



Louisiana

Intravenous Anesthetics for the Treatment of Chronic Pain

Policy # 00463

Original Effective Date: 02/18/2015

Current Effective Date: 02/21/2018

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.

Note: Cochlear Implant is addressed separately in medical policy 00017.

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**.*

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.

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 effects may include arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given IV to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Ketamine

Ketamine is an antagonist of the *N*-methyl-D-aspartate (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; 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 of pain control must be carefully weighed against the potential for serious, harmful adverse events.

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Indications

IV administration of anesthetic has been reported for various 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. Therefore, treatments focus on reducing activity and desensitizing pain pathways, thought to be mediated through 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 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 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 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.

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.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

IV lidocaine is approved by the U.S. 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 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 is an off-label use.

Centers for Medicare and Medicaid Services (CMS)

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.

Rationale/Source

It is recognized that randomized controlled 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 IV anesthetics.

CHRONIC PAIN

Lidocaine

A review of the peer-reviewed literature revealed that the degree and duration of pain relief with IV lidocaine does not appear to be clinically significant in most patients. While some patients have reported diminished pain concurrent with IV administration of lidocaine that may continue for an extended duration beyond the infusion period, 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 double-blinded RCTs to determine the incremental effects of lidocaine over active placebo and to compare IV lidocaine with other standard treatments for chronic pain, such as the use of antidepressants for fibromyalgia. The studies concluded that a placebo response, due to the significant adverse events with IV lidocaine, warrants the use of active placebos to increase the probability of determining the true analgesic effect of lidocaine in clinical trials. Additionally, further studies are 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.

Complex Regional Pain Syndrome

Wallace et al (2000) reported on a randomized, double-blind, placebo-controlled study of 16 patients with CRPS types I and II. While IV lidocaine significantly reduced the pain response to cool stimuli, mechanical pain relief was not significantly improved.

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Fibromyalgia

In a randomized, double-blind, crossover study of 18 patients with fibromyalgia, Sorensen et al (1997) 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 (2011) 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 4 weeks. Pain intensity decreased in both groups over the course of treatment; however, there was no significant difference between the treatment groups (visual analog scale [VAS], 4.1 for combined treatment vs 4.0 for monotherapy).

Chronic Headache

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

Chronic Neuropathic Pain

Tremont-Lukats et al (2006) 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 6 hours was observed to decrease pain by approximately 30%. This effect lasted for the next 4 hours of observation. Adverse events were frequent; in 2 subjects, infusion was terminated early due to adverse events. In a 2007 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 numeric rating scale (NRS) for pain (range, 0-10). Forty-two (42%) of the patients 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 trial, Kvarnstrom et al (2003) 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 the VAS. Wu et al (2002) evaluated the effects of IV lidocaine on 31 patients with postamputation pain in a randomized, double-blind, active placebo-controlled, crossover trial. They found stump pain was significantly reduced with IV lidocaine, yet phantom pain was not, and the stump pain relief was short-lived. In a study of 24 patients with postherpetic neuralgia, Baranowski et al (1999) reported IV lidocaine provided significant pain reduction over placebo; however, the pain was not eliminated. Medrik-Goldberg et al (1999) evaluated 30 patients with sciatica in a randomized, double-blind, 3-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 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 trials of lidocaine and its oral analogs (i.e., mexiletine, tocainide, flecainide) for neuropathic pain treatment and found the drugs safely provided more pain relief

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than placebo and with similar effectiveness as other analgesics. Reviewers 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. Although adverse events were reported as 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 minutes) precludes its use for chronic pain and (2) all 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 events and the short duration of action, the health benefits of IV lidocaine remain unclear for chronic pain.

A retrospective analysis by Przeklasa-Muszynska et al (2016) examined the use of 3 to 25 IV infusions of lidocaine (5 mg/kg of body weight over 30 min) in 85 patients (57% women; mean age 63 years) with neuropathic pain. These disorders included: trigeminal neuralgia (n=18), chemo-induced peripheral neuropathy (n=6), post-herpetic neuralgia (n=16), diabetic neuropathy (n=7), persistent postoperative pain (n=21), and other pain syndromes, including phantom pains, mononeuropathies, compression neuropathies, central pain syndrome, CRPS, and facial neuropathy (n=17). A total of 814 infusions were delivered to 85 patients; however, treatment was discontinued in 4 patients after the first infusion due to the lack of efficacy. Assessment of pain using a NRS ranged from 0 to 10. Efficacy increased significantly with age (71-90 years, $p<0.05$). There was a correlation between treatment efficacy and the number of infusions (6-10 infusions, $p<0.01$) and the severity of pain (NRS range, 9-10; $p<0.001$). There was no correlation between treatment efficacy and the number of years patients had experienced pain symptoms (range, 19-30 years; $p<0.05$). Reviewers reported that infusions were not interrupted due to adverse events; however, they did not report whether adverse effects occurred. Additionally, the authors reported no study limitations. It should be noted that use of single pain assessment tools may not be useful in measuring pain over time because patients may develop coping strategies for pain, acceptance, and tolerance of chronic pain; moreover, patients may have anxiety about reporting pain.

Spinal Cord Injury

In a double-blind, placebo-controlled, crossover study of 16 patients either poststroke or spinal cord injury, Attal et al (2000) reported IV lidocaine significantly reduced pain over placebo. However, the duration of this reduction lasted only 45 minutes. The 2005 literature review update identified a randomized, double-blind crossover trial of IV lidocaine in 24 patients with spinal cord injury-related neuropathic pain. In this trial, spontaneous and evoked pain were significantly reduced as measured on a VAS, as administered before infusion and 25 to 35 minutes after infusion initiation. Mostly mild adverse events (experienced by 19 patients) and 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, thus limiting interpretation of results. This concern about successful blinding also suggests the need for an active placebo in future trials, as noted. The authors concluded that IV lidocaine (and similar agents) may be a treatment option for spinal cord injury pain—although, the authors also noted that long-term treatment with lidocaine is usually not suitable.

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Section Summary: Lidocaine for Chronic Pain

The evidence for IV anesthetics in patients with CRPS, fibromyalgia, chronic headache, chronic neuropathic pain, or spinal cord injury includes several RCTs, systematic reviews, and a recent retrospective analysis of a range of neuropathic conditions. Evidence suggests that courses of IV lidocaine may provide temporary pain relief, particularly in elderly patients at a low dose (5 mg/kg of body weight over 30 min). However, there is little data on long-term usage. Additionally, there are limitations to measuring pain over time in retrospective studies, particularly without the use of multiple assessment tools (this is because patients may develop coping strategies for pain, acceptance, and tolerance of chronic pain; moreover, patients might have anxiety about reporting pain). Intense treatment protocols, the presence of severe adverse events, and limited durability raise questions about the net health benefit.

Ketamine

A 2003 systematic review of the treatment of chronic neuropathic pain with IV ketamine assessed the quality of evidence for ketamine's effectiveness in central pain, CRPS, fibromyalgia, ischemic pain, nonspecific pain of neuropathic origin, acute pain in patients with chronic neuropathic pain, orofacial pain, phantom/stump pain, and postherpetic neuralgia. 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 its routine use for patients with chronic pain. Of particular concern were the significant adverse events of this NMDA receptor antagonist in the central and peripheral nervous systems. Few data were available on appropriate dosing and long-term administration.

A prospective, randomized, double-blind, double-dummy trial published in 2017 by Motov et al compared IV low-dose ketamine (as a push dose over 5 min) with short infusion (over 15 min) in a convenience sample of 48 patients in an emergency department setting (n=24 push group; n=24 drip group). There were similar pain scores at baseline (NRS score, 8). From baseline to 15 min, the NRS score decreased in the IV push group 5.17 (95% CI, 3.67 to 6.66) and in the short infusion group 5.75 (95% CI, 4.28 to 7.22; p=0.026). Adverse events were similar in both groups. However, the sample size was inadequate to evaluate safety variances between the 2 routes of drug administration.

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. Sixteen studies on bisphosphonates, calcitonin, NMDA analogues, analgesics, vasodilators, steroids, anticonvulsive agents, and radical scavengers were included in the analysis. Of these, only bisphosphonates, NMDA analogues (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), the latter of which is described below.

The same 16 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; however the effects of such a course were not sustained beyond 4 to 11 weeks posttreatment.

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The largest double-blind RCT of ketamine for CRPS was the aforementioned European report by Sigtermans et al. Sixty patients were randomized 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 adverse events. Two patients terminated ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, NRS scores for pain 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. Moreover, 60% of 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. 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 patients received a second infusion, with a reported mean relief duration of 25 months (median, 36 months). Dosing was titrated by the occurrence of adverse events, 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. Symptoms were either long-standing (range, 6-68 months), spreading, rapidly progressive, refractory to conventional nonmedical (physical therapy, psychological approaches), or pharmacologic (mono- or combined therapy); further, at least 3 interventional treatments included selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, IV regional sympathetic blocks, spinal cord stimulation, surgical sympathectomy, or intrathecal drug delivery systems. 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 adverse events. All patients received IV low-dose heparin, the proton pump inhibitor pantoprazole, and clonidine to control cardiovascular and psychomimetic adverse events 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 then at 1, 3, and 6 months after treatment. Pain intensity decreased from a NRS score 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; three,

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severe impairment; six, moderate impairment; and ten, no impairment. Impairment in the ability to work was rated at baseline as complete by 11, severe by 5, and moderate by 4 patients. At 6 months, 2 patients remained unable to work, 4 had moderate impairment, and 14 patients reported no impairment. Psychotropic adverse events 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 up to 4 to 6 weeks posttreatment. As indicated by the authors, a strong placebo response to this intensive intervention was 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 IV infusions. 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). 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 score for pain of greater than 50% than in the placebo group (8 vs 3). There were no significant differences between the groups at 180 minutes after infusion (6 vs 3), at the end of week 1 (2 vs 0), or at the 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). 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. 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 score 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. Adverse events, which included confusion and hallucination, were considered

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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 line. With an average infusion duration of 16 days, pain severity decreased 38% (VAS range, 7.7-4.8) with an 85% response rate. About half of the patients reported a perceived benefit 1 month after treatment. Adverse events included fatigue, dizziness, confusion, and spinal pain. No patients reported hallucinations.

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. This randomized, double-blind, placebo-controlled crossover trial 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. Adverse events were common with both active treatments; ketamine produced 39 adverse events in 9 of 10 subjects. They 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) 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 both groups at baseline (VAS of 84 of 100). During the week of infusion, VAS scores decreased more in the ketamine-infused group than in 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.

Section Summary: Ketamine for Chronic Pain

Evidence, primarily from outside of the United States, has suggested that courses of IV ketamine both as a push dose or short infusion may provide temporary relief to some chronic pain patients in some settings. However, the intense treatment protocols, the severity of adverse effects, and the limited treatment durability raise 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.

PSYCHIATRIC DISORDERS

There is very limited evidence on the use of lidocaine or ketamine for treatment of psychiatric disorder such as depression and obsessive-compulsive disorder.

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SUMMARY OF EVIDENCE

For individuals who have chronic pain syndromes (e.g., CRPS, fibromyalgia, headache, neuropathic pain, spinal cord injury) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence includes several RCTs. Relevant outcomes are 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, has suggested that courses of IV lidocaine and ketamine may provide—at least temporary—relief to some chronic pain patients. However, the intense treatment protocols, the severity of adverse events, and the limited treatment 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.

For individuals who have psychiatric disorders (e.g., depression, obsessive-compulsive disorder) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence is limited. Relevant outcomes are 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, “Intravenous Anesthetics for the Treatment of Chronic Pain”, 5.01.16, 11:2017.
2. Attal N, Gaude V, Brasseur L, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. *Neurology*. Feb 8 2000;54(3):564-574. PMID 10680784
3. Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage*. Jun 1999;17(6):429-433. PMID 10388248
4. Kvarnstrom A, Karlsten R, Quiding H, et al. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. *Acta Anaesthesiol Scand*. Aug 2003;47(7):868-877. PMID 12859309
5. Medrik-Goldberg T, Lifschitz D, Pud D, et al. Intravenous lidocaine, amantadine, and placebo in the treatment of sciatica: a double-blind, randomized, controlled study. *Reg Anesth Pain Med*. Nov-Dec 1999;24(6):534-540. PMID 10588558
6. Sorensen J, Bengtsson A, Ahlner J, et al. Fibromyalgia--are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs. *J Rheumatol*. Aug 1997;24(8):1615-1621. PMID 9263160
7. Wallace MS, Ridgeway BM, Leung AY, et al. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. *Anesthesiology*. Jan 2000;92(1):75-83. PMID 10638902
8. Wu CL, Tella P, Staats PS, et al. Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial. *Anesthesiology*. Apr 2002;96(4):841-848. PMID 11964590
9. Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. *Clin J Pain*. May 2011;27(4):285-288. PMID 21178598
10. Reutens DC, Fatovich DM, Stewart-Wynne EG, et al. Is intravenous lidocaine clinically effective in acute migraine? *Cephalalgia*. Dec 1991;11(6):245-247. PMID 1790567
11. Hand PJ, Stark RJ. Intravenous lignocaine infusions for severe chronic daily headache. *Med J Aust*. Feb 21 2000;172(4):157-159. PMID 10772585
12. Williams DR, Stark RJ. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. *Cephalalgia*. Dec 2003;23(10):963-971. PMID 14984229
13. Tremont-Lukats IW, Hutson PR, Backonja MM. A randomized, double-masked, placebo-controlled pilot trial of extended IV lidocaine infusion for relief of ongoing neuropathic pain. *Clin J Pain*. Mar-Apr 2006;22(3):266-271. PMID 16514327

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14. Carroll I, Gaeta R, Mackey S. Multivariate analysis of chronic pain patients undergoing lidocaine infusions: increasing pain severity and advancing age predict likelihood of clinically meaningful analgesia. *Clin J Pain*. Oct 2007;23(8):702-706. PMID 17885349
15. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. *Cochrane Database Syst Rev*. Oct 19 2005(4):CD003345. PMID 16235318
16. Tremont-Lukats IW, Challapalli V, McNicol ED, et al. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. *Anesth Analg*. Dec 2005;101(6):1738-1749. PMID 16301253
17. Rathmell JP, Ballantyne JC. Local anesthetics for the treatment of neuropathic pain: on the limits of meta-analysis. *Anesth Analg*. Dec 2005;101(6):1736-1737. PMID 16301252
18. Przeklasa-Muszynska A, Kocot-Kepska M, Dobrogowski J, et al. Intravenous lidocaine infusions in a multidirectional model of treatment of neuropathic pain patients. *Pharmacol Rep*. Oct 2016;68(5):1069-1075. PMID 27552062
19. Finnerup NB, Biering-Sorensen F, Johannesen IL, et al. Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. *Anesthesiology*. May 2005;102(5):1023-1030. PMID 15851891
20. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg*. Dec 2003;97(6):1730-1739. PMID 14633551
21. Motov S, Mai M, Pushkar I, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. *Am J Emerg Med*. Aug 2017;35(8):1095-1100. PMID 28283340
22. Wertli MM, Kessels AG, Perez RS, et al. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. *Pain Med*. Sep 2014;15(9):1575-1589. PMID 25234478
23. Schwartzman RJ, Alexander GM, Grothusen JR, et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*. Dec 15 2009;147(1-3):107-115. PMID 19783371
24. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain*. Oct 2009;145(3):304-311. PMID 19604642
25. O'Connell NE, Wand BM, McAuley J, et al. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*. 2013;4:CD009416. PMID 23633371
26. Correll GE, Maleki J, Gracely EJ, et al. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med*. Sep 2004;5(3):263-275. PMID 15367304
27. Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. *Pain Med*. Nov 2008;9(8):1173-1201. PMID 18266808
28. Noppers IM, Niesters M, Aarts LP, et al. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. *Pain*. Sep 2011;152(9):2173-2178. PMID 21546160
29. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain*. Oct 2011;15(9):942-949. PMID 21482474
30. Eichenberger U, Neff F, Svetlic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg*. Apr 2008;106(4):1265-1273, table of contents. PMID 18349204
31. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med*. Feb 2012;13(2):263-269. PMID 21939497
32. Webster LR, Walker MJ. Safety and efficacy of prolonged outpatient ketamine infusions for neuropathic pain. *Am J Ther*. Jul-Aug 2006;13(4):300-305. PMID 16858163
33. Kvarnstrom A, Karlsten R, Quiding H, et al. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. *Acta Anaesthesiol Scand*. Apr 2004;48(4):498-506. PMID 15025615
34. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. *Pain Physician*. May-Jun 2010;13(3):245-249. PMID 20495588
35. American Society of Anesthesiologists Task Force on Chronic Pain M, American Society of Regional Anesthesia and Pain Medicine, Pain M. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*. Apr 2010;112(4):810-833. PMID 20124882

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 02/17/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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