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MEDICAL POLICY – 5.01.586

Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric or Substance Use Disorders

BCBSA Ref. Policy:	5.01.16	
Effective Date:	Feb. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Jan. 13, 2025	None
Replaces:	5.01.16	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Anesthetics are drugs to control pain. Anesthesia can be used to aid relaxation, block pain, or make a person unconscious during surgery. A local anesthetic is used to block pain in a small part of the body. Regional anesthesia is used to block pain in larger areas of the body, like the arms or legs. General anesthesia affects the whole body and makes a person unconscious. Different types of anesthesia have been well studied and are approved by the Food and Drug Administration for specific uses. Other uses of anesthesia have not been as well studied. One area of current inquiry is the use of certain anesthesia's given intravenously (through a vein) to try to treat pain from conditions like complex regional pain syndrome, fibromyalgia, or chronic headache. Another area of inquiry is the use of anesthesia's for depression, anxiety, or other psychiatric symptoms or disorders. Using intravenous anesthetic for chronic pain or for psychiatric disorders is investigational (unproven). More and larger studies are needed in both areas.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Investigational
Intravenous infusion of anesthetics	**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 headache, and fibromyalgia, is considered investigational.** **Intravenous infusion of ketamine for the treatment of depression, anxiety, or other psychiatric symptoms or disorders, including substance use disorders, is considered investigational.** **Intravenous infusion of ketamine in conjunction with psychotherapy (ketamine-assisted therapy) for the treatment of depression, anxiety, or other psychiatric symptoms or disorders, including substance use disorders, is considered investigational.**

Coding

Code	Description
CPT	
0820T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; first physician or other qualified health care professional, each hour
0821T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; second physician or other qualified health care professional, concurrent with first physician or other qualified health care professional, each hour (List separately in addition to code for primary procedure)
0822T	Continuous in-person monitoring and intervention (e.g., psychotherapy, crisis intervention), as needed, during psychedelic medication therapy; clinical staff under the direction of a physician or other qualified health care professional, concurrent with

Code	Description
	first physician or other qualified health care professional, each hour (list separately in addition to code for primary procedure)
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	
J2001	Injection, lidocaine hydrochloride for intravenous infusion, 10 mg
J3490	Unclassified drugs

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

Intravenous (IV) infusion of lidocaine or 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 treatment-resistant depression and obsessive-compulsive disorder (OCD). For these applications, a series of IV infusions would be administered daily for up to a week.

Background

Intravenous Anesthetic Agents

Courses of intravenous (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 one to six hours for up to ten days.

Lidocaine

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias.[1] 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 events may include arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given intravenously to individuals with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Ketamine

Ketamine is an antagonist of the N-methyl-D-aspartate receptor and a dissociative anesthetic.[2] Respiratory depression may occur with overdosage or a rapid rate of ketamine administration. Ketamine is a schedule III-controlled substance. Psychological manifestations vary in severity from pleasant dream-like states to hallucinations and delirium; further, these manifestations can be accompanied by confusion, excitement, aggression, or irrational behavior. The occurrence of adverse events with IV anesthetics may be reduced by the careful titration of subanesthetic doses. However, the potential benefits must be carefully weighed against the potential for serious, harmful adverse events.

Indications

The IV administration of anesthetics has been reported for various conditions, including chronic headache, chronic pain of neuropathic origin, fibromyalgia, depression, and obsessive-compulsive disorders.

Chronic daily headache is defined as a headache disorder that occurs 15 or more days a month for at least three months.[3] Chronic daily headache includes 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.[4] 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 longer (e.g., ≥6 months) than clinically expected after an illness or 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. Therefore, treatments focus on reducing activity and desensitizing pain pathways, thought to be mediated through N-methyl-D-aspartate receptors in the peripheral and central nervous system. Sympathetic ganglion blocks with lidocaine have been used to treat sympathetically maintained chronic pain conditions, such as complex regional pain syndrome (previously known as reflex sympathetic dystrophy). Test infusion of an anesthetic has also been used in treatment planning to assess individual responsiveness to determine whether medications, such as oral mexiletine or oral ketamine, may be effective. A course of 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 managing chronic pain conditions, such as terminal cancer pain, which is not discussed herein.

Fibromyalgia is a chronic state of widespread pain and tenderness.[5] Although fibromyalgia is generally considered 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 associated with fibromyalgia include alterations in N-methyl-D-aspartate 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.

The 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.[6] Particularly challenging are individuals with treatment-resistant depression with

suicidal ideation. Several studies are ongoing to test the efficacy of IV ketamine in individuals with suicidal ideation who present to the emergency department.

Summary of Evidence

For individuals who have chronic pain syndromes (e.g., neuropathic pain or fibromyalgia) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence includes systematic reviews, several randomized controlled trials (RTCs), and observational studies. The 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 IV lidocaine for postherpetic neuralgia (PHN), complex regional pain syndrome (CRPS), 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 individuals 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. A third trial found no benefit from a single infusion of ketamine or ketamine/magnesium. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this therapy. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have psychiatric disorders (e.g., treatment resistant depression (TRD), anxiety, PTSD, obsessive-compulsive disorder (OCD)) who receive a course of IV ketamine, the evidence consists of 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 infusion with an infusion of saline for TRD. Additionally, one open-label study comparing ketamine infusion to 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 individuals 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 in the short-term, there is limited evidence beyond a single infusion. One study with 26 individuals found no significant difference in a depression scale at the end of infusion. A larger RCT (n=68) 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 use an active control, raising the possibility of placebo effects and unblinding of individuals 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 individuals 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 individuals with serotonin reuptake inhibitor (SRI)-resistant OCD (n=15) found that ketamine infusion provided 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 (N=14) identified only 1 individual who demonstrated prespecified significant YBOCS response after 2 to 3 weeks. A single small RCT in individuals with chronic PTSD (n=30) 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.

Although reports of reduction in depression, anxiety, and suicidal ideation are promising, the strength of evidence is weak, limited by relatively small sample sizes, loss of effectiveness after 2 to 7 days, lack of longer-term data on efficacy, limited data on safety, and lack of blinding even in double-blind randomized controlled trials. As one expert has noted, it is relatively easy for subjects and investigators to distinguish between the effects of ketamine and saline, which is used most often as the control agent, or midazolam, which was used as the control agent in a recently published study. The midazolam-controlled trial purported to demonstrate a significant reduction in suicidal ideation within 24 hours but was also limited by open-label uncontrolled assessment after day 1 for up to 6 weeks, and by the fact that the study population was a cohort of psychiatric inpatients; there is no evidence that their experience can be generalized to individuals in outpatient or other settings. The evidence is therefore insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

Over 100 trials evaluating intravenous infusion of ketamine for depression are listed on **ClinicalTrials.gov**.[41] The majority are completed but not published. Some currently ongoing and unpublished trials that include over 40 participants are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05339074	Maintenance Ketamine Infusions for Treatment-Resistant Bipolar Depression: An Open-Label Extension Trial	60	Feb 2026
NCT05045378	Low-dose Ketamine Infusion Among Adolescents With Treatment-resistant Depression: a Randomized, Double-blind Placebo-control Study	54	Dec 2026
NCT05973851	A Randomised, Controlled Trial to Investigate the Effect of a Sixweek Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment.	418	Jun 2026
NCT06034821	Rapid Reversal of Suicidal Depression: Comparative Effectiveness of ECT vs. KETAMINE Over the Lifespan (REaKT-SD)	1500	Mar 2030
NCT04032301	Characterization of Comorbid Post-traumatic Stress Disorder and Major Depressive Disorder Utilizing Ketamine as an Experimental Medicine Probe	108	Apr 2025
Unpublished			
NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Oct 2023

NCT: national clinical trial

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Regional Anesthesia and Pain Medicine et al

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.[39] 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

American Psychiatric Association

In 2017, the American Psychiatric Association (APA) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression.[40] 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."

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Intravenous lidocaine is approved by the US 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 or psychiatric disorders is considered off-label use.

Ketamine hydrochloride injection is approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia before 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.

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History

Date	Comments
08/01/18	New policy, approved July 10, 2018. This policy replaces 5.01.16; Policy title and Policy Coverage Criteria amended to include IV ketamine for psychiatric symptoms and disorders. References 35-37 added.
02/01/19	Annual Review, approved January 4, 2019. Policy updated with literature review through September 2018; reference 8 added. Policy statement unchanged.
02/01/20	Annual Review, approved January 9, 2020. Policy updated with literature review through October 2019; references added. Policy statements unchanged.
02/01/21	Annual Review, approved January 6, 2021. Policy updated with literature review through October 10, 2020; references added. Policy statements unchanged.
02/01/22	Annual Review, approved January 10, 2022. Policy updated with literature review through October 5, 2021; references added. Policy statements unchanged.

Date	Comments
05/01/22	Interim Review, approved April 25, 2022. Policy updated to clarify that psychiatric disorders includes substance use disorders, and that IV infusion of ketamine for psychiatric disorders includes ketamine-assisted therapy. Policy title modified.
02/01/23	Annual Review, approved January 9, 2023. Policy updated with literature review through September 27, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
02/01/24	Annual Review, approved January 8, 2024. No changes to policy statements. Literature reviewed. Added new CPT codes 0820T-0822T.
02/01/25	Annual Review, approved January 13, 2025. Policy updated with literature review through September 24, 2024; references added.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.