MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Ketamine for the Treatment of Psychiatric Disorders**
Policy Number	**3.01.13**
Category	**Technology Assessment**
Original Effective Date	**02/19/15**
Committee Approval Date	**02/18/16, 02/16/17, 02/15/18, 01/17/19, 01/16/20, 01/21/21, 01/19/23, 01/18/24**
Current Effective Date	**01/18/24**
Archived Date	**N/A**
Archive Review Date	**N/A**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

Based upon our criteria and assessment of the peer-reviewed literature, the use of 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), has not been medically proven to be effective and, therefore, is considered **investigational**.

This policy does not address Spravato (esketamine) nasal spray (s-enantiomer of ketamine). Refer to Pharmacy Management Drug Policy #63 Clinical Review Prior Authorization (CRPA)Medical Drug Policy for prior authorization criteria.

Refer to Corporate Medical Policy #7.03.03 Ketamine Infusion Therapy for the Treatment of Chronic Pain Syndromes

Refer to Corporate Medical Policy # 1.01.03 Experimental and Investigational Services

DESCRIPTION

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. Researchers have explored antidepressant options that sidestep the lag period for improvements in symptoms. There has been a growing investigation into the pathophysiology of mood disorders and more extensive research into other neurotransmitter signaling cascades such as the glutamatergic systems, which may offer a realistic, rapid-acting target for drug development in mood disorders. More recently, ketamine, a non-competitive, high-infinity antagonist of the N-methyl-D-aspartate (NMDA)-

type glutamate receptor used for the induction and maintenance of anesthesia, has been investigated for treatment-resistant depression (TRD). It is also being investigated in the treatment of other psychiatric conditions, including bipolar depression, post-traumatic stress disorder, obsessive-compulsive disorder, and autism spectrum disorders.

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.

RATIONALE

Ketamine hydrochloride (referred to as “ketamine” interchangeably) is a Schedule III controlled substance only approved by the U.S. Food and Drug Administration (FDA) as an intravenous or intramuscular injection solution for induction and maintenance of general anesthesia (FDA, 2023).

Ketamine is not FDA approved for the treatment of psychiatric disorders. 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.

The majority of peer-reviewed literature investigates the use of ketamine in the treatment of depression. While preliminary studies demonstrate promising short-term outcomes in patients suffering from TRD, there is insufficient long-term data to support its integration into the clinical treatment armamentarium at this time. Not only do investigators need to decipher the neurobiological mechanisms underlying the putative antidepressant actions of ketamine, more studies demonstrating its safety and efficacy are necessary on critical issues such as dose optimization, delivery drug routes and methods to prevent relapse following the resolution of depressive symptoms. There are several known potential risks associated with repeat ketamine administration, including physiological and psychological effects, substance abuse potential, urinary cystitis, and hepatotoxicity.

The first study to examine the anti-depressant effects of ketamine was a repeated measures design of nine patients (Berman et al., 2000). Only seven patients completed the study, and, of those seven, four experienced positive benefits of a diluted ketamine infusion. This was a short-term, “proof of concept” study that was designed just to test whether ketamine had the anti-depressant effects that were reported in other studies, but not carefully analyzed. This study demonstrated fairly strongly that ketamine did have such effects. Additional studies since then have demonstrated the positive short-term effects of ketamine in TRD and other related affective disorders.

Numerous concerns about most of the research trials performed to date have been noted. It is difficult to perform a truly blinded intervention with ketamine due to its psychological effects. Blier et al. (2012) point out that using a saline injection as a placebo sham treatment is not really adequate, as patients detect ketamine’s “mild psychotomimetic effects.” They also point out holes in the research, namely, “the level of physiologic monitoring that should be implemented, its potential neurotoxicity, and its dependence potential.” Ketamine can produce dependence on the drug, and there are studies that have looked at ketamine-dependent individuals. These studies have demonstrated that such dependence results in abnormalities of white matter in bilateral frontal and left temporoparietal regions of the brain (Liao et al. 2010, 2011). Further investigations into the consequences of long-term ketamine use are necessary.

Recent meta-analyses (Zheng et al., 2019 and Ainsworth et al., 2020) have found no evidence that ketamine anesthesia enhances the total antidepressant effect of electroconvulsive therapy (ECT).

Feder et al (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.

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%; OR, 0.52; 95% CI, 0.29 to 0.92). 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.

The intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this therapy. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine for psychiatric disorders. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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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*Key Article

KEY WORDS

Ketamine, N-methyl-D-aspartate antagonist, Treatment resistant depression.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

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.