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MEDICAL POLICY

Ketamine

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

DESCRIPTION

The intent of the Ketamine Policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Off-label use of ketamine injection for the treatment of psychiatric disorders, chronic pain, and migraine pain has been increasing in popularity. Studies available currently are of poor design, lacking adequate sample size and duration. Because of this, additional studies are needed to determine the safety and efficacy for the use of ketamine for these indications.

Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. The mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system (CNS).

FDA-Approved Indications

Ketamine hydrochloride injection is 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.

Compendial Indications

Complex Regional Pain Syndrome (CRPS)

All other indications are considered experimental/investigational and are not a covered benefit.

POLICY

I. Ketamine is considered medically necessary and may be covered for:
- Anesthesia for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- The induction of anesthesia prior to administration of other anesthesia agents
- As supplemental anesthesia for low-potency agents, such as nitrous oxide
- For the treatment of Complex Regional Pain Syndrome for up to 12 weeks

II. Ketamine is considered investigational and not covered when used for:
- Psychiatric disorders (including, but not limited to depression, bipolar disorder, obsessive compulsive disorder (OCD), autism spectrum disorder, and posttraumatic stress disorder)
- Chronic pain (including but not limited to mixed neuropathic pain, fibromyalgia, cancer pain, spinal pain)
- Chronic daily headache (includes chronic migraine, new daily persistent headache, hemicranias continua, and chronic tension-type headache)

CLINICAL RATIONALE

Ketamine hydrochloride injection is FDA-approved and 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. It is not FDA-approved for intranasal, oral, topical or subcutaneous use. Intravenous (IV) infusion ketamine has been investigated for the treatment of migraine and chronic daily headache, fibromyalgia, and chronic neuropathic pain. Chronic neuropathic pain disorders include phantom limb pain, post-herpetic neuralgia, complex regional pain syndrome, diabetic neuropathy, and pain related to stroke or spinal cord injuries. An IV infusion of ketamine has also been investigated for the treatment of depression, obsessive-compulsive disorder, and other psychiatric disorders. For these investigational indications, one or more courses of IV infusion would be administered over several hours or several days.

Safety

Ketamine is a schedule III controlled substance. There are several known potential risks associated with the administration of ketamine that includes but not limited to physiological and psychological effects, substance abuse potential, hepatoxicity, and urinary cystitis. Psychological manifestations vary in severity from pleasant dream-like states to hallucinations and delirium and can be accompanied by confusion, excitement, aggression, or irrational behavior. Respiratory depression may occur with high doses or with rapid administration of ketamine.

Efficacy

Psychiatric disorders

In 2017, the American Psychiatric Association (APA) published a consensus statement on the use of ketamine in the treatment of mood disorders in response to the increased use of ketamine as an off-label treatment for mood and other psychiatric disorders. The review and consensus statement provided a general overview of the data, highlighted important limitations in the available data, and made it clear that the consensus statement was not intended to serve as a standard, guideline, clinical policy, or absolute requirement but instead it identified the current state of the field and the factors that need considered in determining the appropriateness of ketamine therapy. The statement urged caution and pointed out areas for further study, noting a lack of data on long-term safety and efficacy and evidence largely made up of smaller studies.

For individuals who have psychiatric disorders (e.g., depression, obsessive-compulsive disorder) who receive a course of IV ketamine, the evidence is limited. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Several trials on the IV infusion of ketamine for the treatment of suicidal ideation in patients with depression are ongoing. The evidence is insufficient to determine the effects of ketamine on health outcomes for those with psychiatric disorders at this time.

Chronic Pain

The 2018 American Society of Regional Anesthesia and Pain Medicine (ASRA), The American Academy of Pain (AAP) and The American Society of Anesthesiologists (ASA) consensus guidelines on the use of intravenous ketamine infusions for different types of chronic pain and determined that evidence supporting the use of ketamine for chronic pain varies by condition and dose range with most studies being small, uncontrolled, and either unblinded or ineffectively blinded. The guideline concluded that for spinal cord injury pain, there is weak evidence supporting ketamine infusions for short-term improvements in pain (grade C recommendation, low level of certainty), for complex regional pain syndrome (CRPS), there is moderate evidence supporting ketamine infusions to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty), and for mixed neuropathic pain, phantom limb pain, post-herpatic neuralgia, fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty). They also concluded that excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.

Patil and Anitescu (2012) retrospectively analyzed data from 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a 5-year period at a U.S. academic medical center.28, Eighteen patients were diagnosed with CRPS, and 31 had other diagnoses including refractory headache (n=8) and severe back pain (n=7). All patients exhibited signs of central sensitization. Following pretreatment with midazolam and ondansetron, ketamine infusions were administered at the highest tolerated dose for a duration ranging from 30 minutes to 8 hours. The interval between infusions ranged from 12 to 680 days (median, 233.7 days). The immediate reduction in VAS score was 7.2 for patients with CRPS and 5.1 for non-CRPS pain. Query of available patients (59%) indicated that, for 38%, pain relief lasted more than 3 weeks. Adverse events, which included confusion and hallucination, were considered minimal.

Webster and Walker (2006) published retrospective analysis describing outpatient ketamine treatment in 13 patients with severe neuropathic pain; diagnoses included CRPS (n=8), migraine (n=1), neuropathy (n=3), and phantom limb (n=1).29, Low-dose ketamine (beginning at 0.12 mg/kg/h with slow upward titration) was delivered by a programmable pump. With an average infusion duration of 16 days, pain severity decreased by 38% (VAS score range, 7.7-4.8), with an 85% response rate. About half of the patients reported a perceived benefit 1 month after treatment. Adverse events included fatigue, dizziness,

Amr (2010) published results from a double-blind, randomized, placebo-controlled study of 40 patients with neuropathic pain secondary to spinal cord injury that was conducted in Egypt. All patients received gabapentin (300 mg) 3 times daily. The experimental group also received ketamine infusion (80 mg) over a 5-hour period daily for 7 days. The control group received an infusion of isotonic saline over the same period. VAS scores for pain were similar in both groups at baseline (VAS of 84 of 100). During the week of infusion, VAS scores decreased more in the ketamine-infused group than in the gabapentin-only group (VAS score of 14 in the ketamine group vs 43 in the control group at day 7). In the control group, VAS pain scores remained about the same during the 4-week follow-up. Pain scores in the ketamine-infused group

increased from 14 to 22 at 1-week follow-up and remained at that level for 2 weeks after infusion. By the third week after the ketamine infusion, VAS scores had increased to 43 and were the same as the placebo-control group. Three patients were reported to have had short-lasting delusions with ketamine infusion.

Kvarnstrom et al (2004) assessed the effect of subanesthetic levels of IV ketamine or lidocaine on pain after spinal cord injury.31, This randomized, double-blind, placebo-controlled crossover trial found a 38% reduction in pain during ketamine infusion, with 5 of 10 subjects responding to treatment, compared with 1 of 10 in the lidocaine infusion group and 0 of 10 in the placebo group. Adverse events were common with both active treatments; ketamine produced 39 adverse events in 9 of 10 subjects. They included somnolence, dizziness, out-of-body sensation, changes in hearing and vision, paresthesia, and other "unpleasant experiences."

Blonk et al (2010) conducted a review of the available clinical data on the use of oral ketamine in chronic pain management. A literature search was performed in MEDLINE, EMBASE, and the Cochrane Library, resulting in 22 relevant articles. Searches included the keywords: 'ketamine', 'administration, oral'. 'chronic pain', 'pain', 'neuropathic pain', 'cancer pain'. The articles were reviewed for information about the number of included patients receiving oral ketamine, study design, pain type, dosage regimen, efficacy and adverse effects. Because most retrieved articles were of a descriptive nature (e.g., case reports and case series) a quantitative analysis was not possible. There was no consistent dose-response relation. A high number of withdrawals due to adverse effects were seen. The most frequently observed adverse effects were sedation, somnolence, dizziness, sensory illusions, hallucinations, nightmares, dissociative feeling and blurred vision. The duration of treatment was often limited due to these adverse effects. They concluded that the lack of evidence regarding efficacy, and the poor safety profile, do not support routine use of oral ketamine in chronic pain management.

Schoevers et al (2016) reviewed the literature about the dosing regimen, duration, effects and side-effects of oral, intravenous, intranasal, and subcutaneous routes of administration of ketamine for treatment-resistant depression and pain. Searches in PubMed with the terms 'oral ketamine', 'depression', 'chronic pain', 'neuropathic pain'. 'intravenous ketamine', 'intranasal ketamine' and 'subcutaneous ketamine' yielded 88 articles. These articles were reviewed for information about dosing regimen, number of individuals who received ketamine, number of ketamine days per study, results and side-effects, as well as study quality. Overall, the methodological strength of studies investigating the anti-depressant effects of ketamine was considered low, regardless of route of administration. The doses for depression were in the lower range compared with studies that investigated analgesic use. Studies on pain suggested that oral ketamine may be acceptable for treatment-resistant depression in terms of tolerability and side-effects but not effectiveness. The researchers concluded that oral ketamine, given for longer time periods in the described doses, appeared to be well-tolerated, but few studies had systematically examined the longer-term negative consequences. The authors concluded more rigorous randomized controlled trials were needed that studied the short- and longer-term depression outcomes as well as side-effects.

Lauritsen et al (2016) evaluated the use of intravenous ketamine in patients with refractory migraine treated in the hospital setting. The authors completed a retrospective chart review, which identified six patients with refractory migraine admitted from 2010 through 2014 for treatment with intravenous ketamine. A standard protocol was used to administer ketamine starting with a dose of 0.1 mg/kg/hr and increased by 0.1 mg/kg/hr every 3 to 4 h as tolerated until a target pain score of 3/10 was achieved and maintained for 8 hours or more. Visual Analogue Scale (VAS) scores at time of hospital admission were obtained as well as average baseline VAS scores prior to ketamine infusion. The age range of study patients was 29-54 years with a median age of 36.5. Additionally, 83% were women. Pre-treatment pain scores ranged from 9 to 10. All

patients achieved a target pain level of 3 or less for 8 h; the average ketamine infusion rate at target was 0.34 mg/kg/hour (range 0.12-0.42 mg/kg/hr). One patient reported a transient out-of-body hallucination following an increase in infusion rate, which resolved after decreasing the rate. There were no other significant side effects. The authors conclude that IV ketamine was safely administered in the hospital setting to patients with refractory chronic migraine. Treatment was associated with short term improvement in pain severity in 6 of 6 patients with refractory chronic migraine. Prospective placebo-controlled trials are needed to assess short term and long-term efficacy of IV ketamine in refractory chronic migraine.

Pomeroy et al investigate the use of intravenous, subanesthetic ketamine for chronic migraine (CM) or new daily persistent headache (NDPH) in a retrospective review. Upon admission, the mean headache pain rating, using a 0-10 pain scale was an average of 7.1 and decreased to 3.8 at discharge ($P < .0001$). Seventy-two percent (55/77) of patients experienced at least a 2-point improvement in headache pain at discharge. There were some acute responders that maintained this improvement in headache pain at their follow-up office visit but sustained response did not achieve statistical significance (15/77, 27.3%). The mean duration of infusion was 4.8 days. Overall, patients tolerated ketamine. The authors conclude that subanesthetic ketamine infusions may be beneficial in individuals with CM or NDPH who have failed other treatments. Controlled trials are needed to confirm this.

For individuals who have chronic pain syndromes (e.g., fibromyalgia, headache, neuropathic pain, spinal cord injury) who receive a course of IV ketamine, the evidence includes several randomized controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Evidence, primarily from outside of the United States, has suggested that courses of IV ketamine may provide-at least temporary-relief to some chronic pain patients. However, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the overall health benefit of this procedure. Additional clinical trials are needed to evaluate the long-term safety of repeat courses of IV anesthetics. The evidence is insufficient to determine the effects of ketamine on health outcomes in these conditions at this time.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J3490 Unclassified drugs

REFERENCES

- 5.01.16 BCBS Association Medical Policy Reference Manual. Intravenous Anesthetics for the Treatment of Chronic Pain. Re-issue date 11/08/2018, issue date 04/16/2004.
- Ketalar [prescribing information]. Chestnut Ridge, NJ; Par Pharmaceutical; August 2018.
- Sanacora G, Frye MA, McDonald W, et al. American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments. A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry. 2017;74:399–405.
- Cohen S, Bhatia A, Buvanendran A, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Regional Anesthesia and Pain Medicine. 2018;43:521-546.

- Kvarnstrom A, Karlsten R, Quiding H, et al. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand. Aug 2003;47(7):868-877. PMID 12859309
- Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. Anesth Analg. Dec 2003;97(6):1730-1739. PMID 14633551
- Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med. Aug 2017;35(8):1095-1100. PMID 28283340
- Wertli MM, Kessels AG, Perez RS, et al. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. Pain Med. Sep 2014;15(9):1575-1589. PMID 25234478
- Schwartzman RJ, Alexander GM, Grothusen JR, et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. Dec 15 2009;147(1-3):107-115. PMID 19783371
- Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. Oct 2009;145(3):304-311. PMID 19604642
- O'Connell NE, Wand BM, McAuley J, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013;4:CD009416. PMID 23633371
- Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain. Oct 2011;15(9):942-949. PMID 21482474
- Eichenberger U, Neff F, Sveticic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. Anesth Analg. Apr 2008;106(4):1265-1273, table of contents. PMID 18349204
- Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. Pain Med. Feb 2012;13(2):263-269. PMID 21939497
- Webster LR, Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. Am J Ther. Jul-Aug 2006;13(4):300-305. PMID 16858163
- Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician. May-Jun 2010;13(3):245-249. PMID 20495588
- Kvarnstrom A, Karlsten R, Quiding H, et al. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand. Apr 2004;48(4):498-506. PMID 15025615
- American Society of Anesthesiologists Task Force on Chronic Pain Management, American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology. Apr 2010;112(4):810-833. PMID 20124882
- Lauritsen C, Mazuera S, Lipton RB, Ashina S. Intravenous ketamine for subacute treatment of refractory chronic migraine: a case series. J Headache Pain. 2016;Dec;17(1):106.
- Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine infusions for treatment refractory headache. Headache. 2017;Feb;57(2):276-282.
- Bartoli F, et al. Ketamine as a rapid-acting agent for suicidal ideation: A meta-analysis. Neurosci Beiobehav Rev 2017 June;77:232-236.

- Kraus C, et al. Administration of ketamine for unipolar and bipolar depression. Int J Psychiatry Clin Pract 2017 March;21(1):2-12.
- 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.
- 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.
- 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.
- 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).
- Wan LB, et al. Ketamine safety and tolerability in clinical trials for treatment-resistant depression. J Clin Psychiatry 2015 Mar;76(3):247-52.
- Ballard ED, et al. Characterizing the course of suicidal ideation response to ketamine. J Affect Disord 2018 Dec 1;241:86-93.
- 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].
- 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.
- Jones JL, et al. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. Front Psychiatry 2018 Jul 24;9:277.
- Blonk, Maren I., et al. Use of oral ketamine in chronic pain management: a review. European journal of pain 14.5 (2010): 466-472.
- Schoevers, Robert A., et al. Oral ketamine for the treatment of pain and treatment-resistant depression. The British Journal of Psychiatry 208.2 (2016): 108-113.

POLICY HISTORY

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