MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**KETAMINE INFUSION THERAPY FOR THE TREATMENT OF CHRONIC PAIN SYNDROMES**
Policy Number	**7.03.03**
Category	**Technology Assessment**
Effective Date	**05/28/15**
Revised Date	**05/25/16, 05/18/17, 05/17/18, 04/18/19**
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 criteria and assessment of peer-reviewed literature, intravenous infusion (IV) of ketamine for the treatment of chronic pain, including, but not limited to chronic neuropathic pain and fibromyalgia, has not been medically proven to be effective and therefore is considered **investigational**.

Refer to Corporate Medical Policy # 3.01.13 regarding Ketamine for the Treatment of Psychiatric Disorders.

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

This policy does not address Spravato (esketamine). Please see the Clinical Review Prior Authorization (CRPA) Medical Drug Policy for prior authorization criteria.

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

Chronic neuropathic pain disorders include phantom limb pain, postherpetic neuralgia, complex regional pain syndromes, diabetic neuropathy, and pain related to stroke or spinal cord injuries. Chronic neuropathic pain, often disproportionate to the extent of the primary triggering injury, may consist of thermal or mechanical allodynia, dysesthesia, and/or hyperalgesia and presents a great challenge to patients and their healthcare providers. It is proposed that chronic neuropathic pain results from peripheral afferent sensitization, neurogenic inflammation, and sympathetic afferent coupling, along with sensitization and functional reorganization of the somatosensory, motor, and autonomic circuits in the central nervous system (CNS). Therefore, treatments focus on reducing activity and desensitizing pain pathways, thought to be mediated through N-methyl-d-aspartate (NMDA) receptors in the peripheral and CNS.

Ketamine is an antagonist of the NMDA receptor and a dissociative anesthetic. IV infusion therapy utilizing ketamine has been proposed for the treatment of chronic neuropathic pain that is refractory to standard therapies. This treatment usually involves low dose, multi-day ketamine infusion therapy in either an inpatient or outpatient setting as part of a pain management program. It requires the direct supervision of a physician experienced in administering general anesthetics due to the intensity of treatment protocols and severity of side effects.

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. IV ketamine for the treatment of chronic pain is an off-label use.

A 2006 retrospective analysis by Webster, et al. described outpatient ketamine treatment in 13 patients with severe neuropathic pain; diagnoses included chronic regional pain syndrome (CRPS) (n=8), migraine (n=1), neuropathy (n=3), and phantom limb (n=1). Low-dose ketamine (beginning at 0.12 mg/kg/h with slow upward titration) was delivered by a programmable pump through a peripherally inserted central catheter (PICC) line. With an average infusion duration of 16 days, pain severity decreased 38% (VAS of 7.7 to 4.8) with an 85% response rate. About half of the patients reported a perceived benefit one month after treatment. Adverse effects included fatigue, dizziness, confusion, and spinal pain. No patients reported hallucinations.

In 2008, Kiefer, et al. reported a multicenter (U.S. and Europe) prospective open-label Phase II study of anesthetic dosing of ketamine in 20 patients with refractory CRPS. Symptoms were either long-standing (range, 6-68 months), spreading, or rapidly progressive, and refractory to conventional nonmedical (physical therapy, psychological approaches), or pharmacologic (mono- or combined therapy) and interventional treatments (at least three) including selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, IV regional sympathetic blocks, spinal cord stimulation, surgical sympathectomy, or intrathecal drug delivery systems. Following consent, patients were intubated and mechanically ventilated (except for the first three patients). Ketamine infusion was titrated up to a dose of 7 mg/kg/h with infusion over five days, then tapered downward until consciousness was attained. Midazolam was co-administered to a level of deep sedation to attenuate agitation and other adverse effects. All patients received IV low-dose heparin, the proton pump inhibitor pantoprazole, and clonidine to control cardiovascular and psychomimetic side effects of ketamine. Intubated patients received enteral nutrition with insulin as needed to maintain normoglycemia. Standard intensive care monitoring along with blood gas analysis, blood chemistry, and screening for infectious complications was performed regularly. Outcomes were assessed at one week and one, three, and six months after treatment. Pain intensity decreased from a numerical rating scale of nine at baseline to 0.5 at one week and remained low (2.0) at six months. Three patients relapsed but with lower pain (3.8) than at baseline. Pain relief was 94%, 89%, and 79% at one, three, and six months, respectively. Upper- and lower-extremity movement improved from 3.2 at baseline to 0.4 at six months for arm movement and from 2.3 at baseline to 0.6 at six months for walking. At six months, there was a significant difference in the ability to perform activities of daily living; one patient rated total impairment, three severe impairment, six moderate impairment, and 10 patients no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by five, and as moderate by four patients. At six months, two patients remained unable to work, 4 had moderate impairment, and 14 patients reported no impairment. Psychotropic adverse effects resolved in the first week in the majority of patients, although five patients reported difficulties with sleeping and recurring nightmares for 1 month following treatment. Muscle weakness was reported in all patients for as long as four to six weeks following treatment. As indicated by the authors, a strong placebo response to this intensive intervention might be expected, and a large, multicenter randomized controlled trial (RCT) would be needed to definitively establish efficacy and safety.

Amr, et al. (2010) published results from a double-blind randomized placebo-controlled study of 40 patients with neuropathic pain secondary to spinal cord injury. All patients received gabapentin (300 mg) three times daily. The experimental group also received ketamine infusion (80 mg) over a five-hour period daily for seven days. The control group received infusion of isotonic saline over the same period. VAS scores for pain were similar in the two groups at baseline (VAS of 84 out of 100 for both groups). During the week of infusion, VAS scores decreased more in the ketamine-infused group than the gabapentin-only group (VAS score of 14 in the ketamine group vs 43 in the control group at day seven). In the control group, VAS pain scores remained about the same during the four-week follow-up. Pain scores in the ketamine-infused group increased from 14 to 22 at one-week follow-up and remained at that level for two 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.

The largest double-blind RCT of ketamine for CRPS was a European report by Sigtermans and colleagues in 2009. 60 patients were randomly assigned to ketamine (titrated up to 30 mg/h for a 70-kg patient) or saline infused over four days.

The mean ketamine infusion rate was 22 mg/h (normalized to a 70-kg patient) at the end of the treatment phase. Blood samples were collected to assess the plasma concentration of ketamine, and patients were monitored for side effects. Two patients terminated the ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, numerical pain scores were 7.2 (maximum, 10) for ketamine and 6.9 for the placebo group. The lowest pain scores (ketamine 2.7, placebo 5.5) were observed at the end of the first week (no patients were lost to follow-up for the primary outcome measure). Although pain scores remained statistically lower through week 11, the clinically significant difference of two points was maintained until week 4. None of the secondary (functional) outcome measures were improved by treatment. 60% of the patients in the placebo group correctly indicated treatment assignment (slightly better than chance); 93% of patients in the ketamine group correctly indicated treatment assignment due primarily to psychomimetic effects.

Collins and colleagues (2010) performed a meta-analysis evaluating the effects of (individual) NMDA receptor antagonists on neuropathic pain, and the response (sensitivity) of individual neuropathic pain disorders to NMDA receptor antagonist therapy. The outcome of measurements was the reduction of spontaneous pain. A total of 28 studies were included, meeting the inclusion criteria. Summary effect sizes were calculated for subgroups of studies evaluating ketamine IV in CRPS, oral memantine in post-herpetic neuralgia and, respectively, ketamine IV, and oral memantine in post-amputation pain. Treatment with ketamine significantly reduced pain in post-amputation pain ($p = 0.004$). No significant effect on pain reduction could be established for ketamine IV in CRPS ($p = 0.11$) oral memantine in post-herpetic neuralgia ($p = 0.92$) and for oral memantine in post-amputation pain ($p = 0.21$). The authors concluded that based on this systematic review, no conclusions can yet be made about the efficacy of NMDA receptor antagonists on neuropathic pain. They stated that additional RCTs in homogenous groups of pain patients are needed to explore the therapeutic potential of NMDA receptor antagonists in neuropathic pain.

In 2011, Noppers and colleagues reported a randomized, double-blind, active placebo-controlled trial that was conducted in Europe using a 30-minute infusion of S(+)-ketamine (n=12) or midazolam n=12). Baseline VAS pain scores were 5.4 in the ketamine group and 5.8 in the midazolam group. At 15 minutes after termination of infusion, significantly more patients in the ketamine group showed a reduction in VAS pain of greater than 50% compared to placebo (eight versus three). There was no significant difference between the groups at 180 minutes after infusion (six versus three), at the end of week one (two versus zero) or end of week eight (two versus two, all respectively). There was no difference between groups on the fibromyalgia impact questionnaire measured weekly over eight weeks. In this well-conducted study, a short infusion of ketamine (30 minutes) did not have a long-term analgesic effect on fibromyalgia pain.

A 2012 retrospective analysis from an academic medical center in the U.S. (Patil, et al.) identified 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a five-year period. 18 patients were diagnosed with CRPS, and 31 had other diagnoses including refractory headache (n=eight) and severe back pain (n=seven). 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 eight hours. The interval between infusions ranged from 12 to 680 days (median, 233.7 days). The immediate reduction in VAS 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 three weeks. Adverse events, which included confusion and hallucination, were considered minimal.

Azari and colleagues (2012) reviewed published literature for evidence of the safety and effectiveness of ketamine in the treatment of CRPS. Their search methodology yielded three randomized, placebo-controlled trials, seven observational studies and nine case studies/reports. In aggregate, the data available reveal ketamine as a promising treatment for CRPS. The optimum dose, route and timing of administration remain to be determined. The authors concluded that RCTs are needed to establish the safety and effectiveness of ketamine and to determine its long-term benefit in CRPS.

A 2013 Cochrane overview of interventions for CRPS found low-quality evidence that a course of IV ketamine may be effective for CRPS-related pain, although the effects were not sustained beyond four to 11 weeks post-treatment. This conclusion was reached on the basis of two RCTs.

In summary, recent evidence, primarily from outside of the United States, suggests that IV courses of ketamine may provide at least temporary relief to some chronic pain patients. However, there was insufficient evidence to advocate the

routine use of this treatment for patients with chronic pain. Of particular concern were the significant adverse effects of this *N*-methyl-D-aspartate (NMDA) receptor antagonist in the central and peripheral nervous system. Few data were available concerning appropriate dosing and long-term administration. The intense treatment protocols, severity of side effects, and limited durability raises 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.

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
No specific codes, however, J3490, unclassified drug, may be billed for ketamine	

ICD10 Codes

Code	Description
Investigational for all diagnosis codes	

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*Key Article

KEY WORDS

Chronic neuropathic pain, complex regional pain syndrome, CRPS, ketamine, intravenous infusions

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based upon our review, ketamine infusion therapy is not specifically addressed in National or regional CMS coverage determinations or policies.