MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**KETAMINE FOR THE TREATMENT OF PSYCHIATRIC DISORDERS**
Policy Number	**3.01.13**
Category	**Technology Assessment**
Effective Date	**02/19/15**
Revised Date	**02/18/16, 02/16/17, 02/15/18, 01/17/19**
Product Disclaimer	• *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 product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare 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.*

POLICY STATEMENT

Based upon our review and assessment of the peer-reviewed literature, the use of ketamine (administered via oral, parenteral, sublingual or intranasal methods) for the treatment of psychiatric disorders, including but not limited to treatment resistant depression, has not been medically proven effective and is considered **investigational**.

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

Refer to Corporate Medical Policy # 11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

Major depressive disorder (MDD) is a severe, recurrent and disabling mental illness that is highly prevalent worldwide and often associated with a negative impact on the quality of life and productivity. 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 that may offer a realistic, rapid-acting target for drug development in mood disorders. More recently, ketamine, a noncompetitive, high-infinity antagonist of the 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 that include bipolar depression, post-traumatic stress disorder, obsessive compulsive disorder, and autism spectrum disorders.

Ketamine is manufactured in liquid form or as a crystallized powder for reconstitution into a liquid. It is usually administered parentally (intravenous, subcutaneous or intramuscular) but can be administered orally (liquid or pill form), sublingually, or intra-nasally (spray or powder). Ketamine has been safely used for the induction and maintenance of general anesthesia and procedural sedation for many years. The mechanism of action through which ketamine exerts its antidepressant effects is not fully understood. It has the potential to cause marked changes acutely in cognitive function and psychological wellbeing, both through the dense population of NMDA receptors located in the cerebral cortex and hippocampus and via its effects on the transmission of modulatory, ascending monoamines such as dopamine and serotonin in the striatum and cortex.

RATIONALE

Ketamine hydrochloride injection is FDA-indicated for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide. Ketamine for the treatment of psychiatric disorders is an off-label use.

The majority of literature investigates the use of ketamine in depression. While preliminary studies demonstrate promising short-term outcomes in patients suffering from treatment-resistant depression, 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 that include 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 9 patients (Berman et al, 2000). Only 7 patients completed the study, and of those 7, four experienced positive benefits of a diluted ketamine infusion. This was a short-term, "proof of concept" study that was designed to just test whether ketamine had the anti-depressant effects reported in other studies, but not carefully analyzed. This study demonstrated pretty 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. For example, Murrough and colleagues (2013) conducted a clinical study in patients with TRD. Subjects were randomized in a 2:1 ratio to receive either 0.5 mg/kg ketamine or 0.045 mg/kg midazolam. Treatments were infused over 40 minutes. Of 73 patients, 47 received ketamine and 25 received midazolam. Reduction in MADRS at 24 hours post-infusion was the primary outcome. Baseline MADRS scores were 32.6±6.1 and 31.1±5.6 for ketamine and midazolam groups, respectively. The ketamine group demonstrated lower MADRS scores than the midazolam group (7.95 mean reduction). Mean MADRS scores 24 hours post infusion were 14.77 and 22.72 for ketamine and midazolam groups, respectively. Response, defined as ≥50% decrease in MADRS scores, was a secondary outcome. In the ketamine group, 64% met response and 28% met response in the midazolam group ($p \leq 0.001$). The most common side effects associated with ketamine were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. Dissociative symptoms occurred in 17% of ketamine subjects but resolved by two hours post-infusion. No severe psychotic symptoms were reported.

Numerous concerns about most of the research trials done 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 isn't really adequate, as patients detect ketamine's "mild psychotomimetic effects." They also point out holes in the research: "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 actually looked at ketamine-dependent people. 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.

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)*

CPT Codes

Code	Description

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

REFERENCES

*Aan het Rot M, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 2010 Jan 15;67(2):139-45.

*Aan het Rot M, et al. Ketamine for depression: where do we go from here? Biol Psychiatry 2012 Oct 1;72(7):537-47.

Andrade C. Intranasal drug delivery in neuropsychiatry: focus on intranasal ketamine for refractory depression. J Clin Psychiatry 2015 May;76(5):628-31.

Ballard ED, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. J Psychiatr Res 2014 Nov;58:161-6.

Ballard ED, et al. Characterizing the course of suicidal ideation response to ketamine. J Affect Disord 2018 Dec 1;241:86-93.

Bartoli F, et al. Ketamine as a rapid-acting agent for suicidal ideation: A meta-analysis. Neurosci Beiobehav Rev 2017 June;77:232-236.

*Berman RM, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000 Feb 15;47(4):351-4.

*Blier P, et al. On the safety and benefits of repeated intravenous injections of ketamine for depression. Biol Psychiatry 2012 Aug 15;72(4):e11-12.

*Bloch MH, et al. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry 2012 Dec 1;72(11):964-70.

Bobo WV, et al. Ketamine for treatment-resistant unipolar and bipolar major depression: critical review and implications for clinical practice. Depress Anxiety 2016 Aug;33(8):698-710.

Caddy C, et al. Katamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev 2015 Sept 23;(9):CD11612.

*Covvey JR, et al. Intravenous ketamine for treatment-resistant major depressive disorder. Ann Pharmacother 2012 Jan;46(1):117-23.

Diamond PR, et al. Ketamine infusion for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol 2014 Jun;28(6):536-44.

*Diazgranados N, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010 Aug;67(8):793-802.

*Diazgranados N, et al. Rapid resolution of suicidal ideation after a single infusion of an NMDA antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010 Dec;71(2):1605-1611.

Fava M, et al. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment resistant depression (TRD). Mol Psychiatry 2018 Oct 3 [Epub ahead of print].

Feder A, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. JAMA Psychiatry 2014 Jun;71(6):681-8.

Feifel D, et al. Low-dose ketamine for treatment resistant depression in an academic clinical practice setting. J Affect Disord 2017 Oct 15;221:283-288.

Grunebaum MF, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry 2018 Apr 1;175(4):327-335.

Haile CN, et al. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. Int J Neuropsychopharmacol 2014 Feb;17(2):331-6.

Hu YD, et al. Single IV ketamine augmentation of newly initiated escitalopram for major depression: results from a randomized, placebo-controlled 4-week study. Psychol Med 2016 Feb;46(3):623-35.

*Ibrahim L, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 2012 May;37(6):1526-33.

*Ibrahim L, et al. Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. Prog Neuropsychopharmacol Biol Psychiatry 2011 Jun 1;35(4):1155-9.

Ionescu DF, et al. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. J Affect Disord 2019 Jan 15;243:516-524.

Irwin SA, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med 2013 Aug;16(8):958-65.

*Irwain SA, et al. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. J Palliat Med 2010;13(7):903-8.

Jones JL, et al. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. Front Psychiatry 2018 Jul 24;9:277.

Katalinic N, et al. Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. Aust N Z J Psychiatry 2013 Aug;47(8):710-27.

Kraus C, et al. Administration of ketamine for unipolar and bipolar depression. Int J Psychiatry Clin Pract 2017 March;21(1):2-12.

Lapidus KA, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 2014 Dec 15;76(12):970-976.

Lara DR, et al. Antidepressant, mood stabilizing and precognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. Int J Neuropsychopharmacol 2013 Oct;16(9):2111-7.

*Larkin GL, et al. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol 2011 Sep;14(8):1127-31.

*Liao Y, et al. Reduced dorsal prefrontal gray matter after chronic ketamine use. Biol Psychiatry 2011 Jan 1;69(1):42-8.

*Liao Y, et al. Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. Brain 2010 Jul;133(Pt 7):2115-22.

*Mathew SJ, et al. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs 2012 Mar 1; 26(3):189-204.

McCloud TL, et al. Ketamine and other glutamate receptors for depression in bipolar disorder in adults. Cochrane Database Syst Rev 2015 Sept 29;(9):CD011611.

McGirr A, et al. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med 2015 Mar;45(4):693-704.

Murrough JW. Et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial. Psychol Med 2015 Dec;45(16):3571-80.

Murrough JW, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013 Oct 1;170(10):1134-42.

Naughton M, et al. A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J Affect Disord 2014 Mar;156:24-35.

Newport DJ, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry 2015 Oct;172(10):950-966.

Niciu MJ, et al. Clinical predictors of ketamine response in treatment-resistant major depression. J Clin Psychiatry 2014 May;75(5):e417-23.

Papolos DF, et al. Clinical experience using intranasal ketamine in the treatment of pediatric bipolar disorder/fear of harm phenotype. J Affect Disord 2013 May;147(1-3):431-6.

Parsaik AK, et al. Efficacy of ketamine in bipolar depression: Systematic review and meta-analysis. J Psychiatry Pract 2015 Nov;21(6):427-35.

*Price RB, et al. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009 Sept 1;66(5):522-6.

Rasmussen KG, et al. Serial infusions of low-dose ketamine for major depression. J Psychopharmacol 2013 May;27(5):444-50.

Reinstatler L, et al. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. Drug R D 2015 Mar;15(1):37-43.

Romeo B, et al. Meta-analysis of short- and long-term efficacy of ketamine in unipolar and bipolar depression. Psychiatry Res 2015 Dec 15;230(2):682-88.

Saligan LN, et al. An assessment of the anti-fatigue effects of ketamine from a double-blind, placebo-controlled, crossover study in bipolar disorder. J Affect Disord 2016 April;194:115-119.

Sanacora G, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 2017 April 1;74(4):399-405.

*Sanjay J, et al. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol 2010 Feb;13(1):71-82.

Schoevers RA, et al. Oral ketamine for the treatment of pain and treatment-resistant depression. Br J Psychiatry 2016 Feb;208(2):108-113.

Segmiller F, et al. Repeated S –ketamine infusions in therapy resistant depression: a case series. J Clin Pharmacol 2013 Sep;53(9):996-8.

Shiroma PR, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J Affect Disord 2014 Feb;155:123-9.

Singh JB, et al. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry 2016 Aug 1;173(8):816-826.

*Valentine GW, et al. The antidepressant effect of ketamine is not associated with changes in occipital amino acid neurotransmitter content as measured by [(1)H]-MRS. Psychiatry Res 2011 Feb 28;19(2):122-7.

Wan LB, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry 2015 Mar;76(3):247-52.

Xu Y, et al. Effects of low-dose and very low-dose ketamine among patients with major depression: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2016 April 20;19(4).

Zarate CA, et al. replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012 Jun 1;71(11):939-46.

*Zarate CA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006 Aug;63(8):856-64.

Zhang MW, et al. Is off-label repeat prescription of ketamine as a rapid antidepressant safe? Controversies, ethical concerns, and legal implications. BMC Med Ethics 2016 Jan 14;17:4.

Zhou Y, et al. Neurocognitive effects of six ketamine infusions and the association with antidepressant response in patients with unipolar and bipolar depression. J Psychopharmacol 2018 Oct;32(10):1118-1126.

Zunszain PA, et al. Ketamine: synaptogenesis, immunomodulation and glycogen synthase kinase-3 as underlying mechanisms of its antidepressant properties. Mol Psychiatry 2013 Dec;18(12):1236-41.

*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 CMS coverage determinations or policies.