Intravenous Anesthetics for the Treatment of Chronic Pain

Number 5.01.16
Effective Date November 10, 2015
Revision Date(s) 11/10/15
Replaces N/A

Policy

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.

Related Policies

N/A

Policy Guidelines

N/A

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 (CRPS), diabetic neuropathy, and pain related to stroke or spinal cord injuries. IV infusion of ketamine has also been investigated for the treatment of depression and obsessive compulsive disorder. For these applications, 1 or more courses of IV infusion would be administered over a period of several hours or several days.

Background

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.

Ketamine is an antagonist of the 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 AEs 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 AEs.

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. Adverse effects (AEs) 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.

IV administration of anesthetic has been reported for a variety of conditions, including chronic pain of neuropathic origin, chronic headache, 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 (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) 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 (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 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 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**

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 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 is an off-label use.

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.

Benefit Application

N/A

Rationale

This evidence review was created in 2004 and updated periodically using the MEDLINE database. The most recent literature review was performed through August 27, 2015.

It is recognized that randomized clinical trials (RCTs) are extremely important to assess treatments of psychiatric and painful conditions, due to the expected placebo effect, the subjective nature of assessment in general, and the variable natural history. Uncontrolled trials and case series offer little useful evidence on the efficacy of intravenous (IV) anesthetics.

Lidocaine

A review of the peer-reviewed literature on MEDLINE for the period of 1994 through February 2004, when this evidence review was created, revealed that the degree and duration of pain relief with IV lidocaine does not appear to be clinically significant in most patients. (1-7) While some patients have reported diminished pain concurrent with IV administration of lidocaine that may continue beyond the infusion period for an extended duration, overall, responses to IV lidocaine in relief of allodynia, dysesthesia, and hyperalgesia were mixed. These studies and a review of the evidence available in 2004 indicated a need for additional randomized, controlled, and double-blinded studies to determine the incremental effects of lidocaine over active placebo and compared with other standard treatments for chronic pain, such as the use of antidepressants for fibromyalgia. It was concluded that a placebo response due to the significant adverse effects (AEs) with IV lidocaine warrants the use of active placebos to increase the probability of determining the true analgesic effect of lidocaine in clinical trials. In addition, further studies were needed to determine appropriate patient selection criteria, predictive values, effective dosage ranges, frequencies, and duration of treatment. Key studies, focusing on RCTs, are described next.

Spinal Cord Injury

In a double-blind, placebo-controlled, crossover study of 16 patients either post-stroke or spinal cord injury, Attal et al. reported IV lidocaine significantly reduced pain over placebo.1 However, the duration of this significance lasted only 45 minutes. The 2006 literature review update identified a randomized, double-blind crossover trial of
IV lidocaine in 24 patients with spinal cord injury neuropathic pain.8 In this trial, spontaneous and evoked pain were significantly reduced on the visual analog scale (VAS), as measured before infusion and 25 to 35 minutes after the start of the infusion. Mostly mild AEs (experienced by 19 patients) and the relief of pain formed the basis of 21 patients identifying the lidocaine treatment period correctly. Identification of the correct treatment group draws into question whether successful blinding was achieved in this study, thus limiting interpretation of results. This also suggests the need for an active placebo in future trials, as noted. The authors concluded that IV lidocaine (and like agents) may be a treatment option for spinal cord injury pain. Although, the authors note, long-term treatment with lidocaine is usually not suitable.

**Complex Regional Pain Syndrome**
Wallace et al reported on a randomized, double-blind, placebo-controlled study of 16 patients with complex regional pain syndrome (CRPS) types I and II. (6) While IV lidocaine significantly reduced the pain response to cool stimuli, mechanical pain relief was not significantly improved.

**Fibromyalgia**
In a randomized, double-blind, crossover study of 18 patients with fibromyalgia, Sorensen et al found mixed responses with IV lidocaine with ketamine, morphine, or both, suggesting that pain-processing mechanisms must differ in fibromyalgia.5 None of these patients responded to IV lidocaine alone. Vlainich et al. reported a randomized double-blind trial of IV lidocaine plus amitriptyline versus amitriptyline monotherapy in 30 patients with fibromyalgia. (9) Infusion of lidocaine or saline was given once a week for 4 weeks. Pain intensity decreased in both groups over the course of treatment; but there was no significant difference between the treatment groups (VAS 4.1 for combined treatment vs 4.0 for monotherapy).

**Headache**
A small RCT from 1991 found no significant difference between IV lidocaine and placebo for the treatment of acute migraine. (10) No RCTs were identified that evaluated the long-term relief of chronic daily headache following IV infusion of lidocaine. Uncontrolled studies were identified, (11,12) but these do not provide sufficient evidence on the efficacy of IV lidocaine treatment for this condition.

**Other Neuropathic Pain**
Tremont-Lukats et al. reported results of a randomized, double-blinded, placebo-controlled pilot trial in 32 subjects with ongoing neuropathic pain. (13) Infusion of 5 mg/kg/h, but not 1 or 3 mg/kg/h, over a period of 6 hours was observed to decrease pain by approximately 30%. This effect lasted for the next 4 hours of observation. AEs were frequent; in 2 subjects, infusion was terminated early due to bothersome AEs. In a retrospective analysis, 104 patients with suspected neuropathic pain who had undergone diagnostic IV lidocaine were found from screening 635 sequential charts; of these, 5 patients had requested discontinuation mid-infusion, resulting in a cohort of 99 patients with baseline and posttreatment numerical pain ratings (score of 0-10). (14) Forty-two of the patients (42%) met the criteria of 30% or greater pain reduction; some of this subset was subsequently treated with mexiletine.

In a randomized, double-blind, placebo-controlled, crossover-designed trial, Kvarnstrom et al. evaluated the effects of lidocaine in 12 patients with long-term peripheral neuropathic pain of traumatic origin. (3) The authors reported no significant differences in pain reduction over placebo on VAS. Wu et al evaluated the effects of IV lidocaine on 31 patients with postamputation pain in a randomized, double-blind, active placebo-controlled, crossover trial. (7) Wu et al. found stump pain was significantly reduced with IV lidocaine, yet phantom pain was not relieved, and the stump pain relief was short-lived. In a study of 24 patients with postherpetic neuralgia, Baranowski et al reported IV lidocaine provided significant pain reduction over placebo; however, the pain was not eliminated. Medrik-Goldberg et al evaluated 30 patients with sciatica in a randomized, double-blind, 3-arm crossover trial. (4) The authors found that lidocaine significantly reduced spontaneous pain as reported by VAS and pain evoked by straight leg raises. The pain reduction continued during saline infusion for 1 hour after the 2-hour lidocaine infusion. However, the evaluation did not extend beyond the 3-hour treatment period.

A 2005 Cochrane review examined controlled clinical trials on lidocaine and its oral analogs (i.e., mexiletine, tocainide, flecaïnide) for neuropathic pain treatment and found these drugs safely provided more pain relief than placebo and with similar effectiveness as other analgesics. (15) The Cochrane review noted that further
investigation is needed to determine the clinical meaning of statistically significant pain relief and to test for less toxic analogs. A separate publication by the same authors estimated an 11-point (of 100) improvement in pain scales, with IV lidocaine or oral analogs compared with placebo. (16) Although AEs were reportedly not significantly different from other active controls (amitriptyline, carbamazepine, gabapentin, morphine), the severity and nature of the AEs could not be assessed, as indicated in an accompanying editorial, “the limitations of the contributing studies preclude drawing useful conclusions about the adverse effect profiles of these drugs.” (17) In addition, the authors noted that (1) lidocaine’s short serum half-life (120 minutes) precludes the use of this drug for chronic use, and (2) all of the trials measured pain relief within 24 hours because in most patients, the effect disappears a few hours after treatment. Given the high frequency of AEs and the short duration of action, the health benefits of IV lidocaine remain unclear.

**Ketamine**

A comprehensive systematic review of the treatment of chronic neuropathic pain with IV ketamine, published in 2003, assessed the quality of evidence for ketamine’s effectiveness in central pain, CRPSs, fibromyalgia, ischemic pain, nonspecific pain of neuropathic origin, acute pain in patients with chronic neuropathic pain, orofacial pain, phantom/stump pain, and post-herpetic neuralgia. (18) Some small RCTs were available for review, and meta-analysis was considered not appropriate. The report concluded that despite the use of ketamine for more than 30 years, there was insufficient evidence to advocate the routine use of this treatment for patients with chronic pain. Of particular concern were the significant AEs of this N-methyl-D-aspartate receptor antagonist in the central and peripheral nervous system. Few data were available concerning appropriate dosing and long-term administration.

**Spinal Cord Injury**

In 2004, Kvarnstrom et al. assessed the effect of subanesthetic levels of IV ketamine or lidocaine on pain after spinal cord injury. (19) This randomized, double-blind, placebo-controlled crossover design found a 38% reduction in pain during ketamine infusion, with 5 of 10 subjects responding to treatment, compared with 1 of 10 in the lidocaine infusion group and 0 of 10 in the placebo group. No significant pain reduction was observed following IV administration of lidocaine or saline. AEs were common with both treatments; ketamine produced 39 AEs in 9 of 10 subjects. These included somnolence, dizziness, out-of-body sensation, changes in hearing and vision, paresthesia, and other "unpleasant experiences."

In 2010, Amr published results from a double-blind randomized placebo-controlled study of 40 patients with neuropathic pain secondary to spinal cord injury that was conducted in Egypt. (20) All patients received gabapentin (300 mg) 3 times daily. The experimental group also received ketamine infusion (80 mg) over a 5-hour period daily for 7 days. The control group received infusion of isotonic saline over the same period. VAS scores for pain were similar in the 2 groups at baseline (VAS of 84 of 100 for both groups). During the week of infusion, VAS scores decreased more in the ketamine-infused group than the gabapentin-only group (VAS score of 14 in the ketamine group vs 43 in the control group at day 7). In the control group, VAS pain scores remained about the same during the 4-week follow-up. Pain scores in the ketamine-infused group increased from 14 to 22 at 1-week follow-up and remained at that level for 2 weeks after infusion. By the third week after the ketamine infusion, VAS scores had increased to 43 and were the same as the placebo-control group. Three patients were reported to have had short-lasting delusions with ketamine infusion.

**Complex Regional Pain Syndrome**

A network meta-analysis from 2014 evaluated the efficacy of all agent classes investigated in RCTs and provided a rank order of various substances. (21) A total of 16 studies on bisphosphonates, calcitonin, NMDA analogs, analgetics, vasodilators, steroids, anticonvulsive agents, and radical scavengers were included in the analysis. Of these, only bisphosphonates, NMDA analogs (ketamine), and vasodilators showed better long-term pain reduction than placebo. The 2 RCTs on ketamine were published in 2009 by Schwartzman et al (n=19) and Sigtermans et al (n=60), which is described in further detail below. (22,23)

These same studies were included in A 2013 Cochrane overview of interventions for CRPS, which found low-quality evidence that a course of IV ketamine may be effective for CRPS-related pain, although the effects were not sustained beyond 4 to 11 weeks posttreatment. (24)

The largest double-blind RCT of ketamine for CRPS was a European report by Sigtermans et al. in 2009. (23)
Sixty patients were randomly assigned to ketamine (titrated up to 30 mg/h for a 70-kg patient) or saline infused over 4 days. The mean ketamine infusion rate was 22 mg/h (normalized to a 70-kg patient) at the end of the treatment phase. Blood samples were collected to assess the plasma concentration of ketamine, and patients were monitored for AEs. Two patients terminated the ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, numerical pain scores were 7.2 (maximum, 10) for ketamine and 6.9 for the placebo group. The lowest pain scores (ketamine, 2.7; placebo, 5.5) were observed at the end of the first week (no patients were lost to follow-up for the primary outcome measure). Although pain scores remained statistically lower through week 11, the clinically significant difference of 2 points was maintained until week 4. None of the secondary (functional) outcome measures were improved by treatment. Sixty percent of the patients in the placebo group correctly indicated treatment assignment (slightly better than chance); 93% of patients in the ketamine group correctly indicated treatment assignment due primarily to psychomimetic effects.

Multiday courses of ketamine infusion in an inpatient setting have been reported for treatment of CRPS. A 2004 retrospective analysis described the effect of ketamine infusion in 33 patients with CRPS. (25) Inpatient infusion of a subanesthetic dose of ketamine over 2 to 20 days was found to provide relief for 9 months (median, 4 months). Twelve of the patients received a second infusion, with a reported mean relief duration of 25 months (median, 36 months). Dosing was titrated by the occurrence of AEs, which included a feeling of inebriation, dizziness, blurred vision, or nausea. Hallucinations occurred in 6 of the 33 patients.

In 2008, Kiefer et al. reported a multicenter (United States and Europe) prospective open-label phase 2 study of anesthetic dosing of ketamine in 20 patients with refractory CRPS. (26) Symptoms were either long-standing (range, 6-68 months), spreading, or rapidly progressive, and refractory to conventional nonmedical (physical therapy, psychological approaches), or pharmacologic (mono- or combined therapy) and interventional treatments (at least 3) including selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, intravenous regional sympathetic blocks, spinal cord stimulation, surgical sympathectomy, or intrathecal drug delivery systems. Following consent, patients were intubated and mechanically ventilated (except for the first 3 patients). Ketamine infusion was titrated up to a dose of 7 mg/kg/h with infusion over 5 days, then tapered downward until consciousness was attained. Midazolam was coadministered to a level of deep sedation to attenuate agitation and other AEs. All patients received IV low-dose heparin, the proton pump inhibitor pantoprazole, and clonidine to control cardiovascular and psychomimetic AEs of ketamine. Intubated patients received enteral nutrition with insulin as needed to maintain normoglycemia. Standard intensive care monitoring along with blood gas analysis, blood chemistry, and screening for infectious complications was performed regularly.

Outcomes were assessed at 1 week and 1, 3, and 6 months after treatment. Pain intensity decreased from a numerical rating scale of 9 at baseline to 0.5 at 1 week and remained low (2.0) at 6 months. Three patients relapsed but with lower pain (3.8) than at baseline. Pain relief was 94%, 89%, and 79% at 1, 3, and 6 months, respectively. Upper- and lower-extremity movement improved from 3.2 at baseline to 0.4 at 6 months for arm movement and from 2.3 at baseline to 0.6 at 6 months for walking. At 6 months, there was a significant difference in the ability to perform activities of daily living: 1 patient rated total impairment, 3, severe impairment, 6, moderate impairment, and 10 patients, no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by 5, and as moderate by 4 patients. At 6 months, 2 patients remained unable to work, 4 had moderate impairment, and 14 patients reported no impairment. Psychotropic AEs resolved in the first week in most patients, although 5 patients reported difficulties with sleeping and recurring nightmares for 1 month following treatment. Muscle weakness was reported in all patients for as long as 4 to 6 weeks following treatment. As indicated by the authors, a strong placebo response to this intensive intervention might be expected, and a large, multicenter RCT would be needed to definitively establish efficacy and safety. At this time, the beneficial effect of IV administration of ketamine is considered suggestive but not proven; additional trials are needed.

In 2011, Noppers et al. reported ketamine-induced hepatotoxicity in 3 of 6 patients during the second of two 100-hour intravenous infusions. (27) The 3 patients developed elevated liver enzymes during the start of the second 100-hour infusion, which began 16 days after the first. One of the patients also developed an itching rash and fever. Infusions were terminated and the liver enzymes returned to reference values within 2 months. The study was stopped early due to the adverse events.

Fibromyalgia

In 2011, Noppers et al. reported a randomized, double-blind, active placebo-controlled trial that was conducted in Europe using a 30-minute infusion of S(+)-ketamine (n=12) or midazolam (n=12). (28) Baseline VAS pain scores
were 5.4 in the ketamine group and 5.8 in the midazolam group. At 15 minutes after termination of infusion, significantly more patients in the ketamine group showed a reduction in VAS pain of greater than 50% compared with placebo (8 vs 3). There was no significant difference between the groups at 180 minutes after infusion (6 vs 3), at the end of week 1 (2 vs 0) or end of week 8 (2 vs 2, all respectively). There was no difference between groups on the fibromyalgia impact questionnaire measured weekly over 8 weeks. In this well-conducted study, a short infusion of ketamine (30 minutes) did not have a long-term analgesic effect on fibromyalgia pain.

Other Chronic Pain
A study published in 2008 compared the efficacy of placebo, ketamine, calcitonin, and combined calcitonin and ketamine to relieve phantom limb pain (n=20, within-subject design). (29) One-hour infusion of ketamine or ketamine plus calcitonin resulted in greater than 40% improvement in pain immediately after treatment. The mean and maximum pain scores remained significantly better than placebo for 48 hours after treatment.

A 2012 retrospective analysis from an academic medical center in the United States identified 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a 5-year period. (30) Eighteen patients were diagnosed with CRPS, and 31 had other diagnoses including refractory headache (n=8) and severe back pain (n=7). All patients exhibited signs of central sensitization. Following pretreatment with midazolam and ondansetron, ketamine infusions were administered at the highest tolerated dose for a duration ranging from 30 minutes to 8 hours. The interval between infusions ranged from 12 to 680 days (median, 233.7 days). The immediate reduction in VAS was 7.2 for patients with CRPS and 5.1 for non-CRPS pain. Query of available patients (59%) indicated that for 38%, pain relief lasted more than 3 weeks. AEs, which included confusion and hallucination, were considered minimal. A 2006 retrospective analysis described outpatient ketamine treatment in 13 patients with severe neuropathic pain; diagnoses included CRPS (n=8), migraine (n=1), neuropathy (n=3), and phantom limb (n=1). (31) Low-dose ketamine (beginning at 0.12 mg/kg/h with slow upward titration) was delivered by a programmable pump through a peripherally inserted central catheter line. With an average infusion duration of 16 days, pain severity decreased 38% (VAS, 7.7-4.8) with an 85% response rate. About half of the patients reported a perceived benefit 1 month after treatment. AEs included fatigue, dizziness, confusion, and spinal pain. No patients reported hallucinations.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review 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>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02106325</td>
<td>A Randomized, Double-Blinded Controlled Trial of an N-Methyl D-Aspartate Antagonist as a Rapidly-Acting Antidepressant in Depressed Emergency Department Patients</td>
<td>100</td>
<td>December 2015</td>
</tr>
<tr>
<td>NCT01920555</td>
<td>Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in Treatment-Resistant Depression (TRD)</td>
<td>100</td>
<td>March 2016</td>
</tr>
<tr>
<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>June 2016</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01371110</td>
<td>Intravenous Ketamine in the Treatment of Obsessive-Compulsive Disorder</td>
<td>12</td>
<td>August 2015</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Summary of Evidence
The evidence on IV anesthetics in patients who have CRPS, fibromyalgia, chronic headache, or other chronic neuropathic pain conditions consists of several RCTs. Relevant outcomes include symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Evidence, primarily from outside of the United States, suggests that intravenous (IV) courses of ketamine may...
provide at least temporary relief to some chronic pain patients. However, the intense treatment protocols, severity of adverse 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.

The evidence on IV anesthetics in patients who have depression or obsessive compulsive disorder is limited. Relevant outcomes include symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. Several trials on the IV infusion of ketamine for the treatment of suicidal ideation in patients with depression are ongoing. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
The 2010 practice guidelines for chronic pain management from the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine discuss a variety of treatment options for chronic pain. (32) Use of ionotropic N-methyl-D-aspartate receptor antagonists and topical agents for neuropathic pain is addressed; IV infusion of lidocaine or ketamine is not mentioned.

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

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

References
### Coding

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>96366</td>
<td>Each additional hour (list separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>96374</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J2001</td>
<td>Injection, lidocaine hydrochloride for intravenous infusion, 10 mg</td>
</tr>
<tr>
<td></td>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
</tbody>
</table>

### Appendix

N/A

### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/08/14</td>
<td>Policy reinstated; previously in archive status. Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of chronic pain is considered investigational.</td>
</tr>
</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2015 Premera All Rights Reserved.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).


Ikollo (Ilocano): Daytoy a Pakdaak ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaak mabalini nga adda ket naglaon iti napateg nga impormasion maipanggpe iti aplikasyon no winngyoy ngi winngyo coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pepsa iti daytoy a pakdaak. Mabalini nga adda rumbeng nga aramideno nga adda sakkay dagiti partikular a naituding nga aldaw tapno mapagtaludleyo ti coverage ti saluy-ayo winngyoy tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bikodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).
