Name of Policy:  
**Intravenous Anesthetics for the Treatment of Chronic Neuropathic Pain**

Policy #: 446  
Category: Pharmacology  
Policy Grade: C  
Latest Review Date: September 2013

**Background/Definitions:**

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
**Description of Procedure or Service:**

Intravenous (IV) infusion of lidocaine or ketamine has been used for the treatment of chronic neuropathic pain. Chronic neuropathic pain disorders include phantom limb pain, post-herpetic neuralgia, complex regional pain syndromes, diabetic neuropathy, and pain related to stroke or spinal cord injuries.

For this application, one or more courses of IV infusion would be administered over a period of several hours or several days.

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 when pain occurs from a stimulus that normally does not elicit a painful response (e.g., light touch, warmth). Dysesthesia is when there is a constant or ongoing unpleasant or electrical sensation of pain. Hyperalgesia is when there is an exaggerated response to normally painful stimuli. Symptoms may continue for a period of time that is longer (e.g., six months or more) 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 (NMDA) receptors, in the peripheral and central nervous system. Sympathetic ganglion blocks with lidocaine have been used for a number of years to treat sympathetically maintained chronic pain conditions such as complex regional pain syndrome (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 sub-anesthetic 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.

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 sub-anesthetic dose preceded by a bolus infusion to achieve desired blood levels sooner. 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 and can be mild to moderate, including general fatigue, somnolence, dizziness, headache, peri orbital and extremity numbness and tingling, nausea, vomiting, tremors, and changes in blood pressure and pulse. Severe adverse effects can be 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 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 side effects with IV anesthetics may be reduced by the careful titration of sub-anesthetic doses. However, the potential benefits of pain control must be carefully weighed against the potential for serious, harmful side effects.

**Policy:**

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the management of chronic neuropathic pain do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**

Lidocaine

A review of the peer-reviewed literature on MEDLINE revealed that the degree and duration of pain relief with IV lidocaine does not appear to be clinically significant in the majority of patients. While some patients have reported diminished pain concurrent with the 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 have been mixed. These studies and a review of the evidence that was 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 to 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 side effects 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 randomized controlled trials, are described below.

**Spinal Cord Injury**

In a double-blind, placebo-controlled, crossover study of 16 patients either post-stroke or spinal cord injury, Attal and colleagues reported IV lidocaine significantly reduced pain over placebo. 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. 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 adverse effects (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 intravenous 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 Types I and II. 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 and colleagues found mixed responses with IV lidocaine with ketamine, morphine, or both, suggesting that pain-processing mechanisms must differ in fibromyalgia. 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. Infusion of lidocaine or saline was given once a week for four 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).

*Other Neuropathic Pain*

Tremont-Lukats and colleagues reported results of a randomized, double-blinded, placebo-controlled pilot trial in 32 subjects with ongoing neuropathic pain. Infusion of 5 mg/kg/h, but not 1 or 3 mg/kg/h, over a period of six hours was observed to decrease pain by approximately 30%. This effect lasted for the next four hours of observation. Adverse effects were frequent; in two subjects, infusion was terminated early due to bothersome adverse effects. 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, five patients had requested discontinuation mid-infusion, resulting in a cohort of 99 patients with baseline and post-treatment numerical pain ratings (score of 0-10). 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 and colleagues evaluated the effects of lidocaine in 12 patients with long-term peripheral neuropathic pain of traumatic origin. 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. Wu and colleagues 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 and colleagues evaluated 30 patients with sciatica in a randomized, double-blind, three-arm crossover trial. 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 one hour after the two-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, and flecainide) for neuropathic pain treatment and found these drugs safely provided more pain relief than placebo and with similar effectiveness as other analgesics. 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 analogues compared with placebo. Although adverse effects were reportedly not significantly different from other active controls (amitriptyline, carbamazepine, gabapentin, morphine), the severity and nature of the adverse events 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.” In addition, the authors noted that 1) lidocaine’s short serum half-life (120 min) 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 adverse effects 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, complex regional pain syndromes, fibromyalgia, ischemic pain, non-specific pain of neuropathic origin, acute pain in patients with chronic neuropathic pain, orofacial pain, phantom/stump pain, and post-herpetic neuralgia. Some small randomized controlled trials were available for review, and meta-analysis was considered not appropriate. The report concluded that despite the use of ketamine for over 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 side effects of this NMDA 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 and colleagues assessed the effect of subanesthetic levels of IV ketamine or lidocaine on pain after spinal cord injury. This randomized, double-blind, placebo-controlled crossover design found a 38% reduction in pain during ketamine infusion, with five of ten subjects responding to treatment, compared with one of ten in the lidocaine infusion group and zero of ten in the placebo group. No significant pain reduction was observed following IV administration of lidocaine or saline. Adverse events were common with both treatments; ketamine produced 39 adverse effects in nine of ten 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. All patients received gabapentin (300 mg) three times daily. The experimental group also received...
ketamine infusion (80 mg) over a five-hour period daily for seven days. The control group received infusion of isotonic saline over the same period. VAS scores for pain were similar in the two groups at baseline (VAS of 84 out 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 seven). In the control group, VAS pain scores remained about the same during the four-week follow-up. Pain scores in the ketamine-infused group increased from 14 to 22 at one-week follow-up and remained at that level for two 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 (CRPS)**

A 2013 Cochrane overview of interventions for CRPS found low quality evidence that a course of IV ketamine may be effective for CRPS-related pain, although the effects were not sustained beyond four to 11 weeks post-treatment. This conclusion was reached on the basis of two RCTs. One of the RCTs studied 19 subjects, the second is described below.

The largest double-blind RCT of ketamine for CRPS was a European report by Sigtermans et al in 2009. Sixty patients were randomly assigned to ketamine (titrated up to 30 mg/h for a 70-kg patient) or saline infused over four 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 side effects. Two patients terminated the ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, numerical pain scores were 7.2 (maximum of ten) for ketamine and 6.9 for the placebo group. The lowest pain scores (ketamine 2.7 and 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 two points was maintained until week four. 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.

Multi-day 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. Inpatient infusion of a subanesthetic dose of ketamine over two to 20 days was found to provide relief for nine months (median of four months). Twelve of the patients received a second infusion, with a reported mean relief duration of 25 months (median of 36 months). Dosing was titrated by the occurrence of adverse effects, which included a feeling of inebriation, dizziness, blurred vision, or nausea. Hallucinations occurred in six of the 33 patients.

In 2008, Kiefer et al reported a multicenter (U.S. and Europe) prospective open-label Phase II study of anesthetic dosing of ketamine in 20 patients with refractory CRPS. Symptoms were either long-standing (range: 6 to 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 three) including selective

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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 three patients). Ketamine infusion was titrated up to a dose of 7mg/kg/h with infusion over five days, then tapered downward until consciousness was attained. Midazolam was coadministered to a level of deep sedation to attenuate agitation and other adverse effects. All patients received IV low-dose heparin, the proton pump inhibitor pantoprazole, and clonidine to control cardiovascular and psychomimetic side effects 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 one week and one, three, and six months after treatment. Pain intensity decreased from a numerical rating scale of nine at baseline to 0.5 at one week and remained low (2.0) at six months. Three patients relapsed but with lower pain (3.8) than at baseline. Pain relief was 94%, 89%, and 79% at one, three, and six months, respectively. Upper and lower extremity movement improved from 3.2 at baseline to 0.4 at six months for arm movement and from 2.3 at baseline to 0.6 at six months for walking. At six months, there was a significant difference in the ability to perform activities of daily living; one patient rated total impairment, three severe impairment, six moderate impairment, and ten patients no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by five, and as moderate by four patients. At six months, two patients remained unable to work, four had moderate impairment, and 14 patients reported no impairment. Psychotropic adverse effects resolved in the first week in the majority of patients, although five patients reported difficulties with sleeping and recurring nightmares for one month following treatment. Muscle weakness was reported in all patients for as long as four to six 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 intravenous administration of ketamine is considered suggestive but not proven; additional trials are needed.

In 2011, Noppers et al reported ketamine-induced hepatotoxicity in three of six patients during the second of two 100-hour intravenous infusions. The three 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 two 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). 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 to 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 one (2 vs. 0) or end of week eight (2 vs. 2, all respectively). There was no difference
between groups on the fibromyalgia impact questionnaire measured weekly over eight 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). 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 U.S. identified 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a five-year period. 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 eight hours. The interval between infusions ranged from 12-680 days (median of 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 three weeks. Adverse events, 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). 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 (PICC) line. With an average infusion duration of 16 days, pain severity decreased 38% (VAS of 7.7 to 4.8) with an 85% response rate. About half of the patients reported a perceived benefit one month after treatment. Adverse effects included fatigue, dizziness, confusion, and spinal pain. No patients reported hallucinations.

Summary
Intractable pain presents a great challenge to patients and their healthcare providers. Recent evidence, primarily from outside of the U.S., suggests that IV courses of ketamine may provide at least temporary relief to some chronic pain patients. However, the intense treatment protocols, severity of side 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. Therefore, this treatment is considered investigational.

Key Words:
Pain, Chronic, Intravenous Lidocaine, Chronic Pain, Fibromyalgia, Ketamine, Neuropathic pain disorders, complex regional pain syndrome

Approved by Governing Bodies:
Not applicable
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Pre-certification requirements: Not applicable

**Current Coding:**

**CPT Codes:**
- 96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- 96366 Each additional hour (list separately in addition to code for primary procedure)
- 96374 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug

**HCPCS:**
- J2001 Injection, lidocaine hydrochloride for intravenous infusion, 10 mg

**References:**


Policy History:
Medical Policy Group, August 2010 (3)
Medical Policy Administration Committee, September 2010
Available for comment September 22-November 5, 2010
Medical Policy Group, September 2011 (3): Updated Key Points and References
Medical Policy Group, October 2012 (3): Updated Key Points and References
Medical Policy Panel, September 2013
Medical Policy Group, September 2013 (3): Updated Key Points and References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.