MEDICAL POLICY

Excellus
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Medical Policy Title	**Ketamine Infusion Therapy for the Treatment of Chronic Pain Syndrome**
Policy Number	**7.03.03**
Current Effective Date	March 20,2025
Next Review Date	March 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)

Intravenous infusion (IV) of ketamine for the treatment of chronic pain, including, but not limited to, chronic neuropathic pain and fibromyalgia, is considered **investigational**.

RELATED POLICIES

Corporate Medical Policy

3.01.13 Ketamine for the Treatment of Psychiatric Disorders

11.01.03 Experimental or Investigational Services

Pharmacy Policy

This policy does not address Spravato (esketamine). Please refer to Pharmacy policy #63 Clinical Review Prior Authorization (CRPA).

POLICY GUIDELINE(S)

Not Applicable

DESCRIPTION

Ketamine is primarily known as an anesthetic agent used in a variety of medical settings. In lower doses it can be used to treat chronic pain (e.g., neuropathic pain, complex regional pain syndrome CRPS), certain types of headaches, fibromyalgia, and depression that are refractory to conventional treatments. Ketamine is typically administered intravenously (IV) with infusions lasting from 40 minutes to several hours. Infusion requires caution and close monitoring due to potential side effective such as disassociation experiences (feeling disconnected from yourself and the world around you), hallucinations, memory loss, panic attacks, nausea/vomiting, somnolence, possibly cardiac stimulation, increased blood pressure and in some cases the potential for abuse.

Ketamine is an N-methyl-D aspartate (NMDA) receptor antagonists that modulates glutamate activity which plays a critical role in pain perception and neuroplasticity. By inhibiting the NMDA receptor, ketamine can alleviate pain through both analgesic and anti-inflammatory effects. Ketamine infusions are sometimes used clinically in the off-label treatment of psychiatric disorders such as major depressive disorder and PTSD, though no standard operating procedure exists. There has been increased interest surrounding the use of ketamine IV infusions for CRPS and other types of chronic

pain. NMDA receptor antagonists like ketamine have been hypothesized to reverse central sensitization and maladaptive cortical neuroplastic changes in CRPS individuals. In clinical practice not all patients experience good pain relief with ketamine and its pain-relieving effects are usually temporary with serious side effects especially if ketamine is used frequently and repeatedly.

SUPPORTIVE LITERATURE

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 (1) month after treatment. Adverse effects included fatigue, dizziness, confusion, and spinal pain. No patients reported hallucinations.

In 2008, Kiefer et al. reported a multi-center (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 (ranging from six (6) to eight (8) months), spreading, or rapidly progressive and refractory to conventional non-medical (physical therapy, psychological approaches), 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, were performed regularly. Outcomes were assessed at one week and at one, three, and six months after treatment. Pain intensity decreased from a numerical rating scale of 9.0 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 rated severe impairment, six rated moderate impairment, and 10 rated no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by five, and moderate by four patients. At six months, two patients remained unable to work, four had moderate impairment, and 14 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 one 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, multi-center, 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 versus 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. In that study, 60 patients were randomly assigned to ketamine (titrated up to 30 mg/h for a 70-kg patient) or were 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 (out of a maximum of 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 four. None of the secondary (functional) outcome measures was improved by treatment. Sixty percent 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.

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 at the 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. Eighteen patients were diagnosed with CRPS; 31 had other diagnoses, including refractory headache (n=eight) and severe back pain (n=seven). All patients exhibited signs of central sensitization. Following pre-treatment 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 confirmed 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.

A study by Voute (2022) discusses the role ketamine in the management of chronic pain. A collaborative four round internet-based questionnaire was used to gather information. The review highlights the effectiveness of ketamine for various chronic pain conditions such as neuropathic pain, fibromyalgia, and complex regional pain syndrome. Various routes of administration (IV, intranasal, oral) and dosing protocols were examined. Twenty-eight experts completed all rounds of the survey with a total of 81.3% items reaching a consensual answer. Neuropathic pain represents the first indication to use ketamine, followed, with a good to moderate utility, by other situations (fibromyalgia, complex regional pain syndrome, central neuropathic pain, peripheral neuropathic pain, nociceptive pain, sensitization, opioid withdrawal, palliative care, depression). Experts agreed on the rare occurrence of adverse events. Concerning routes of administration, intravenous infusion with doses of 0.5-0.9 mg/kg/d for 4 days of treatment was preferred. Place of care was a hospital, as inpatient or outpatient, with a quarterly administration of ketamine.

Ketamine effectiveness was assessed at one (1) month after infusion, and experts encourage combination with non-pharmacological treatment and often noting that lower doses regimen might be effective for chronic pain management. Ketamine is generally considered safe, the study discussed potential side effects including cognitive impairments and dissociative experiences and emphasizes the importance of careful patient selection and monitoring. The authors presented data from clinical trials and patient outcomes, pointing out that ketamine can provide significant pain relief to patients who have not responded well to other treatments. The reviews suggest further research is needed to better understand the long-term effects of ketamine in chronic pain management and its potential integration into multidisciplinary pain clinics.

In summary, recent evidence suggests that IV courses of ketamine may provide at least temporary relief to some chronic pain patients. However, there is insufficient evidence to advocate the routine use of this treatment for patients with chronic pain. Of particular concern are the significant adverse

effects of this NMDA receptor antagonist on the central and peripheral nervous system. Few data are available concerning appropriate dosing and long-term administration. The intense treatment protocols, severity of side effects, and limited 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.

PROFESSIONAL GUIDELINE(S)

In 2018, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists issued a joint consensus guideline on the use of IV ketamine for treatment of chronic pain. The guideline found:

- Weak evidence supporting use of IV ketamine for short-term improvement in patients with spinal cord injury pain;
- Moderate evidence supporting use of IV ketamine for improvement in patients with chronic regional pain syndrome up to 12 weeks; and
- Weak or no evidence for immediate improvement with IV ketamine use for other pain conditions, including mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache and spinal pain (Cohen, 2018).

REGULATORY STATUS

Ketamine hydrochloride injection is United States Food and Drug Administration (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.

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)

Code	Description
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

REFERENCES

ACPA- Stanford Resource Guide. [Internet] The American Chronic Pain Association and Stanford Medicine 2024 [accessed 2025 Feb 10]. Available from: acpa_stanford_resource_guide_2024.pdf

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. 2010 May-Jun;13(3):245-9.

Azari P, et al. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. CNS Drugs. 2012 Mar 1;26(3):215-28**.**

Chitneni A, et al. Use of ketamine infusions for treatment of complex regional pain syndrome: a systematic review. Cureus. 2021 Oct 19;13(10):e18910.

Cohen SP, 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. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

Fassio, Angelo, et al. Pharmacological treatment in adult patients with CRPS-I: a systematic review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2022 Aug 30;61(9):3534-3546.

Kiefer RT, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med. 2008 Nov;9(8):1173-201

Lumanauw DD, et al. Subdissociative-dose ketamine is effective for treating acute exacerbations of chronic pain. Acad Emerg Med. 2019 Sep;26(9):1044-1051.

Masaracchia MM, et al. Subanesthetic ketamine infusions for the management of pediatric pain in non-critical care settings: An observational analysis. Acta Anaesthesiol Scand. 2019 Oct;63(9):1225-1230.

Noppers I, 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 2011;15(9):942-9.

O'Connell NE, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome. Cochrane Database Syst Rev. 2013 Apr 30;2013(4):CD009416.

Orhurhu V, et al. Ketamine infusions for chronic pain: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg. 2019 Jul;129(1):241-254.

Patil S and Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. Pain Med. 2012 Feb;13(2):263-9.

Pickering, et al. Magnesium for refractory neuropathic pain: a randomized, double-blind, crossover trial. Anesthesiology. 2020 Jul;133(1):154-164.

Sigtermans MJ, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009;145(3):304-11.

Schwenk ES, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018 Jul;43(5):456-466.

Voute M, et al. Ketamine in chronic pain: A Delphi survey. Eur J Pain. 2022 Apr;26(4):873-887.

Webster LR and Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. Am J Ther. 2006 Jul-Aug;13(4):300-5**.**

Xu J, et al. Intravenous ketamine infusion for complex regional pain syndrome: survey, consensus, and a reference protocol. Pain Med. 2019 Feb 1;20(2):323-334.

SEARCH TERMS

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

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based on our review, ketamine infusion therapy is not specifically 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	
05/25/16, 05/18/17, 05/17/18, 04/18/19, 03/19/20, 03/18/21, 03/24/22, 03/23/23, 03/23/23, 03/21/24, 03/20/25	
Date	**Summary of Changes**
03/20/25	• Annual review; policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
05/28/15	• Original effective date