VHA Office of Integrated Veteran Care

Clinical Determination and Indication

Intravenous Ketamine for Treatment Resistant Depression

CDI Number: 00030

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I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Intravenous Ketamine:

Intravenous (IV) ketamine may be considered **medically necessary** for the following indications:

- Treatment resistant depression (TRD)
- Depression with severe suicidal ideation

Veterans receiving IV ketamine for TRD must meet **ALL** the following criteria:

- Diagnosis of unipolar, major depressive disorder (MDD), as per DSM-5
- Veteran has one of the following:
  - Failed to achieve a full therapeutic response to **four adequate trials** of antidepressants from different classes, including pharmacologic augmentation and/or psychotherapy, when appropriate
  - Severe suicidal depression (where rapid treatment response is important)
- Score of 15 or greater on the Patient Health Questionnaire-9 (PHQ-9) (moderate or severe depression) within the past 30 days or an equivalent severity measure from an appropriate test, when the patient can participate in the assessment, such as Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D)
- Veteran has been considered, if appropriate, for electroconvulsive therapy (ECT) as a treatment option

Note: This document is in alignment with the VA National Formulary Guidance. Please visit the VA Formulary Advisor to access VA Pharmacy Benefits Management Services' resources and additional information on clinical criteria.

- *National Protocol Guidance*: Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation

b. Limitations/Exclusions

IV ketamine is **not recommended** for treatment resistant depression and depression with suicidal ideation if any of the following is applicable:

- Current or past history of schizophrenia, schizoaffective disorder, or bipolar disorder
- Dementia
- Current or recent (within 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 Veterans with childbearing potential
- Positive urine drug screen or current or previous abuse of ketamine
- Veterans 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
- Current use or treatment with other ketamine products such as esketamine
- Veterans in acute intoxication or in need of detoxification should not receive IV ketamine
- Allergy or previous serious adverse effects to ketamine

For all off-label conditions/indications not listed in section II.a. of this document, intravenous ketamine is considered **not medically necessary** due to insufficient evidence of efficacy and safety.

c. Description of Treatment

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which can provide a rapid response to depressive symptoms and suicidal ideation at subanesthetic doses. The exact mechanism of action has not been established. Dosing and frequency parameters are individualized based on the Veteran's response, tolerability, and preference/availability. Each ketamine treatment session is approximately two hours and includes arriving

one hour prior to receiving ketamine to obtain vital signs, start an intravenous (IV) line, and conduct tests to measure mood and mental state. The remaining time will include 40 minutes to infuse ketamine and recovery time. Veterans will be supervised by a physician, nurse, or other qualified health professional during each treatment session. Clinician-Administered Dissociative States Scale (CADSS) will be administered prior to discharge.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background Information

Treatment-resistant depression is a type of major depressive disorder (MDD) where the patient has not responded adequately to multiple antidepressant regimens of adequate dose and duration (six to eight weeks). Despite treatment attempts with numerous antidepressants, about 30% of patients diagnosed with MDD do not achieve remission and are diagnosed with TRD. Intravenous ketamine is a Food & Drug Administration (FDA) approved general anesthetic for surgical and medical procedures. The use of ketamine infusions as an antidepressant for TRD has been increasing, though it is still considered an off-label use. The effective dose for depression is lower than the typical anesthetic doses, and side-effects are generally transient and mild. Ketamine delivered in low doses can provide rapid relief of TRD over days to weeks.

b. Research, Clinical Trials, and Evidence Summaries

Several clinical trials have established ketamine's effectiveness in treating depressive disorders, as treatments have been shown to reduce symptoms of TRD within 24 hours of administration. Research on IV ketamine has also reported a rapid decrease of suicidal thoughts in depressed patients with suicidal ideation.

Sanacora et al. (2021) provided a consensus statement intended to highlight the current state of the field and the critical issues to be considered when contemplating the use of ketamine for treatment-resistant depression. Several studies now provide evidence of ketamine hydrochloride's ability to produce rapid and robust antidepressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Patient selection for ketamine treatment requires consideration of the risks and benefits of the treatment in the context of the patient's severity of depression, duration of current episode, previous treatment history, and urgency for treatment.

Seshadri et al. (2024) conducted a systematic review and meta-analysis on the efficacy of intravenous ketamine and intranasal esketamine with dose escalation for major depression. The systematic review aimed to evaluate the efficacy and safety of ketamine and esketamine at various dosages for depression. Randomized controlled trials (RCTs) were included with parallel group dose comparison of ketamine and esketamine for TRD. Standardized mean differences were calculated using Hedges'-g to complete random effects meta-analysis. The data for ketamine included adults with TRD that received ketamine at different doses, compared to placebo/control, with the following dosage conditions: dosages of IV ketamine- ≤0.2 mg/kg (low-dose), >0.2–0.5 mg/kg (standard dose), >0.5 mg/kg (high dose). The efficacy outcomes were measured by changes in depression outcomes for IV ketamine. Safety was assessed by reported adverse effects. Results for IV ketamine provided evidence of clinical efficacy of IV ketamine at doses as low as 0.2 mg/kg, with increasing dose response at 0.5 mg/kg. Random effects meta-analysis of studies showed efficacy in reducing depression symptoms with IV ketamine compared to control/placebo. The existing data does not provide sufficient evidence that the higher IV ketamine doses (>0.5 mg/kg) are more effective than the standard dose (0.5 mg/kg), based on a small number of studies. The most common reported side-effects with IV ketamine were dizziness, headache, dissociative symptoms, dysgeusia, and transient elevation of blood pressure tending to occur more at the higher doses.

c. U.S. Food & Drug Administration (FDA) Information

VA review of a pharmaceutical for inclusion in the VA formulary is generally only for FDA-approved indications or uses. However, VA may provide recommendations regarding off-label use of an otherwise FDA-approved drug after reviewing safety and efficacy evidence.

While IV ketamine has not received FDA approval for the treatment of TRD, multiple clinical studies have demonstrated it can be a safe and effective treatment for patients with TRD when properly administered by a qualified practitioner.

d. Medicare Coverage Determinations

Currently there are no available Medicare coverage determinations available for IV ketamine for TRD. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

IV. Definitions

Term	Definition
Dissociative	A break in how the mind handles information, disconnecting from thoughts, feelings, memories, surroundings, and sense of identity
Dysgeusia	Distortion of the sense of taste
Racemic Mixture	A mixture containing two enantiomers (molecules that are mirror images of each other) in equal proportions
Suicidal Ideation	Thoughts about self-harm, with deliberate consideration or planning of possible techniques of causing one's own death
Unipolar	Refers to the idea that there is only one “pole,” or side, to your abnormal mood state; also referred to as MDD

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VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	