MEDICAL POLICY

Medical Policy Title	**Ketamine for the Treatment of Psychiatric Disorders**
Policy Number	**3.01.13**
Current Effective Date	**January 23, 2025**
Next Review Date	**January 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Ketamine (administered via oral, parenteral, sublingual, or intranasal methods) for the treatment of any psychiatric disorder including, but not limited to, treatment-resistant depression (TRD), is 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

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)

Not applicable.

DESCRIPTION

Ketamine hydrochloride injection is being investigated for its benefit-risk profile and safe-use conditions in the treatment of psychiatric disorders. The U.S. Food and Drug Administration (FDA) has not determined the safety or efficacy of ketamine for this indication and use for the treatment of a psychiatric disorder is an off-label use (FDA, 2023).

Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine. It is an antagonist of the N-methyl-d-aspartate (NMDA) receptor and is a dissociative anesthetic. It is usually administered parentally (intravenous, subcutaneous, or intramuscular), but can be administered orally (liquid or pill), sublingually, or intra-nasally (spray or powder). Respiratory depression may occur with overdosage or a rapid rate of ketamine administration. Psychological manifestations vary in severity from pleasant, dream-like states to hallucinations and delirium; further, these manifestations can be accompanied by confusion, excitement, aggression, or irrational behavior. The mechanism of action through which ketamine exerts its antidepressant effects is not fully understood.

It has the potential to cause marked acute changes in cognitive function and psychological well-being, both through the dense population of NMDA receptors located in the cerebral cortex and hippocampus and through its effects on the transmission of modulatory, ascending monoamines, such as dopamine and serotonin, in the striatum and cortex.

Major depressive disorder (MDD) is characterized by discrete episodes of at least 2 weeks' duration (although most episodes last considerably longer) involving clear-cut changes in affect, cognition, and neurovegetative functions and interepisode remissions (APA, 2022). The efficacy of current pharmacological agents for depression is disappointing. In addition to the low response rate, the long delay of traditional antidepressants in the onset of therapeutic action (up to 12 weeks) increases the burden of illness, morbidity, and the risk of suicidal behavior.

SUPPORTIVE LITERATURE

Researchers have explored antidepressant options that provide more rapid improvements in depressive symptoms. Ketamine, a non-competitive, high-infinity antagonist of the N-methyl-D-aspartate (NMDA)-type glutamate receptor is approved for the induction and maintenance of anesthesia and is being investigated for the treatment of psychiatric conditions such as treatment-resistant depression (TRD), bipolar depression, post-traumatic stress disorder, and obsessive-compulsive disorder.

There are several known potential risks associated with repeat ketamine administration, including physiological and psychological effects, substance abuse potential, urinary cystitis, and hepatotoxicity.

Treatment-Resistant Depression

In a trial comparing ketamine infusion to ECT, Ekstrand et al (2022) randomized patients to 3 times weekly ketamine (0.5 mg/kg) or ECT in an open label, noninferiority trial. A total of 186 patients received treatment with a maximum of 12 treatment sessions. More patients achieved remission (MADRS ≤ 10) with ECT than ketamine (63% vs. 46%). A median of 6 treatment sessions were required for remission. The authors noted that despite being inferior to ECT, ketamine is a potential treatment option for depression. Relapse rates during the 12-month follow-up were similar between treatments (70% with ketamine vs. 64% with ECT). Serious AEs were more common with ECT, but treatment-emergent AEs leading to dropout were more common with ketamine.

Anand et al (2023) reported 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 (lack of response to ≥2 adequate trials of antidepressant therapy and MADRS score >20). Suicide had previously been attempted in 36.5% of ketamine recipients and 41.4% of ECT recipients. In the primary analysis, 55.4% of participants assigned to ketamine and 41.2% of participants assigned to ECT experienced a response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks ($p<.001$ for noninferiority). Among participants who achieved an initial response, relapse occurred in 19% of ketamine and 35.4% of ECT recipients at 1-month follow-up and 34.5% of ketamine and 56.3% of ECT recipients at 6-month follow-up. Patient-reported memory function scores were higher in the ketamine group than the ECT group, and fewer patients in the

ketamine group reported cognitive symptoms. Patients in both groups experienced similar improvements in quality-of-life scores. Moderate or severe adverse events were reported in 25.1% of ketamine recipients and 32.4% of ECT recipients; individual events occurred at similar rates with the exception of muscle pain or weakness, which was reported in 0.5% of ketamine recipients and 5.3% of ECT recipients (p=.01).

Petrucci et al. (2024) conducted an updated systematic review and non-inferiority meta-analysis to investigate the comparative effectiveness of ketamine versus electroconvulsive therapy (ECT) for the treatment of adults diagnosed with major depressive disorder who were currently experiencing major depressive episodes. A total of six RCTs (n=655 patients), with 348 patients (53.1%) randomized to receive ketamine and 307 patients (46.9%) to undergo ECT. The response rate was not significantly different between the groups (p = 0.198). Among patients without psychotic features, ketamine and ECT had similar results. In hospitalized patients, ketamine was inferior to ECT. Remission rates were not significantly different in the overall population, or among patients with psychosis. For hospitalized inpatients, ECT was superior to ketamine. For depression scoring, ECT was superior to ketamine in the overall population and inpatients, with moderate effect size. Follow-up assessment showed no significant different in terms of relapse rates at 1 month or 6 months. The comparative efficacy of ketamine and ECT in patients with psychotic depression could not be assessed in this meta-analysis, because only one study reported stratified results for this subgroup. This study has several limitations including slight differences in the inclusion and exclusion criteria among studies, the majority of the eligible studies had some concerns of bias, and the lack long-term follow-up. The authors concluded that among patients with a major depressive episode, ketamine did not meet the prespecified criteria for non-inferiority compared with ECT and may be inferior among inpatients. Further RCTs are needed to clarify the relative efficacy of ketamine in this patient population.

Post Traumatic Stress Disorder (PTSD)

Feder and colleagues (2021) performed a double-blind trial comparing IV ketamine with IV midazolam, each administered 3 times weekly over 2 weeks, in adult patients with PTSD. The primary outcome measure was change in PTSD symptom severity from baseline to 2 weeks. The mean duration of PTSD was 14.9 years. Thirteen (43.3%) patients were receiving concomitant psychotropic medications, and 17 (56.7%) were receiving concomitant psychotherapy. At week 2, the mean CAPS-5 total score was lower in the ketamine group compared to the midazolam group (difference, 11.88 points; p=.004). The most common adverse events that occurred more frequently with ketamine included nausea or vomiting (33% vs. 20%), headache (33% vs. 20%), and fatigue (20% vs. 7%). The authors noted the potential for unblinding in the ketamine group due to the higher rate of dissociative symptoms.

Obsessive Compulsive Disorder (OCD)

Banderia and colleagues (2022) conducted a systematic review to investigate the effects of ketamine in OCD. A total of nine (9) articles (n=55 patients) published through 2021 were included. Three were randomized controlled trials, three case reports, two open-label trials, and one a retrospective chart review. Reported data showed a potential for fast onset of action and good tolerability of ketamine for OCD, even though the principal studies used only single-session racemic ketamine treatments, administered intravenously, and the results have been erratic. None of the available

evidence demonstrated whether racemic ketamine, S-ketamine, or R-ketamine had the best efficacy in controlling OCD symptoms, and only sparse evidence suggests that a combination of ketamine and psychotherapy could benefit patients with OCD. Limitations include the heterogeneity between studies, sample size, range of study designs, different therapeutic schemes, and psychiatric comorbidity profiles differed from study to study. The authors concluded that ketamine has emerged as an alternative agent; however, further randomized, double-blind, placebo-controlled trials, with larger samples 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 electroconvulsive therapy (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

Ketamine is not FDA approved for the treatment of psychiatric disorders, including use as an adjunct treatment (e.g., transcranial magnetic stimulation). The FDA published a warning in 2023 acknowledging awareness that compounded ketamine products have been marketed for off label use for a wide variety of psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder [PTSD], and obsessive-compulsive disorder [OCD]); however, the FDA has not determined that ketamine is safe and effective for such uses. The published warning indicates there is a lack of evidence to suggest that it is safer, is more effective, or works faster than medications that are FDA approved for the treatment of certain psychiatric disorders.

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

HCPCS Codes

Code	Description
J3490	Unclassified Drug

ICD10 Codes

Code	Description
	Investigational for all diagnosis codes

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SEARCH TERMS

Not applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based upon our review, 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	
02/18/16, 02/16/17, 02/15/18, 01/17/19, 01/16/20, 01/21/21, 01/19/23, 01/18/24, 01/23/25	
Date	**Summary of Changes**
01/23/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
02/19/15	• Original effective date