Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

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 anesthetics 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 anesthetics 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 of these 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, is considered investigational. |

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>CPT</strong></td>
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</tr>
<tr>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
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<tr>
<td>96366</td>
<td>Each additional hour (list separately in addition to code for primary procedure)</td>
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<tr>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
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<tr>
<td><strong>HCPCS</strong></td>
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<tr>
<td>J2001</td>
<td>Injection, lidocaine hydrochloride for intravenous infusion, 10 mg</td>
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<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
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## 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 the treatment-resistant depression and obsessive-compulsive disorder. 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. 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 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 overdosage 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.

**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 several randomized controlled trials (RTCs). 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 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 of 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 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 (e.g., treatment resistant depression (TRD), anxiety, PTSD, obsessive-compulsive disorder) who receive a course of IV ketamine, the evidence consists of rRTCs. 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. 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 an 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.

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 patients 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. 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td><strong>Ongoing</strong></td>
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<tr>
<td>NCT02556606</td>
<td>Ketamine for Treatment-Resistant Late-Life Depression</td>
<td>72</td>
<td>Mar 2021</td>
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<tr>
<td>NCT02461927</td>
<td>Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder</td>
<td>65</td>
<td>Jun 2021</td>
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<tr>
<td>NCT03666390</td>
<td>A Double-blind, Randomized-controlled Trial Using a Low Dose of Ketamine vs Active Placebo in Treating Severe Depression and Suicide</td>
<td>48</td>
<td>Dec 2021</td>
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<tr>
<td>NCT03674671</td>
<td>Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy</td>
<td>240</td>
<td>Dec 2021</td>
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<td>NCT03113968</td>
<td>ELEKT-D: Electroconvulsive Therapy (ECT) vs Ketamine in Patients With Treatment-Resistant Depression (TRD)</td>
<td>400</td>
<td>Apr 2022</td>
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<tr>
<td>NCT03237286</td>
<td>Testing a Synergistic, Neuroplasticity-Based Intervention for Depressive Neurocognition</td>
<td>150</td>
<td>Oct 2023</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<td></td>
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<tr>
<td>NCT01920555</td>
<td>Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in Treatment-Resistant Depression (TRD)</td>
<td>99</td>
<td>Feb 2017 (completed)</td>
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<td>NCT02299440</td>
<td>Evaluation of the Effects of Ketamine in the Acute Phase of Suicidal Ideation: a Multicenter Randomized Double-blind Trial</td>
<td>156</td>
<td>Mar 2019 (completed)</td>
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<tr>
<td>NCT02659085</td>
<td>A Randomized Controlled Non-inferiority Trial Comparing Ketamine With ECT in Patients With Major Depressive Disorder</td>
<td>198</td>
<td>Aug 2019 (completed)</td>
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<tr>
<td>NCT02360280</td>
<td>Intravenous Sub-anesthetic Ketamine Treatment in Treatment-Resistant Depression</td>
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<td>Mar 2019 (completed)</td>
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NCT: national clinical trial

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.”

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

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 or psychiatric disorders is an 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.


### History

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<th>Date</th>
<th>Comments</th>
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<tr>
<td>08/01/18</td>
<td>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.</td>
</tr>
<tr>
<td>02/01/20</td>
<td>Annual Review, approved January 9, 2020. Policy updated with literature review through October 2019; references added. Policy statements unchanged.</td>
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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at:
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