Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

Policy # 00463
Original Effective Date: 02/18/2015
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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 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. 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 intravenously 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 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 over dosage or too rapid a rate of administration of ketamine. 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 anesthetic 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 more than 15 days a month for at least 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 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 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)

IV 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

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. For these applications, a series of IV infusions would be administered daily for up to a week.

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 several randomized controlled trials (RCTs). 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 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, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. 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 the effects of the technology on health outcomes.

For individuals who have psychiatric disorders (eg, treatment-resistant depression, obsessive-compulsive disorder) who receive a course of IV ketamine, the evidence consists of RCTs. The 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 treatment-resistant depression. There is a possibility of publication bias due to the lack of publication

of many other small trials. 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 active control, raising the possibility of placebo effects and unblinding of patients and investigators. 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 procedure. 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 the effects of the technology on health outcomes.

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, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Supplemental Information

Practice Guidelines and Position Statements

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. 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. 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
Around 100 completed or ongoing trials evaluating intravenous 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			
NCT02556606	Ketamine for Treatment-Resistant Late-Life Depression	72	Mar 2021

NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Jun 2021
NCT03666390	A Double-blind, Randomized-controlled Trial Using a Low Dose of Ketamine vs Active Placebo in Treating Severe Depression and Suicide	48	Dec 2021
NCT03674671	Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy	240	Dec 2021
NCT03113968	ELEKT-D: Electroconvulsive Therapy (ECT) vs Ketamine in Patients With Treatment-Resistant Depression (TRD)	400	Apr 2022
NCT03237286	Testing a Synergistic, Neuroplasticity-Based Intervention for Depressive Neurocognition	150	Oct 2023
Unpublished			
NCT01920555	Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in	99	Feb 2017 (completed)

	Treatment-Resistant Depression (TRD)		
NCT02659085	A Randomized Controlled Non-inferiority Trial Comparing Ketamine With ECT in Patients With Major Depressive Disorder	200	Dec 2018
NCT02299440	Evaluation of the Effects of Ketamine in the Acute Phase of Suicidal Ideation: a Multicenter Randomized Double-blind Trial	156	Mar 2019 (completed)
NCT02360280	Intravenous Sub-anesthetic Ketamine Treatment in Treatment-Resistant Depression	62	Mar 2019 (completed)

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.
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.

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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

Next Scheduled Review Date: 02/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.
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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.

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