Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

Policy # 00463
Original Effective Date: 02/18/2015
Current Effective Date: 03/13/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers intravenous (IV) 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 to be **investigational.***

Based on review of available data, the Company considers intravenous infusion (IV) of anesthetics (eg, ketamine or lidocaine) for the treatment of psychiatric disorders, including but not limited to depression and obsessive-compulsive disorder to be **investigational.***

Background/Overview

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 for 1 to 6 hours for up to 10 days.

Lidocaine

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. Adverse events 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 IV to patients 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 is a dissociative anesthetic. 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 more than 3 months. 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. Allodynia is pain that occurs from a stimulus that normally does not elicit a painful response (eg, 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 (eg, ≥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 patient 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. 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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Intravenous lidocaine is approved by the U.S. Food and Drug Administration 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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).

Summary of Evidence

For individuals who have chronic pain syndromes (eg, neuropathic pain or fibromyalgia) who receive a course of IV anesthetics (eg, lidocaine, ketamine), the evidence includes systematic reviews , several randomized controlled trials (RCTs), and observational studies. 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 post-herpetic 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. 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 (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 (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 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 (N=15) 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 (N=14) identified only 1 patient who demonstrated prespecified significant YBOCS response after 2 to 3 weeks. A single small RCT in patients 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.

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Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' 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 (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
- 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. 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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Over 100 trials evaluating IV infusion of ketamine for depression are listed on clinicaltrials.gov. 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	Aug 2024
NCT05168735	Ketamine + Mindfulness for Depression	60	Mar 2025
NCT05045378	Low-dose Ketamine Infusion Among Adolescents With Treatment-resistant Depression: a Randomized, Double-blind Placebo-control Study	54	Dec 2026
NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Dec 2022
NCT03674671	Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy	240	Mar 2023
NCT03113968	ELEKT-D: Electroconvulsive Therapy (ECT) vs. Ketamine in Patients With Treatment-Resistant Depression (TRD)	400	Dec 2022
NCT03237286	Testing a Synergistic, Neuroplasticity-Based Intervention for Depressive Neurocognition	154	Nov 2022
Unpublished			

NCT02556606	Ketamine for Treatment-Resistant Late-Life Depression	72	Mar 2021

NCT: national clinical trial.

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Policy History

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02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

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02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Added psychiatric disorders to the investigational statement.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed from "Intravenous Anesthetics for the Treatment of Chronic Pain" to "Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders". INV statement separated into two statements one for pain and the other for psychiatric disorders, including but not limited to depression and obsessive-compulsive disorder.
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/22/2021	Coding update
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2024

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	96365, 96366
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.