MEDICAL POLICY

Medical Policy Title	**Ketamine for the Treatment of Psychiatric Disorders**
Policy Number	**3.01.13**
Current Effective Date	**January 22, 2026**
Next Review Date	**January 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Ketamine administered by any route (e.g., oral, intravenous, intramuscular, sublingual, or intranasal formulations other than esketamine [Spravato]) for the treatment of any psychiatric disorder including but not limited to anxiety, depression, obsessive compulsive disorder, post-traumatic stress disorder, or substance use disorder is considered **investigational**.

II. Subsequent monitoring of investigational ketamine administration is also considered **investigational**.

RELATED POLICIE(S)

Corporate Medical Policy

3.01.09 Transcranial Magnetic Stimulation

7.03.03 Ketamine Infusion Therapy for the Treatment of Chronic Pain Syndromes

11.01.03 Experimental or Investigational

11.01.27 New/Emerging Technology & Services

Pharmacy Management Drug Policy

63 Clinical Review Prior Authorization (CRPA) Medical Drug Policy, for Spravato (esketamine) nasal spray (s-enantiomer of ketamine) criteria.

POLICY GUIDELINE(S)

The U.S. Food and Drug Administration (FDA) has not established the safety or efficacy of ketamine for the treatment of psychiatric disorders. Its use for these indications, including as an adjunct therapy (e.g., with transcranial magnetic stimulation or psychotherapy), is considered off-label.

DESCRIPTION

Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine (arketamine). It is an N-methyl-D-aspartate (NMDA) receptor antagonist and classified as a dissociative anesthetic with psychedelic properties. When administered at sub-anesthetic doses, ketamine produces alterations in perception, cognition, and consciousness similar to other

psychedelic agents. These effects are central to its proposed therapeutic use; however, the mechanism of its antidepressant effect is not fully understood but may involve NMDA receptor blockade and modulation of monoamine pathways.

Ketamine can be administered parenterally (intravenous, intramuscular, or subcutaneous), orally, sublingually, or intranasally. Intranasal ketamine and intranasal esketamine (Spravato) differ in regulatory status and composition. Esketamine is the S-enantiomer of ketamine and is FDA-approved for treatment-resistant depression. In contrast, intranasal racemic ketamine formulations are compounded products used off-label, without FDA approval or standardized safety oversight.

There are risks associated with ketamine administration. According to the American Society of Anesthesiologists (2025), inappropriate administration of ketamine may lead to life-threatening consequences, including respiratory failure, cardiac events, and seizures. Patients receiving ketamine in outpatient or home setting may lack routine and immediate access to vital sign monitoring, rescue personnel, or emergency resuscitation equipment necessary when anesthetic agents are used. Intravenous and intramuscular ketamine should only be administered in a monitored setting under the care of a licensed health care professional where appropriate rescue equipment is immediately available.

SUPPORTIVE LITERATURE

Ketamine hydrochloride injection is being investigated for its benefit-risk profile and safe-use conditions in the treatment of psychiatric disorders, such as treatment-resistant depression (TRD), bipolar depression, post-traumatic stress disorder, and obsessive-compulsive disorder.

Treatment-Resistant Depression

Ekstrand et al (2022) conducted an open-label, randomized, noninferiority trial comparing ketamine infusion with electroconvulsive therapy (ECT) for depression. Patients were assigned to receive either ketamine (0.5 mg/kg) or ECT three times per week, with up to 12 treatment sessions. A total of 186 patients participated. Remission, defined as a Montgomery–Asberg Depression Rating Scale (MADRS) score ≤10, was achieved more frequently with ECT than ketamine (63% vs. 46%). The median number of sessions required for remission was six. Although ketamine was inferior to ECT, the authors concluded it remains a potential treatment option for depression. During the 12-month follow-up, relapse rates were similar between groups (70% for ketamine vs. 64% for ECT). Serious adverse events were more common with ECT, whereas treatment-emergent adverse events leading to dropout occurred more often with ketamine.

Anand et al (2023) conducted an open-label, randomized noninferiority trial comparing ketamine (0.5 mg/kg 3 times weekly) with ECT (3 times weekly) in adults with treatment-resistant moderate or severe depression, defined as a lack of response to ≥2 adequate trials of antidepressant therapy and MADRS score >20. Prior suicide attempts were reported in 36.5% of ketamine recipients and 41.4% of ECT recipients. After three weeks, response, defined as a 50% or greater reduction in Quick Inventory of Depressive Symptomatology–Self-report (QIDS-SR-16) score from baseline, occurred in 55.4% of participants assigned to ketamine and 41.2% assigned to ECT ($p<.001$ for noninferiority). Among responders, relapse rates were 19% for ketamine and 35.4% for ECT at one month, and 34.5% versus 56.3% at six months. Patient-reported memory function scores were higher in the

ketamine group, and fewer patients reported cognitive symptoms compared with ECT. Both groups showed similar improvements in quality-of-life scores. Moderate or severe adverse events occurred in 25.1% of ketamine recipients and 32.4% of ECT recipients; rates were similar across most events except muscle pain or weakness, which was reported in 0.5% of ketamine recipients versus 5.3% of ECT recipients (p=.01).

Petrucci et al (2024) conducted an updated systematic review and noninferiority meta-analysis comparing ketamine and ECT for adults with MDD experiencing a current major depressive episode. The analysis included six randomized controlled trials (n=655), with 348 patients (53.1%) receiving ketamine and 307 (46.9%) undergoing ECT. Overall response rates did not differ significantly between groups (p=0.198). Among patients without psychotic features, outcomes were similar for ketamine and ECT, whereas in hospitalized patients, ketamine was inferior. Remission rates were comparable in the overall population and among patients with psychosis, but ECT was superior for inpatients. Depression severity scores favored ECT in both the overall population and inpatients, with a moderate effect size. Follow-up assessments showed no significant differences in relapse rates at 1 or 6 months. Comparative efficacy in psychotic depression could not be fully assessed because only one study reported stratified results for this subgroup. Limitations included variability in inclusion/exclusion criteria, concerns about bias in most studies, and lack of long-term follow-up. The authors concluded that ketamine did not meet prespecified noninferiority criteria compared with ECT and may be inferior among inpatients. Further randomized trials are needed to clarify ketamine's role in this population.

Post Traumatic Stress Disorder (PTSD)

Feder et al (2021) conducted a double-blind trial comparing intravenous (IV) ketamine with IV midazolam, each administered three times weekly over two weeks, in adult patients with PTSD. The primary outcome was change in PTSD symptom severity from baseline to week 2. The mean duration of PTSD was 14.9 years. At baseline, 13 patients (43.3%) were receiving concomitant psychotropic medications, and 17 patients (56.7%) were receiving concomitant psychotherapy. At week 2, the ketamine group had a significantly lower mean Clinician-Administered PTSD Scale (CAPS-5) total score compared to the midazolam group (difference: 11.88 points; p=.004). Adverse events more common with ketamine included nausea/vomiting (33% vs. 20%), headache (33% vs. 20%), and fatigue (20% vs. 7%). The authors noted a potential for unblinding in the ketamine group due to higher rates of dissociative symptoms.

Obsessive Compulsive Disorder (OCD)

Bandeira et al (2022) conducted a systematic review of nine studies (n=55 patients) published through 2021 evaluating ketamine for OCD. The included studies comprised three randomized controlled trials, three case reports, two open-label trials, and one retrospective chart review. Findings suggested a potential for rapid onset of action and good tolerability; however, most studies involved single-session IV racemic ketamine, and results were inconsistent. Evidence was insufficient to determine whether racemic ketamine, S-ketamine, or R-ketamine is most effective, and only limited data suggest that combining ketamine with psychotherapy may offer benefit. Limitations included small sample sizes, heterogeneity in study designs and treatment protocols, and varying psychiatric comorbidity profiles. The authors concluded that ketamine shows promise as an

alternative treatment for OCD, but larger randomized, double-blind, placebo-controlled trials are needed.

Adjunctive with Electroconvulsive Therapy (ECT)

Two meta-analyses (Zheng 2019; Ainsworth 2020) found no evidence that ketamine anesthesia enhances the total antidepressant effect of ECT.

PROFESSIONAL GUIDELINE(S)

In 2017, the American Psychiatric Association (APA) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression (Sanacora 2017). The consensus opinion notes that "while ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data, and the potential risk associated with the drug when considering the treatment option. Risks include suicidal ideation and potential substance abuse."

APA guidelines for the treatment of other psychiatric disorders (e.g., posttraumatic stress disorder, 2004; obsessive compulsive disorder, 2007; bipolar disorder, 2002) do not address the use the of ketamine as a potential treatment option.

The U.S. Department of Veterans Affairs Department of Defense (VA/DoD) has several mental health clinical practice guidelines with the following recommendations on the use of ketamine for:

- Major depressive disorder (2022): VA/DoD suggests ketamine as an option for augmentation for patients with MDD who have not responded to several adequate pharmacologic trials (weak recommendation; low quality evidence).
- Bipolar disorder (2023): No recommendation. There is insufficient evidence to recommend for or against the use of ketamine as either monotherapy or as adjunctive therapy.
- Post-traumatic stress disorder (2023): VA/DoD suggests against the use of ketamine for the treatment of PTSD, stating that the body of the evidence had limitations including a lack of strong evidence for the efficacy of these medications for the treatment of PTSD.
- Patients at risk for suicide (2024): VA/DoD suggests offering ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation in patients with the presence of suicidal ideation and major depressive disorder (weak recommendation. However, there is insufficient evidence to recommend for or against ketamine infusions to reduce the risk of suicide or suicide attempts.

REGULATORY STATUS

The FDA is responsible for ensuring the safety, efficacy, and quality of drugs sold in the United States. This includes both prescription and over-the-counter medications. Refer to the FDA Drug website. Available from: https://www.fda.gov/drugs [accessed 2025 Dec 1]

The FDA maintains information for consumers and health professionals on new drug warnings and other safety information, drug label changes, and shortages of medically necessary drug products. Available from: https://www.fda.gov/drugs/drug-safety-and-availability [accessed 2025 Dec 1]

Ketamine hydrochloride injection is FDA approved as a general anesthetic for use as the sole anesthetic agent in diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to other general anesthetic agents, and as a supplement to other anesthetic agents.

In 2023, the FDA issued a warning acknowledging reports that compounded ketamine products have been marketed for off-label use in a wide range of psychiatric conditions (e.g., depression, anxiety, post-traumatic stress disorder [PTSD], and obsessive-compulsive disorder [OCD]). The warning emphasizes that there is insufficient evidence to demonstrate that ketamine is safer, more effective, or faster acting than medications currently approved by the FDA for these indications.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	each additional hour (list separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
0820T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; first physician or other qualified health care professional, each hour
0821T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; second physician or other qualified health care professional, concurrent with first physician or other qualified health care professional, each hour (List separately in addition to code for primary procedure)

Code	Description
0822T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; clinical staff under the direction of a physician or other qualified health care professional, concurrent with first physician or other qualified health care professional, each hour (List separately in addition to code for primary procedure)

HCPCS Codes

Code	Description
J3490	Unclassified Drug

ICD10 Codes

Code	Description
Multiple Codes	Investigational for all diagnosis codes

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The use of ketamine in the treatment of psychiatric disorders is not addressed in National or Regional Medicare coverage determinations or policies.

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.

- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
02/19/15, 02/18/16, 02/16/17, 02/15/18, 01/17/19, 01/16/20, 01/21/21, 01/19/23, 01/18/24, 01/23/25, 01/22/26	
Date	**Summary of Changes**
04/13/26	• Policy edit, added clarification for nasal ketamine (esketamine [Spravato]). Policy intent unchanged.
01/22/26	• Annual review, merged codes (0820T-0822T) for monitoring and intervention from the New/Emerging Technology & Services policy and added an investigational statement. Minor edits without policy intent change.
01/23/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
02/19/15	• Original effective date