Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation

National Protocol Guidance
October 2025

VA Pharmacy Benefits Management Services, National Formulary Committee, and Office of Mental Health

Purpose: To provide general guidance on ensuring access to intravenous ketamine for the treatment of treatment resistant major depressive disorder (TRD) or severe suicidal ideation under a National VA protocol.

Disclaimer: To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of ketamine for treating TRD or severe suicidal ideation. Clinical circumstances for the treatment of individual Veterans may necessitate provider decision making that is outside of this guidance.

Background

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist approved for general anesthesia. Ketamine has demonstrated a rapid response in people with TRD 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). 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. 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.

Despite these preliminary positive findings in a limited number of studies, many questions remain unanswered. Studies to date have given a single dose of ketamine leaving the number and frequency of doses needed to treat an episode of TRD undetermined. Ketamine has also not been adequately studied in people with co-occurring conditions. Thus, the identification of patients who would most benefit fromketamine and the best approach to dosing has not been established.

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

Procedure:

- Patients can either be treated as outpatients or inpatients

Patient Selection

Inclusion Criteria

One of the following must be selected to meet criteria for use

- Remission not achieved from 2 antidepressant trials including a trial of an augmentation strategy in the current episode of depression^1 and 4 total adequate antidepressant trials in the patient's lifetime
- Patient is hospitalized with TRD with acute suicidal ideation/behavior

^1 One augmentation trial could be an adequate course of evidence-based psychotherapy (EBP)

Additional Inclusion Criteria

The answers to **ALL** of the following must be fulfilled to meet criteria

- Patient in current episode of depression is experiencing moderate to severe depressive symptomatology (i.e., PHQ-9 $\geq$ 15 within the last 30 days)
- Antidepressant treatment trials are considered unsuccessful if the patient has not responded to at least 6 weeks of an antidepressant at half maximum dose or greater.
- A VA psychiatrist or a VA licensed Mental Health care provider (i.e., CPP, NP, PA) has evaluated the patient and determined and documented that the patient qualifies for ketamine treatment in the patient's medical record.
- The patient or their legal representative can provide signed informed consent.
- The patient agrees to stay and be monitored after ketamine administration and agrees not to drive or operate heavy machinery/equipment and not to make major financial or legal decisions for the remainder of the day in which ketamine is administered.
- 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.
- For women of childbearing potential
    - Pregnancy should be excluded prior to receiving ketamine and the patient provided contraceptive counseling on potential risks vs. benefits of taking ketamine if the patient were to become pregnant.

Exclusion Criteria

If the answer to ANY item below is met, the patient should NOT receive ketamine

- Current or history of schizophrenia, schizoaffective disorder, or bipolar disorder
- Dementia
- Current or recent (within the 30 days) delirium
- Current uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg)
- Severe cardiac decompensation (Class IV heart failure or unstable angina)
- Severe hepatic impairment (Child-Pugh class C)
- Uncontrolled seizures
- History of non-response to ketamine or esketamine
- Pregnant (via positive pregnancy test) or lack of birth control method in women of childbearing potential
- Patient is breastfeeding

- Current or previous abuse of ketamine or esketamine
- Clinical evidence for current substance misuse except tobacco
- Current moderate or severe substance use disorder (SUD)
- Allergy or previous serious adverse effects to ketamine or esketamine

Issues for Consideration

- In January 2025 FDA approved esketamine for TRD in adults as monotherapy. However, the use of ketamine as the sole agent for antidepressant treatment is not advisable for most Veterans, especially as long-term treatment. However, starting an antidepressant to simply ensure that Veterans meet criteria for ketamine treatment is not advisable either. Using ketamine in a time-limited fashion to achieve response or remission while also developing a long-term plan for an individual Veteran may represent the best course of action.
- Patients prescribed a benzodiazepine, a non-benzodiazepine sedative hypnotic or a monoamine oxidase inhibitor are eligible to receive esketamine; however, it is advised that concurrent use while receiving esketamine may cause sedation or blood pressure changes.
- Carefully review prior to use of esketamine, patients who are less than 6 months in remission from substance use disorder. Review Prescription Drug Monitoring Program (PDMP).
- May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential.

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 60 days prior to acceptance and administration of the first dose of ketamine.
- Screening will include the following:
    - Signed informed consent
    - Psychiatric examination including assessment of inclusion/exclusion criteria
    - The PHQ-9 depression rating scale. The PHQ-9 is required at screening and prior to each treatment. Additional depression rating scales may be used.
    - Evaluation of cognitive status (e.g., Mini-Addenbrooke's Cognitive Examination (M-ACE))
    - Assessment of suicide risk.
        - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation (and within 24hours of discharge or as clinically indicated any time during treatment.
        - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed if it is the first CSREever. Otherwise, the CSRE should be updated as clinically indicated.
    - Physical examination including vitals (blood pressure, heart rate)

        - Patients with a SBP >140 mm Hg or a DBP >90 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 a dose of ketamine. Stimulants may increase blood pressure and heart rate, exacerbating the hypertensive effects of ketamine, increasing the risk of cardiovascular complications. The use of ketamine in individuals receiving a stimulant should be considered on a case-by-case basis.
        - 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.
    - Relevant laboratory measures, and urine toxicology and pregnancy screens.
        - 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 provider

- Whether obtaining 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 Mental Health-care provider (i.e., CPP, NP, PA).
- Concurrent use or abuse of psychoactive substances
    - Considering ketamine's known addictive potential, a history of substance abuse or dependence including ketamine or esketamine, extent of past and current alcohol use, smoking history, a history of medication misuse, a positive urine drug screen, and length of sobriety are important factors to consider.
    - Patients with a history of SUD are at risk for relapse or development of a new SUD when exposed to psychoactive substances. There are case reports of recent substance abuse associated with the risk of relapse with ketamine, one that resulted in death in a single motor vehicle accident. While the length of sobriety may be considered when making a decision, at a minimum, all patients in recovery from SUD should be warned of the risk of inducing a relapse to previous SUD or a new addiction to esketamine or ketamine with this treatment. Other

strategies for managing TRD should be prioritized over strategies involving potentially addictive substances, especially for those with a history of SUD. If ketamine treatment is chosen, close monitoring for signs of substance use including random, monitored urine drug testing is recommended.

- Concurrent use or abuse of CNS depressants
    - Due to the theoretical potential for benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonists hypnotics (e.g., zolpidem), and naltrexone to attenuate ketamine's antidepressant effects, patients taking these agents should allow adequate time for the last dose to washout prior to receiving esketamine.

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 CO_2). Facilities without these capabilities should provide a process for emergency response arrangements in their local SOP.
- The facility must also be capable of administering oxygen, medication and/or restraints to manage potentially dangerous behavioral symptoms. Facilities without these capabilities should provide a response plan in their local SOP.
- 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, Dosing, and Day of Administration Monitoring

- 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 Mental 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) following the facility's policy for ordering schedule III-controlled substances.
- The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will ensure completion of the day of treatment PHQ-9 prior to each treatment. Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at program intake or initial evaluation and within 24hours of discharge from the program. The CSSRS should be completed as clinically indicated at any time during treatment.
- The ordering VA psychiatrist or VA licensed Mental 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 Mental 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 Mental Health-care provider (i.e., CPP, NP, PA) must return 120 minutes after the start of the infusion to clear the patient for discharge. An ACLS certified provider is to remain with the patient until discharge.

- Ketamine infusion timeline guide
  - T-2 days or sooner: Urine drug screen and pregnancy tests are collected.
  - **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 as baseline measure.
  - **T**-5: Time out
  - **T-0**: Provided vitals are acceptable, pregnancy tests are negative, and urine drug screen is acceptable. Administer ketamine 0.5 mg/kg (range 0.5mg/kg – 1mg/kg) by intravenous infusion using an infusion pump over 40 minutes. For patients with a body mass index $\geq$30 kg/m^2 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 eachinch >5 feet)) rather than their actual body weight. 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.
  - **T-0 to +40:** Monitor for sedation, dissociation, and other possible adverse events.
  - **T+10, 20, 30 and 40**: Vital signs
  - **T+80**: Vital signs, and check for resolution of sedation, dissociation, and other possible adverse effects
  - **T+120**: Vital signs, and readiness for discharge assessment (consider Modified Aldrete or Brief Confusion Assessment Method (bCAM))
- Parameters for stopping infusion
  - Blood pressure should always remain <180 mm Hg systolic and < 110 mm Hg diastolic 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.
  - 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.
  - 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 2 days apart and not more frequently than twice a week for 4 weeks
- After 4 weeks the frequency of infusion should be once a week to once every 3 weeks with the goal of extending the interval between to as long as possible (usually monthly). This will need to be individualized based on the patient's response, tolerability, and preference/availability. The time frame for maintenance use in TRD is undefined but long-term maintenance treatment with ketamine may be a reality for some Veterans and is not against guidance. Veterans receiving maintenance treatment should receive regular clinical review and/or re-evaluation for the

continued need for treatment or adverse effects.

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.
- Patients without a response (after 4 weeks) should not move to maintenance treatment
    - 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 (e.g., 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 should be completed prior to each dose of IV ketamine
- A PHQ-9 and cognitive evaluation (such as M-ACE) should be completed at the end of the induction phase, every 6 months of treatment, and at the end of treatment course.
- Suicide risk should be assessed and monitored using a combination of the Comprehensive Suicide Risk Evaluation (CSRE) and Columbia-Suicide Severity Rating Scale (C-SSRS) Screener.
    - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation and within 24hours of discharge or discontinuation from the program for any reason. The CSSRS should be completed as clinically indicated any time during treatment.
    - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed at the intake or initial evaluation if it is the first CSRE ever. Otherwise, the CSRE should be updated as clinically indicated.
    - A positive C-SSRS Screener should result in a CSRE