

Corporate Medical Policy

Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

File Name: intravenous_anesthetics_for_the_treatment_of_chronic_pain
Origination: 8/2010
Last Review: 4/2024

Description of Procedure or Service

Courses of IV anesthetic agents may be given in the inpatient or outpatient setting as part of a pain management program, with the infusion of a subanesthetic dose preceded by a bolus infusion to achieve desired blood levels sooner. Treatment protocols for the initial cycle may include infusion of subanesthetic doses of 1 to 6 hours for up to 10 days.

Ketamine is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and a dissociative anesthetic. It is the sole anesthetic agent approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Respiratory depression may occur with overdosage or too rapid a rate of administration of ketamine; it should be used by or under the direction of physicians experienced in administering general anesthetics. Ketamine is a schedule III controlled substance. 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. The occurrence of adverse effects with IV anesthetics may be reduced by the careful titration of subanesthetic doses. However, the potential benefits of pain control must be carefully weighed against the potential for serious, harmful adverse effects.

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. Adverse effects for lidocaine are common, can be mild to moderate, and include general fatigue, somnolence, dizziness, headache, periorbital and extremity numbness and tingling, nausea, vomiting, tremors, and changes in blood pressure and pulse. Severe adverse effects may include arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given intravenously to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Intravenous (IV) administration of anesthetic has been reported for a variety of conditions, including chronic pain of neuropathy origin, chronic headache, fibromyalgia, depression, and obsessive compulsive disorders.

Chronic daily headaches are defined as a headache disorder that occurs more than 15 days a month for at least 3 months. Chronic daily headaches include chronic migraine, new daily persistent headache, hemicranias continua, and chronic tension-type headache.

Neuropathic pain is often disproportionate to the extent of the primary triggering injury and may consist of thermal or mechanical allodynia, dysesthesia, and/or hyperalgesia. Allodynia is pain that occurs from a stimulus that normally does not elicit a painful response (e.g., light touch, warmth). Dysesthesia is a constant or ongoing unpleasant or electrical sensation of pain. Hyperalgesia is an exaggerated response to normally painful stimuli. In the latter, symptoms may continue for a period of time that is longer (e.g., 6 months or more) than clinically expected after an illness or

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injury. 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. Sympathetic ganglion blocks with lidocaine have been used for a number of years to treat sympathetically maintained chronic pain conditions, such as complex regional pain syndrome (CRPS, previously known as reflex sympathetic dystrophy). Test infusion of an anesthetic has also been used in treatment planning to assess patient responsiveness to determine whether medications, such as oral mexiletine or oral ketamine, may be effective. A course of intravenous (IV) lidocaine or ketamine, usually at subanesthetic doses, has also been examined. This approach for treating chronic neuropathic pain differs from continuous subcutaneous or IV infusion of anesthetics for the management of chronic pain conditions, such as terminal cancer pain, which are not discussed in this policy.

Fibromyalgia is a chronic state of widespread pain and tenderness. Although fibromyalgia is generally considered to be a disorder of central pain processing or central sensitization, others have proposed that the nerve stimuli causing pain originates mainly in the muscle, causing both widespread pain and pain on movement. There are focal areas of hyperalgesia, or tender points, which tend to occur at muscle tendon junctions. Biochemical changes that have been associated with fibromyalgia include alterations in NMDA receptors, low levels of serotonin, suppression of dopamine-releasing neurons in the limbic system, dysfunction of the hypothalamic-pituitary-adrenal axis, and elevated substance P levels. Fibromyalgia is typically treated with neuropathic pain medications such as pregabalin, non-narcotic pain relievers, or low doses of antidepressants.

Use of IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications. Particularly challenging are patients with treatment-resistant depression with suicidal ideation. Several studies are ongoing to test the efficacy of IV ketamine in patients with suicidal ideation who present to the emergency department.

Regulatory Status

Intravenous (IV) lidocaine is approved by the U.S. Food and Drug Administration (FDA) for systemic use in the acute treatment of arrhythmias and locally as an anesthetic. IV lidocaine for the treatment of chronic pain is an off-label use.

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 or psychiatric disorders is an off-label use.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Intravenous anesthetics for the treatment of chronic pain and psychiatric disorders are considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders are covered

Not applicable.

When Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders are not covered

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of chronic pain, including, but not limited to chronic neuropathic pain, chronic daily headaches, fibromyalgia and psychiatric disorders, including but not limited to depression and obsessive-compulsive disorder is considered investigational.

Policy Guidelines

For individuals who have chronic pain syndromes (CRPS, fibromyalgia, headache, neuropathic pain, spinal cord injury) who receive IV anesthetics (lidocaine, ketamine), the evidence includes several randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Several RCTs have been performed using intravenous lidocaine for postherpetic neuralgia, complex regional pain syndrome, and diabetic neuropathy. These trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients in some settings. Neither of the RCTs used an active control, raising concerns about placebo effects. Overall, 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have psychiatric disorders (eg, treatment-resistant depression, OCD) who receive a course of IV ketamine, the evidence consists of systematic reviews, RCTs, and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Two publications of double-blind trials were identified that compared repeated ketamine infusions with infusions of saline for treatment-resistant depression. Additionally, one open-label study comparing ketamine infusion to electroconvulsive therapy (ECT) was identified, as well as one double-blind placebo-controlled trial and case series for OCD treatment, and one double-blind trial comparing multiple ketamine infusions with midazolam in chronic post-traumatic stress disorder (PTSD). There is a possibility of publication bias due to the lack of publication of many other small trials. Systematic reviews in patients with unipolar depression or depression related to bipolar disorder have identified numerous studies evaluating the efficacy of ketamine infusion. While the analyses indicate depression improvement short-term, there is limited evidence beyond use of a single infusion. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT found a significantly greater improvement in a depression scale during the 4-week infusion period, but the effect diminished over 3 weeks post-infusion. The trial did not

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use an active control, raising the possibility of placebo effects and unblinding of patients and investigators. In an open-label trial comparing ketamine to ECT, ECT was found to be more effective in inducing remission. Large observational studies in patients with depression indicate improvement on depression rating scales following ketamine infusions; however, these studies lack a control group, and no firm conclusions on the effectiveness or safety of serial ketamine infusions can be drawn from this evidence. One small double-blind, crossover RCT in patients with serotonin reuptake inhibitor (SRI)-resistant OCD found that ketamine infusion provided a higher frequency of Yale-Brown Obsessive Compulsive Scale (YBOCS) response at day 7 compared with placebo; however, unblinding was suspected and only data from the first phase were analyzed because of a carryover effect of ketamine. A case series identified only 1 patient who demonstrated prespecified significant YBOCS response after 2 to 3 weeks. A single small RCT in patients with chronic PTSD found that ketamine infusion produced significantly greater improvements in a PTSD symptom scale at 2 weeks compared to midazolam. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. 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.

In 2017, the American Psychiatric Association (APA) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression. The APA noted that "while ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option."

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 intravenous 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 CRPS up to 12 weeks
- 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

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J2001, 96365, 96366, 96374

Use CPT code J3490 for Ketamine

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 8/13/2009

Senior Medical Director – 7/2010

Specialty Matched Consultant Advisory Panel – 8/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 8/11/2011

Specialty Matched Consultant Advisory Panel – 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 9/13/12

Specialty Matched Consultant Advisory Panel – 1/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 9/12/13

Specialty Matched Consultant Advisory Panel – 1/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 10/9/14

Specialty Matched Consultant Advisory Panel – 1/2015

Medical Director review – 1/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 10/15/15

Specialty Matched Consultant Advisory Panel 1/2016

Medical Director review 1/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 11/9/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 11/8/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 11/14/19

Specialty Matched Consultant Advisory Panel 04/2020

Sanacora G, Frye MA, McDonald W et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry*, 2017 Mar 2;74(4). PMID 28249076

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.16, 11/12/20

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Peyrovian B, McIntyre RS, Phan L, et al. Registered clinical trials investigating ketamine for psychiatric disorders. *J Psychiatr Res*. Aug 2020; 127: 1-12. PMID 32315806

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Specialty Matched Consultant Advisory Panel 04/2022

Medical Director review 4/2022

Cohen SP, 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. *Reg Anesth Pain Med.* Jul 2018; 43(5): 521-546. PMID 29870458

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Medical Director review 4/2023

Yousefshahi F, Predescu O, Francisco Asenjo J. The Efficacy of Systemic Lidocaine in the Management of Chronic Pain: A Literature Review. *Anesth Pain Med.* Jun 2017; 7(3): e44732. PMID 28856112

Israel JE, St Pierre S, Ellis E, et al. Ketamine for the Treatment of Chronic Pain: A Comprehensive Review. *Health Psychol Res.* 2021; 9(1): 25535. PMID 34746491

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia.* Jan 2018; 38(1): 1-211. PMID 29368949

Gwathmey KG, Pearson KT. Diagnosis and management of sensory polyneuropathy. *BMJ.* May 08 2019; 365: 11108. PMID 31068323

Winslow BT, Vandal C, Dang L. Fibromyalgia: Diagnosis and Management. *Am Fam Physician.* Feb 2023; 107(2): 137-144. PMID 36791450

McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. *World Psychiatry.* Oct 2023; 22(3): 394-412. PMID 37713549

Sanacora G, Frye MA, McDonald W, et al. A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. *JAMA Psychiatry.* Apr 01 2017; 74(4): 399-405. PMID 28249076

Peyrovian B, McIntyre RS, Phan L, et al. Registered clinical trials investigating ketamine for psychiatric disorders. *J Psychiatr Res.* Aug 2020; 127: 1-12. PMID 32315806

Specialty Matched Consultant Advisory Panel 04/2024

Medical Director review 4/2024

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Policy Implementation/Update Information

- 8/3/10 New Evidence Based Guideline. Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the management of chronic neuropathic pain is not recommended. Reviewed by Senior Medical Director 7/6/2010. (btw)
- 1/10/12 Removed the word “neuropathic” from policy title and throughout as appropriate. Specialty Matched Consultant Advisory Panel review 11/30/11. No changes to guideline intent. (btw)
- 9/18/12 Evidence based guideline converted to corporate medical policy. Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of chronic pain, including, but not limited to chronic neuropathic pain and fibromyalgia, is considered investigational. Medical Director review 8/21/12. Notification given 9/18/2012 Policy effective 12/28/2012. (btw)
- 1/29/13 Specialty Matched Consultant Advisory Panel 1/16/2013. No change to policy. Reference added. (btw)
- 10/29/13 Reference added. (btw)
- 2/11/14 Specialty Matched Consultant Advisory Panel review 1/28/2014. No change to policy statement. (btw)
- 11/11/14 References updated. Description section updated. “When Not Covered” section updated to include chronic daily headaches. No change to Policy Statements. (td)
- 2/24/15 References updated. Description section updated. Specialty Matched Consultant Advisory Panel 1/2015. Medical Director review 1/2015. Policy Statement unchanged. (td)
- 2/29/16 Description section updated. Policy Guidelines section extensively revised. References added. Policy statement remains unchanged. Specialty Matched Consultant Advisory Panel 1/27/2016. Medical Director review 1/2016. (td)
- 12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy statement. (an)
- 2/24/17 Last paragraph of Description section regarding IV Ketamine revised for clarity to read: IV ketamine for the treatment of chronic pain **or psychiatric disorders** is an off-label use. (an)
- 5/26/17 Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (an)
- 6/8/18 Minor change to Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 5/23/2018. No change to policy statement. (an)
- 4/30/19 Added “psychiatric disorders” to list of non-covered indications. Reference added. Specialty Matched Consultant Advisory Panel review 4/17/2019. No change to policy statement. (an)

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- 4/28/20 References added. Policy guidelines updated. Specialty Matched Consultant Advisory Panel review 4/15/2020. Policy statement updated to include psychiatric disorders to reflect existing when not covered statement. Policy title changed from “Intravenous Anesthetics for the Treatment of Chronic Pain” to “Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders.” (eel)
- 5/4/21 Description and Policy guidelines updated. References added. Specialty Matched Consultant Advisory Panel review 4/15/2020. Medical Director review 4/2021. No Change to policy statement. (bb)
- 5/3/22 References added. Specialty Matched Consultant Advisory Panel review 4/2022. Medical Director review 4/2022. No Change to policy statement. (tt)
- 5/2/23 Policy guidelines updated. References added. Added the following statement to billing coding section “Use CPT code J3490 for Ketamine”. Specialty Matched Consultant Advisory Panel review 4/2023. Medical Director review 4/2023. No Change to policy statement. (tt)
- 5/1/24 References added. Specialty Matched Consultant Advisory Panel review 4/2024. Medical Director review 4/2024. No Change to policy statement. (tt)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.