Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation
National Protocol Guidance
February 2022
VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives, and Office of Mental Health Somatic Treatment Field Advisory Committee

Purpose: To provide general guidance on ensuring access to intravenous ketamine for the treatment of treatment resistant major depressive disorder or severe suicidal ideation under a National VA protocol that will facilitate collection of safety and effectiveness outcomes via a prospective medication use evaluation (MUE).

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly prescriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of ketamine for treating treatment-resistant depression or severe suicidal ideation.

Background
Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist approved for general anesthesia. Ketamine has demonstrated a rapid response in persons with MDD following a single infusion. A systematic review and meta-analysis assessed nine, non-electroconvulsive therapy studies that compared ketamine to placebo or midazolam in patients with treatment-resistant depression (n=192)\(^1\). Compared to controls, patients who received ketamine had significantly greater improvement on global depression scores within 24 hours of administration. Suicidal ideation was reduced in the two studies in which it was assessed. Ketamine’s efficacy was maintained in patients on or off antidepressants in all subgroups and sensitivity analyses. A small randomized, double blind trial found ketamine to be as effective as ECT with a more rapid onset of effect\(^2\). Common side effects included dry mouth, tachycardia, increased blood pressure and the feeling of disassociation. Additional serious side effects include increased intracranial pressure, increased intraocular pressure, and hypersalivation which can lead to upper airway obstruction or laryngospasm. A 2017 meta-analysis reported ketamine rapidly reduced suicidal thoughts in depressed patients with suicidal ideation\(^3\).

Despite these preliminary positive findings in a limited number of studies, many questions remain unanswered\(^4, 5\). The studies to date have given a single dose of ketamine leaving the number and frequency of doses needed to treat an episode of MDD undetermined. The most common dose has been 0.5 mg/kg of body weight. Higher doses may be more likely to result in cardiovascular adverse effects and no dose ranging studies have been conducted. Ketamine has also not been studied in persons with co-occurring conditions. Thus, the identification of patients who would most benefit from ketamine and the best approach to dosing has not been established.

The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments reviewed the literature on the use of ketamine infusion for treatment-resistant depression and concluded there is “compelling evidence that the antidepressant effects of ketamine infusion are both rapid and robust, albeit transient”\(^6\). The Council also recommended seven components of preprocedural evaluation for appropriateness of ketamine treatment which have been included in this
Ketamine Infusion for Treatment Resistant Depression

The patient has failed to achieve a full response to four adequate therapeutic trials (dose and duration) of antidepressants including augmentation when appropriate or psychotherapy from different classes (either in combination or succession) in the current episode.

- Antidepressant treatment and psychotherapy trials are considered “failed” using a standardized scale such as the Antidepressant Treatment History Form.

The 2016 update of the VA/DoD Major Depressive Disorder Clinical Practice Guidelines includes the following recommendation, “Given the limited information on ketamine’s safety and duration of effect, we recommend against the use of ketamine to treat MDD outside of a research setting” 7. Additional information has been published since and the interest in providing ketamine infusion for treatment-resistant MDD, pain and other conditions has grown both within and outside VHA 3, 6, 8-11. The VHA Office of Mental Health FY2015 survey of 140 VA facilities (100% response rate) found 8 sites (6%) were providing ketamine onsite for the treatment of treatment-resistant depression and 22 sites (16%) were providing it off site; another 35 were interested. Only 3 sites were using ketamine under a research protocol.

Departments Affected: Pharmacy, Nursing, Mental Health (Anesthesia on call)

Procedure:

- Patients can either be treated as outpatients or inpatients

Patient Selection

Inclusion Criteria

- Current diagnosis of unipolar, major depressive disorder (MDD) by DSM-5. Patients with MDD with psychotic features were excluded from clinical trials. Psychosis severity should be taken under consideration when deciding if an individual patient is eligible.

- The patient has failed to achieve a full response to four adequate therapeutic trials (dose and duration) of antidepressants including augmentation when appropriate or psychotherapy from different classes (either in combination or succession) in the current episode.
  - Antidepressant treatment and psychotherapy trials are considered “failed” using a standardized scale such as the Antidepressant Treatment History Form.

OR

- Severe suicidal depression for which a rapid treatment onset is important

- A VA psychiatrist or a VA licensed health-care provider (i.e., CPP, NP, PA) has evaluated the patient and determined and documented that the patient qualifies for ketamine treatment in patient’s medical record.
- The patient has a Patient Health Questionnaire-9 (PHQ-9) score of 15 or greater (moderate or severe depression) within the past 30 days. Other scales to measure severity may be used instead of the PHQ-9 such as the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D).
- The patient has been considered for electroconvulsive therapy (ECT).
- The patient or their legal representative is able to provide verbal informed consent.
The patient has an adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and documented.

Exclusion Criteria

- Current or past history of schizophrenia, schizoaffective disorder, or bipolar disorder
- Dementia
- Current or recent (within the 7 days) delirium
- Current uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg)
- Severe cardiac decompensation
- Pregnant (via positive pregnancy test) or lack of birth control method in women of childbearing potential
- Positive urine drug screen or current or previous abuse of ketamine. Patients prescribed an opioid, benzodiazepine, or barbiturate by a VHA provider (including Community Care) are eligible for ketamine; however, it is advised that concurrent use while receiving ketamine may prolong recovery time. Patients in acute intoxication or in need of detoxification should be excluded until those issues are addressed.
- Allergy or previous serious adverse effects to ketamine

Screening and Referral

- Each facility will be responsible for developing and operationalizing a procedure to screen and refer potential candidates for treatment with ketamine.
- Screening should be completed no more than 30 days prior to acceptance and administration of the first dose of ketamine.
- Screening will include the following: verbal informed consent, inclusion/exclusion criteria, psychiatric examination including PHQ-9 and evaluation of cognitive status (i.e., Mini-Addenbrooke’s Cognitive Examination (M-ACE)), and physical examination including vitals (blood pressure, heart rate, respiratory rate, oxygen saturation, and weight), relevant laboratory measures, and urine toxicology and pregnancy screens.
  - Patients with a SBP >150 mm Hg or a DBP >95 mm Hg at screening should be considered at higher risk and treatment for hypertension should be considered prior to initiating treatment with ketamine. Patients with a diagnosis of hypertension are to be adequately treated prior to receiving an infusion of ketamine.
  - Patients with a history of cardiopulmonary or cerebrovascular disease, recent myocardial infarction, symptomatic ischemic heart disease, dyspnea marked by shortness of breath or wheezing, poor exercise capacity (<6 metabolic equivalent of tasks (METs); bicycling – light effort (10-12 mph) =6.0), or any disease that could be associated with increased risk of acute cardiac demand or blood pressure or respiratory depression should be considered on an individual case basis, considering risk/benefit ratios.
  - Patients with a baseline heart rate of <60 beat per minute (bradycardia) or >100 beats per minute (tachycardia) should be considered on a case-by-case basis for the relative risks of ketamine.
  - SpO₂ at screening should be >94 after mild exertion.
- Other physical and laboratory screening procedures should be determined according to the patient’s individual risk factors based on his/her demographics, medical history and review of systems and is the responsibility of the prescribing VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA).
• Whether to obtain medical clearance from the patient’s primary care provider or consultation from a cardiologist, anesthesiologist, or other medical specialist should be based on the patient’s risk factors and is the responsibility of the prescribing VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA).

• Concurrent use or abuse of CNS depressants
  o In light of ketamine’s abuse as a recreational drug, other factors to consider when screening for appropriate patients is a history of substance abuse including ketamine, extent of past and current alcohol use, smoking history, a history of medication misuse or inappropriate medical care, and a positive urine drug screen. There is no clear evidence of recent substance abuse to be associated with the risk of relapse with ketamine. Length of sobriety should be considered when making a decision.
  o Due to the theoretical potential for benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonists hypnotics (e.g., zolpidem) to attenuate ketamine’s antidepressant effects, patients taking benzodiazepines should be allowed adequate time for the last dose of benzodiazepine to washout prior to receiving ketamine.
  o Concurrent use of barbiturates, opioids and other narcotics may delay recovery following ketamine infusion.

Location of Administration, Monitoring and Recovery
• The facility is responsible for identifying a physical location for the infusion of ketamine and monitoring the patient during and after the infusion. The place for administration and recovery should be private and large enough to accommodate the patient and required personnel.

• The treatment setting should be able to provide immediate care if necessary. A crash cart should be readily accessible. The facility must have the means to monitor basic cardiovascular functions (including electrocardiogram and blood pressure) and respiratory function (oxygen saturation or end-tidal CO2).

• The facility must also be capable of administering oxygen, medication and/or restraints to manage potentially dangerous behavioral symptoms.

• The facility must have a plan to rapidly address any sustained alterations in cardiovascular function including advanced cardiac life support or transfer to a hospital capable of caring for acute cardiovascular events.

• Patients determined to be at high risk for complications based on pretreatment evaluation should be treated at a facility equipped and staffed to manage any cardiovascular or respiratory events that may occur.

Ketamine Procurement and Infusion
• The facility is responsible for determining the procedure that ketamine is ordered, prepared, and transported to the place of administration.

• A VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA) will order the ketamine intravenous infusion and pre-medication and/or concurrent medication to prevent or manage adverse effects (e.g., intravenous lorazepam for agitation).

• The ordering VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA) and an ACLS certified physician or nurse will be present during the infusion. The VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA) can leave once the infusion is completed and the patient considered stable based on vital signs and cognitive status. The VA psychiatrist or VA licensed health-care provider (i.e., CPP, NP, PA) must return at 120 minutes after the start of the infusion to administer the Clinician-Administered Dissociative States Scale (CADSS), and clear the patient for discharge. An ACLS certified provider is to remain with the patient until
• Ketamine infusion timeline
  o T-2 days or sooner: Urine drug screen and pregnancy tests are collected.
  o **T-60:** Intravenous line started by a nurse or other qualified provider. Perform vital signs (sitting/standing blood pressure, sitting/standing pulse, respiratory rate, and oxygen saturation) test. Administer PHQ-9 (or other depression scale), and CADSS (for dissociative state) as baseline measures.
  o **T-0:** Provided vitals are acceptable and urine drug screen and pregnancy tests are negative (See Exclusion Criteria). Administer ketamine 0.5 mg/kg by intravenous infusion using an infusion pump over 40 minutes. For patients with a body mass index ≥30 kg/m² it is suggested that the dose be calculated using the patient’s ideal body weight (Men = 50 kg + (2.3 kg x each inch >5 feet); Women = 45.5 kg + (2.3 kg x each inch >5 feet)) rather than their actual body weight.
  o **T-0 to +40:** Monitor for sedation, dissociation, and other possible adverse events.
  o **T+10, 20, 30 and 40:** Vital signs
  o **T+80:** Vital signs, and check for resolution of sedation, dissociation, and other possible adverse effects
  o **T+120:** Vital signs, CADSS and readiness for discharge assessment (consider Modified Aldrete or Brief Confusion Assessment Method (bCAM))
• Parameters for stopping infusion
  o Blood pressure should remain <180 mm Hg systolic and < 110 mm Hg diastolic at all times during the infusion. Stopping the infusion often results in a rapid decline in blood pressure.
    ▪ Systolic blood pressure can also drop by >10 mm Hg during the infusion. Should such a drop occur and be accompanied by an increased heart rate or any evidence of distress, then the infusion should be stopped.
  o Heart rate should remain below the age adjusted maximum heart rates of 20 yrs <140 bpm, 30 yrs <133, 40 yrs <126, 50 yrs <119, and 60 yrs <112. For patients 65 years and older the maximum heart rate should be individualized based on exercise capacity and other risk factors.
  o The appearance of any of the following necessitates stopping the infusion: 1) pallor, cyanosis, or any symptoms of poor perfusion, 2) respiratory symptoms such as shortness of breath, wheezing, 3) the appearance of chest, jaw or arm pain suggesting cardiac involvement, or 4) the patient’s desire to stop.

**Repeat Infusion Schedule**
• Ketamine infusion should be repeated no less 3 days apart and not more frequently than twice a week for 2 – 3 weeks
• After 2-3 weeks the frequency of infusion should be once a week to once every 3 weeks with the goal to extend the interval between infusions to as long as possible (usually monthly). This will need to be individualized based on the patient’s response, tolerability, and preference/availability.
• In the interest of patient safety, ketamine should be tapered and discontinued. At present this time frame is undefined and will need to be individualized.

**Ketamine Treatment Failure/Discontinuation**
- Discontinue if patient wishes to for any reason.
- Discontinue if the patient needs to have the infusion stopped more than once due to exceeding the blood pressure or heart rate thresholds.
- After 4 to 6 infusions without an adequate response
  - An adequate response is defined as a 50% or greater decline in the PHQ-9 score from baseline
- Discontinue if pronounced or slow to correct cognitive impairment (M-ACE) or repeated dissociative symptoms.
- Discontinue when dosing cannot be spaced out to a minimum of 1 dose per week by the second month of treatment.

**Longitudinal Monitoring of Ketamine Patients**
- A PHQ-9 and M-ACE should be completed at the end of the induction phase, every 6 months of treatment, and at the end of treatment course.
Consent Statement for Ketamine Infusion for the Treatment-Resistant Major Depressive Disorder or Severe Suicide Ideation

The following is to be read to and/or given to the patient or person authorized to approve treatments to read. A verbal acknowledgment of consent is required and is to be documented in the patient’s medical record.

************************************************************************************
* Your VA psychiatrist or VA mental health provider, or a psychiatrist provided by VA Community Care has recommended that you be treated with a drug called KETAMINE because your depression has not responded to other treatments or your thoughts of harming yourself are severe enough to need urgent treatment. Ketamine is not approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression or suicidal thoughts and its use to treat these conditions is considered “off-label.” This is why you are being asked to give verbal consent for treatment with ketamine.

Ketamine is approved by FDA as general anesthetic, a drug that induces deep sleep or an unconscious state during which the patient does not feel pain. General anesthesia is used during surgery. The dose of ketamine used in surgery is much higher than the dose you will receive.

To treat your depression, you will receive a dose of ketamine two times a week for 2 or 3 weeks, at that point your physician will begin to increase the time between treatments to once a week to once every 3 or 4 weeks. This will be done based on your response and how well you tolerate ketamine. If after 4 to 6 treatments your psychiatrist or VA mental health provider determines that you have not responded to ketamine, the treatments will stop, and he/she will discuss other treatment options with you.

What can you expect during the treatment?

Prior to your receiving ketamine, you will be examined to determine if ketamine is safe for you. This will include physical and mental status exams as well as labs and other tests decided on by the examining healthcare provider.

• Patients with certain heart conditions, uncontrolled high blood pressure or breathing conditions may not be eligible for treatment with ketamine.
• Women who are pregnant or who may become pregnant are not eligible for ketamine.
• Many patients who are abusing drugs or have a history of drug abuse may not be eligible for ketamine.

Each ketamine treatment will take approximately 5 hours; this includes your arrival an hour before you receive ketamine so your vital signs (heart rate, blood pressure, and breathing) can be assessed and an intravenous (IV) line started. You will also be given tests to measure your mood and mental state. These will be repeated periodically during your treatment. The remaining 4 hours include the 40 minutes to infuse ketamine and to make sure that you have recovered and are safe to leave. During this time, you will not be alone, a physician, nurse or other qualified health professional will be with you.

Ketamine’s antidepressant effect has been reported to be rapid in some, but not all, patients who are depressed or have suicidal thoughts. However, the effect often quickly wears off and symptoms of depression return which is why you will receive repeated doses.
You are advised not to drive for 24-hours after receiving ketamine. Therefore, you will need a driver or another pre-arranged form of transportation to return home.

**What are the potential risks or discomforts of ketamine infusion?**

When used in general anesthesia ketamine has been reported to increase the risk for certain side effects such as anxiety, panic, fear reactions, hallucinations (such as seeing or hearing things that are not really present), paranoid thinking, agitation, dissociation (to feel disconnected from thoughts, memories, or surroundings), derealization (a sense that things around you are not real), depersonalization (out of body experiences), dream-like states, or agitation upon awakening from general anesthesia. Because ketamine is being used at much lower amounts and delivered over a longer period of time than is typically done in anesthesia practice, it is anticipated that these side-effects, while still possible, are less likely.

Ketamine is a known drug of abuse; in most cases it is swallowed or snorted, at substantially higher dosages and often with other illicit drugs or alcohol. While the dose of ketamine you will receive is generally well-tolerated, repeated doses may increase the side effects described by at risk individuals.

Importantly, there are no known permanent psychological effects reported in patients experiencing the side effects described above. Tolerance (a decreased in effect) to ketamine may develop with repeated use or in susceptible individuals with pre-existing illnesses. Other side-effects, such as high blood pressure and a change in heart rate or rhythm, can occur. You will be frequently monitored for these effects during and after the ketamine infusion.

It is your right to have ketamine discontinued at any time during your treatment—even while receiving the medication.

If you have any additional questions about ketamine or your treatment, please ask your psychiatrist or mental health provider.
References
10. KentuckyOne Health, University of Louisville Hospital Policy/Procedure. Ketamine infusion for treatment resistant depression.