not been approved by the U.S. Food and Drug Administration (FDA) and it must be tested to see if it is a safe and effective treatment for the disease or condition being studied.

You are being asked to participate in this study because you have an established diagnosis of chronic neuropathic pain from a physician.

If you agree to participate in this study, your participation may last up to 6 months, and you will be asked to complete 16 total visits: 10 in-person visits and 6 virtual study visits.

During these visits, you will be asked to complete questionnaires regarding pain, fatigue, physical functioning, emotional distress, and social role participation, have pain assessments, have functional tests involving a brush test, pinprick test, pressure test, temperature pain threshold test, a chilled circulating bath test and receive study drug infusions through a blood vein. For a detailed description of study procedures, please see the "What are the activities you will be doing if you participate in this study?" section of this consent form.

There are risks to you for participating in this study, some of which may be serious, may cause death, or may not go away. In this study, there are risks associated with the study drugs, there is also a risk of discomfort due to the questionnaires, functional tests, and pain sensitivity tests. There are also risks associated with the infusion, electrocardiogram (ECG, a test that measures the electrical activity of the heart), and blood draw. For a detailed list of risks, you should know about, please see the "What are the risks and discomforts of participating in this study?" section of this consent form.

You may benefit from taking part in this study. Based on experience with (2R,6R)-HNK given to animals with similar conditions, such as neuropathic pain, researchers believe it may be of benefit to people with your condition of chronic neuropathic pain or it may be as good as the standard therapy with fewer side effects. However, because individuals respond differently to therapy, no one can know in advance if it will be helpful for you.

You will also receive other treatments during this study. One of these treatments, ketamine, has been shown to benefit some people with chronic neuropathic pain. The other treatment, normal saline (salt water), will be used as the placebo (inactive substance) and may not provide any benefit. You are not expected to get any long-term health benefits from participating in this study.

There are other options available to you if you decide not to participate in this study. You may choose another form of treatment or care for your chronic neuropathic pain without being in a study such as ketamine infusions, neuromodulation devices (spinal cord stimulators), injections or medication. You cannot receive this drug if you do not participate in this research study.

You have the option to not participate in this study.

<u>Detailed Information</u>: Please review the rest of this document for details about the above topics and additional information you should know before making a decision about whether or not you will participate in this study.

<u>Why are you being invited to participate in this study?</u>

You are being asked to participate in this study because you are diagnosed with chronic

neuropathic pain of an extremity, such as your leg or arm.

How many participants will take part in this study?

Approximately 25 participants are expected to take part in this study at Rush University Medical Center.

What are the activities you will be doing if you participate in this study?

After you sign this informed consent form, you will be randomized, (by chance, like flipping a coin), into one of five groups. Each of the groups will receive all three study drugs, but the order in which you receive them will vary. You will have equal chances to be randomized into Group 1 or Group 2 or Group 3 or Group 4 or Group 5 which will determine which drug you receive at the 1st, 2nd, and 3rd, infusion.

The initial baseline assessment will occur approximately 7 days before the first drug administration, where we will collect clinical and pain information. The study team will collect vital signs, information regarding your medical history, complete a 12-lead electrocardiogram (ECG, a test that measures the electrical activity of the heart), as well as a blood draw for clinical laboratory tests and liver function tests. The blood will be drawn from a vein and we will collect 10 milliliters (2 teaspoons) of blood). If your liver function test results are above normal limits or the 12-lead ECG is abnormal, you may not be in the rest of the study. The study doctor will speak with you. At this visit you will be asked to complete some quantitative pain testing, and you will also complete some questionnaires. The testing and questionnaires are discussed in more detail later in this section.

At post-treatment day 14 (±2 days) subjects will be requested to return to Rush to have blood drawn for an assessment of liver function, physical assessment, measurement of vital signs and to complete questionnaires as on days 7 and 21.

You will receive three different study treatments during this study. The treatments will consist of either (2R,6R) HNK (investigational drug), ketamine, or saline separated by 5-week intervals. The study drug will be administered as an infusion via an intravenous (IV) catheter over a 45-minute period. You will be monitored continuously using an ECG, non-invasive blood pressure monitor, blood oxygen saturation using a pulse oximeter to measure the oxygen level in your blood and physical observation during each infusion and for 2 hours continuously after the infusion is complete for safety purposes. Each infusion visit will last approximately 3 to 3.5 hours. You will be assessed at the end of the 2-hour period for general well-being (i.e. your alertness and orientation to time, place and person and for any abnormal ideations) before you are allowed to leave the Rush Pain Center.

Daily for 112 days starting after your baseline visit, you will be asked to electronically (via personal access to a computer or smart phone) answer questions regarding your pain in the last 24 hours. You will be asked to answer on a rating scale of 0 to 10, where 0 equals no pain and 10

equals worst pain ever. You will also be asked to assess which of a series of words best describes the way that your pain feels. You will also answer a question about pain medicine you took in the last 24 hours and a question asking if you have had any adverse effects (side effects) of the medication. These questions should take no more than 4 to 6 minutes to complete. These daily pain assessments will begin the day after the first visit and will continue for 35 days after the final infusion.

Pain Questionnaires:
You will complete the following questionnaires electronically at your baseline visit, and at 7, 14 , 21, and 28 days following each drug infusion (approximately 40 minutes) We would also like to schedule a short telehealth conference (15-minutes) with you on days 7, 14 and 21 to review the medications you are taking.

- PainDETECT- measures pain quality, location and pattern
- PROMIS Global Health- measures overall physical health, mental health, social health, pain, fatigue (feeling tired), and overall perceived quality of life
- PROMIS Depression- measures depression
- PROMIS Anxiety- measures anxiety
- PROMIS Sleep Disturbance- measures sleep quality
- PROMIS Pain Interference- measures how much your pain interferes with your physical, mental, cognitive, emotional, recreational and social activities
- PROMIS Physical Function- measures physical function through grading activities of daily living like walking and chores
- PROMIS Fatigue- measures feelings of tiredness and exhaustion
- NRS Pain Assessment- measures average and worst pain in the last 24 hours as well as current pain
- PROMIS Pain intensity – rate your pain in the last 7 days from no pain to severe pain

Quantitative pain assessments:
You will complete the following pain sensitivity and functional test assessments at baseline, and 28 days after each infusion (approximately 40 minutes):

- **Pinprick testing:** we will measure your response to repeated pokes to your skin using both a plastic fiber and a metal filament (like a very thin wire) used to clinically test for skin sensation. We will poke your skin a single time followed by 10 times over about 20 seconds an ask you to rate any pain it causes at each site at the beginning and end. We will repeat this testing three times at 2 different sites on your body.
- **Touch allodynia:** we will use a brush to stroke the skin of both your affected and non- affected extremity three times consecutively (in a row). You will be asked to rate your pain after the brush is lifted off your skin.
- **Cold allodynia**: we will place an ice cube on the skin in the area of your pain and also on an unaffected area on the opposite side of your body to assess discomfort you feel due to the cold.
- **Deep pain:** a hand-held pressure device will be pressed against your skin. We will apply pressure; when the pressure first feels slightly painful you will tell us, and we will stop. We will perform 1 practice trial and 3 repetitions at each site

- **Pain tolerance**: You will be asked to place the hand of your unaffected limb in a cold-water bath (23 degrees Fahrenheit) and keep it in the water as long as you can. The maximum time will be 2 minutes. When you remove your hand, you will be asked to rate the pain you experienced.
- **Thermal sensory and pain threshold:** this test will measure heat pain threshold (a level which the heat causes no reaction) and tolerance. This task will involve repeated brief applications of a computer-controlled heat stimulus to an area of your non-affected forearm. The equipment used in this task is safe and only produces heat at 127 degrees Fahrenheit or less, which is below the level that causes burns. You will be asked to participate in three brief hot and cold stimulation trials during which you will be asked to indicate when the temperature stimulus first becomes noticeable (sensation), and three brief trials during which you will be asked to indicate when your temperature pain tolerance has been reached. For each trial, as soon as your sensation or pain tolerance is reached, you will press a button and the equipment will rapidly cool your skin to normal body temperature within 2 seconds. Immediately upon completion of each of the pain tolerance trials, you will be asked to rate the intensity of the pain you experienced using the 0 to 10 scale discussed above.

After the 3rd infusion, if you are continuing to have pain relief from the treatments in the study we will continue to contact you at 2-week intervals for a period of up to 6 months to determine how long the pain relief lasted.

Please see the table below for the schedule of assessments:

Table 1: Schedule of Assessments

			Days post treatment			
	Baseline and day 28	**Day of Infusion**	**Daily for 35 days**	**7**	**14**	**21**
Medical history	X					
Physical examination	X					
Neuropathic Pain Questionnaire	X					
Basic metabolic panel	X					
Complete blood count	X					
Hemoglobin / hematocrit	X					
Liver function panel, bilirubin albumin	X				X	
12-lead ECG	X					
Serum pregnancy test	Y					

5-lead ECG monitor		C				
Non-invasive blood pressure		C				
Pulse oximetry		C				
Ramsay sedation scale		A				
Mental and psychomimetic assessments		B				
NRS pain assessments	X	X	X	X	X	X
Pinprick testing (Neuropen™)	X					
Touch allodynia (brush)	X					
Cold allodynia (ice)	X					
Thermal sensory and pain thresholds	X					
Cold pressor pain tolerance test.	X					
PainDETECT™	X			X	X	X
PROMIS depression	X			X	X	X
PROMIS anxiety	X			X	X	X
PROMIS Neuropathic pain qualities			X			
PROMIS Nociceptive pain qualities			X			
Adverse events	X	X	X	X	X	X
Pain medication use	X	X	X			
PROMIS global health 10	X			X	X	X
PROMIS sleep disturbance	X			X	X	X
PROMIS pain interference	X			X	X	X
PROMIS physical function	X			X	X	X
PROMIS fatigue	X			X	X	X

X = test will be administered, or blood drawn. C = continuous monitoring from15-min prior to infusion until discharge of subject (minimum 2h), Y = test will be performed on women of childbearing age before each infusion. A= assessment will be made every 20 minutes prior to infusion through discharge. B= Assessment for orientation (a person's level of awareness of self,

place, time, and situation) and psychomimetic reactions (delusions or hallucinations) will be made at 1 and 2 hours following infusion prior to discharge.

What do you need to know regarding the collection of biospecimens?
Biospecimens are materials that come from your body that may include blood, tissue, urine, bone marrow, saliva, cells, etc. In this study, we will collect blood.

Most biospecimens contain DNA. We will not use biospecimens collected as a part of this study for whole genome sequencing, which involves mapping (identifying the location of genes and the distance between them) of all of your DNA

Will your information or biospecimens be used for research in the future?
Information or biospecimens collected from you for this study may be used for future research or shared with other researchers. If this happens, information which could identify you will be removed before any information or biospecimens are shared. Since identifying information will be removed, you will not be asked for additional consent.

What are the risks and discomforts of participating in this study?
Forseeable risks: There are both physical risks due to the drugs that you will be administered.

Warning: Some of the drugs that are used in this are known to have sedative producing effects (as hallucinations or paranoid delusions) that resemble or are identical with psychotic symptoms. Subjects are warned not to drive or operate heavy machinery on the days that they receive study drug. You are asked to have someone accompany you to the Rush Pain Center on the days you receive study drug who will be able to provide transportation for you. If you are unable to have such a person accompany you, please tell Dr. Buvanendran or study personnel.

Some of these risks are known, such as those that may occur as a result of receiving ketamine and some are unknown,

(2R,6R)-HNK
Currently, little human data exists for (2R,6R)-HNK. Data collected from animal studies suggests that the doses used in this study are safe for humans.
Most likely based on other drugs with this mechanism of action: Headache and nausea

Ketamine

Most Frequent: Delirium (characterized by symptoms such as confusion, disorientation, agitation, and hallucinations), hallucinations, mood changes, nightmares, rapid heart rate and rhythm, tonic-clonic epilepsy seizures (a type of seizure that involves a loss of consciousness and violent muscle contractions), vocalization (hoarseness, trouble speaking).
Less Frequent: Slow heart rate, high blood pressure, reduced breathing, vomiting, increased intraocular pressure (increased pressure in eye), flashbacks several weeks post after receiving the drug.

Rare: Anaphylaxis (a severe, life-threatening allergic reaction), anorexia, diplopia (double vision), injection site irritation, laryngismus (laryngospasms), nausea, nystagmus (rapid eye movements), obstructive pulmonary disease (a group of diseases that cause airflow blockage and breathing-related problems), skin inflammation, skin rash.

Saline

Hypernatremia (high blood sodium)

These side effects are uncommon with the dose used in this study.

Blood Draw

There is a risk of bruising and discomfort at the site of draw. Infection and fainting are also possible but are unlikely. Antiseptic precautions will be taken to minimize the risk of infection.

IV Catheter

The IV catheter will be inserted into your vein for the infusion. The IV catheter may cause discomfort. There is also risk of inflammation and infection. Antiseptic precautions will be taken to minimize the risk of infection.

Electrocardiogram (ECG)

There is a risk the ECG electrode pads will cause skin irritation, itching and redness.

Functional and Pain Sensitivity Tests

There is a slight risk of discomfort from the functional tests like muscle fatigue or pain. You may experience bruising, cold, heat or temporary pain during the pain sensitivity testing.

Surveys

There is a slight risk that you will be uncomfortable by some of the questions asked in the surveys. We consider these survey questions to be similar to speaking with your doctor about your pain, depression, anxiety, and physical function.

There is a possible risk of loss of confidentiality of data. Measures are in place to minimize this risk.

There may be other risks that may happen that we cannot predict.

What are the reproductive risks of participating in this study?

Women

If you are pregnant or breastfeeding, you cannot take part in this study. A serum pregnancy test is required and will be given a test before each study infusion treatment. You are responsible for using an effective birth control method such as birth control pills, barrier method (such as condoms or diaphragms), intrauterine device (IUD), hormone implants or surgical sterility while you are taking part in this study. Once you have completed treatment, you may discontinue birth control 3 months after completion of your study treatment. If you become pregnant, you must notify the study doctor immediately.

Interactions with some drugs, including antibiotics can affect birth control pills. You should discuss with the study doctor a second method of birth control during the study, if birth control pills are used.

Men

You are responsible for using an effective birth control method, such as the ones listed above. If you are a male and your female partner becomes pregnant, you must notify your study doctor immediately. Once you have completed treatment, you may discontinue birth control 3 months after completion of your study treatment.

What if there is new information that may affect your decision to participate in this study?

During this study, you will be told about important findings (either good or bad), such as changes in the risks or benefits of participation in the study or new choices to participation that might cause you to change your mind about being in the study. If new information is shared with you, you may be asked to sign a revised consent form in order to continue participating in this study.

Can you leave or be removed from this study?

You have the right to leave a study at any time without penalty. For your safety, however, you should consider the study doctor's advice about how to leave this study. If you leave this study before the final study visit, the study doctor may ask you to complete the final steps. Withdrawal from the research study would be immediate, unless you are receiving a study drug infusion. Withdrawal from the research study at one of the study drug infusion sessions would require monitoring from a physician following the drug completion to ensure your safety.
The researchers and Sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interests;
- You do not follow the instructions;
- The study is cancelled for any reason.

What about confidentiality of your medical information?

This authorization is voluntary. Rush University Medical Center and its affiliates ("Rush") will not withhold (keep back) or refuse your treatment, payment, enrollment, or eligibility for benefits if you do not sign this authorization. You do not have to sign this authorization, but that means that you cannot be in the study or receive study-related treatment.

By signing this document, you voluntarily authorize (give permission to) Dr. Asokumar Buvanendran, his study team, and other Rush personnel involved with the conduct and review of this study (which may include off-site personnel) to use or disclose (release) health information that identifies you for the study described in this document.

During the study, Dr. Asokumar Buvanendran and his study team will collect Protected Health Information (PHI) about you for the purposes of this research. PHI is your health information that includes your medical history and new information obtained as a result of this study. Some of this information will come from your medical record. The health information that Rush may use or disclose for this research includes:

- Name, phone number, health information relating to chronic neuropathic pain.

Dr. Asokumar Buvanendran and his study team may share your health information and the results of your study-related procedures and tests with people outside of Rush who assist with the conduct and review of this study. The people who receive your health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, but only if permitted by the laws governing them. Your health information described above may be used by or disclosed to:

- The study Sponsor, Department of Defense, and its representatives (Data Safety Monitoring Boards, etc.);
- Monitoring agencies such as the Food and Drug Administration (FDA)

While you participate in the study you will have access to your medical record, but Dr. Asokumar Buvanendran is not required to release to you study information that is not part of your medical record. Rush is required by law to protect your health information, and study records that identify you will be kept confidential. Any study information in your medical record will be kept indefinitely. Your identity will not be revealed on any report, publication, or at scientific meetings.

You have a right to inspect and copy the information to be disclosed with this authorization and you may obtain a copy of the information by contacting the office listed below.

If you no longer want to be in the study and do not want your future health information to be used, you may change your mind and revoke (take back) this authorization at any time by writing to Dr. Asokumar Buvanendran at 1653 W. Congress Pkwy Jelke 739 Chicago, IL 60612. If the authorization is revoked, you will no longer be allowed to participate in the study and previously authorized individuals/entities may still use or disclose health information that they have already obtained about you as necessary to maintain the integrity or reliability of the current study. This authorization is valid for the entirety (the entire time) of this research study. It will expire when the study is completed or if you revoke (take back) the authorization.

If you withdraw from this study, the data already collected from you may not be removed from the study records. The study doctor and/or study team may ask you whether they can continue to collect follow-up data on you. If follow-up information will be requested, you will be asked to sign a separate consent form before this information can be collected.

Records of participation in this study will be maintained and kept confidential as required by law. You will be assigned a unique study identification number. Your study data will not be linked to your name or any other identifiable information. The data will be stored on a secure web platform.

The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews new and ongoing human research

studies to check that the rules and regulations are followed regarding the protection of the rights and welfare of human participants.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov website, 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. This research study can be found by searching for the following Clinical Trial Registry Number (NCT#) - 05864053.

What are the costs to participate in this study?
All costs for the required study visits, like examinations, laboratory procedures, surveys, functional tests, pain sensitivity tests, surveys, 12-lead ECG, infusions of (2R,6R)-HNK, ketamine and normal saline will be paid by the Department of Defense.

Will you be paid for your participation in this study?
You will be paid $125 for each completed study drug infusion visit, for a total of $375. If you do not finish this study, you will be paid for the study visits you have completed. You will be paid within approximately 30 days. You will be paid after each completed study drug infusion visit by amazon gift card. We may need to collect your social security number or Taxpayer Identification Number (TIN) in order to pay you and for tax reporting purposes to the United States Internal Revenue Service (IRS).

What if you are injured as a result of your participation in this study?
If you get ill or injured from being in the study, Rush University Medical Center will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Asokumar Buvanendran at telephone number 312-942-3685. In case of emergency, please use the 24-hour telephone number 312-942-5000 and contact pager 3958.

You should let any health care provider who treats you know that you are in this study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact your study doctor.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

What other information should you know about?
Investigator Dual-Role

Your health care provider is an investigator on this research study, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from a clinician who is not associated with this study. You are not obligated to participate in any research study offered by your clinician. The decision to not participate will not affect your clinical care now or in the future.

Who can you contact for more information about this study?
Questions are encouraged. If you have further questions about this study, you may call study coordinator, Asokumar Buvanendran, at 312-942-6504 or email him at asokumar_buvanendran@rush.edu.

Who can you contact if you have concerns about your rights as a study participant?
Questions about the rights of research participants may be addressed to the Rush University Medical Center Office of Research Affairs at 1-800-876-0772.

What are your rights as a study participant?
Taking part in this study is voluntary. If you choose not to participate in this study or to leave the study at any time, your health care, benefits or relationship at Rush University Medical Center will not change or be affected.

If you choose to leave this study and you do not want any of your information to be used, you must inform Dr. Asokumar Buvanendran in writing at the address on the first page. Dr. Asokumar Buvanendran may still use your information that was collected prior to your written notice.

SIGNATURE BY THE PARTICIPANT
By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study staff. You do not waive any of your legal rights by signing this consent/authorization form. You will be given a signed copy of this document.

Name of Participant	Signature of Participant	Date of Signature

SIGNATURE BY THE INVESTIGATOR/INDIVIDUAL OBTAINING CONSENT:
I attest that all the elements of informed consent described in this consent document have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

Name of Individual Obtaining Consent

Signature of Individual Obtaining Consent	Date of Signature

SIGNATURE OF THE PRINCIPAL INVESTIGATOR:
I attest that I am aware of the enrollment of this subject in the study discussed in this consent document.

Name of the Principal Investigator

Signature of the Principal Investigator	Date of Signature