Medical Policies - Surgery

Print

Intravenous Anesthetics for the Treatment of Pain and Psychiatric Disorders

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CAREFULLY CHECK STATE REGULATIONS AND/OR THE MEMBER CONTRACT

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and nationally recognized authoritative references. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage 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, or fibromyalgia, **is considered experimental, investigational and/or unproven.**

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for psychiatric disorders (e.g., depression, obsessive-compulsive disorder) **is considered experimental, investigational and/or unproven.**

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of pain associated with acute or chronic migraine headache **is considered experimental, investigational and/or unproven.**

Description:

Intravenous (IV) infusion of lidocaine or ketamine has been investigated for the treatment of migraine and chronic daily headache, fibromyalgia, and chronic neuropathic pain. Chronic neuropathic pain disorders include phantom limb pain, post-herpetic neuralgia, complex regional pain syndrome, diabetic neuropathy, and pain related to stroke or spinal cord injuries. An IV infusion of ketamine has also been investigated for the treatment of depression and obsessive-compulsive disorder. For these applications, one or more courses of IV infusion would be administered over several hours or several days.

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.

Indications

IV administration of anesthetic has been reported for various conditions, including migraine, chronic pain of neuropathic origin, chronic headache, fibromyalgia, depression, and obsessive-compulsive disorders.

Migraine is a common headache disorder with a prevalence in the United States (U.S.) of approximately 18% in women and 6% in men. (1) According to the International Headache Society, migraine headache is a recurrent disorder with attacks lasting 4 to 72 hours. Typical features of migraine headaches include unilateral location, pulsating quality, moderate or severe intensity, and associated symptoms such as nausea, photophobia, and/or phonophobia. (2)

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 complex regional pain syndrome (CRPS) and 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.

Regulatory Status

IV lidocaine is approved by the United States (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 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.

Rationale:

This policy was created in 2012 and has been updated periodically with searches of the MEDLINE database. The most recent literature update was performed through September 6, 2018.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Intravenous Anesthetics for Migraine Headache Pain and Chronic Pain Syndromes

Clinical Context and Test Purpose

The purpose ofa course of intravenous (IV) anesthetics (e.g., lidocaine, ketamine)is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with migraine (acute or chronic) headache pain and chronic pain syndromes (e.g.,complex regional pain syndrome [CRPS],fibromyalgia, chronic headache, neuropathic pain, spinal cord injury).

The question addressed in this medical policy is: Doesa course ofIVanesthetics improve the net health outcome in individuals with migraine (acute or chronic) headache pain and chronic pain syndromes (e.g., CRPS, fibromyalgia, chronic headache, chronic neuropathic pain, spinal cord injury)?

The following PICOTS were used to select literature to inform this policy.

Patients

The relevant populations of interestareindividuals withmigraine headache pain or chronic pain syndromes (e.g.,CRPS,fibromyalgia, chronic headache, neuropathic pain, spinal cord injury).

Interventions

The therapy being considered isa course of IV anesthetics (e.g., lidocaine, ketamine).

Comparators

The following therapy is currently being used to treatmigraine headache pain and chronic pain syndromes:oral pain medication.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Timing

Follow-up at 4 weeks is of interest to monitor for outcomes.

Setting

Patients withchronic pain syndromesare actively managed byphysical therapists, neurologists, and primary care providers in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with apreferencefor prospective studies;
- To assesslonger termoutcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Lidocaine

Early studies (1994 through February 2004) revealed that the degree and duration of pain relief with IV lidocaine does not appear to be clinically significant in most patients. (3-9) 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 prior to 2005 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. 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 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 (CRPS)

Tables 1 and 2 summarize the characteristics and results of selected RCTs.

Table 1. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Kim et al. (2018) (10)	South Korea	1	2015-2016	Patients had PHN or CRPS type II with an	21 patients received IV lidocaine 3 mg/kg	21 patients received IV saline for 4

				11-point NRS score of 4 or ≥3 months without pain relief from conservative treatment	for 4 weekly treatments of 1 hour each	weekly treatments of 1 hour each
Wallace et al. (2000) (8)	U.S.	1	NR	Patients had CRPS type I or II with allodynia	Patients received IV infusion of lidocaine and diphenhydramine separated by 1 week	Treatment order reversed

CRPS: complex regional pain syndrome; IV: intravenous; NRS: numeric rating scale; NR: not reported; PHN: postherpetic neuralgia.

Table 2. Summary of Key Randomized Controlled Trial Results

Study	**Lidocaine Dose, mg**	**Plasma Level**		**Effect of Lidocaine on Allodynia and Pain Scores**	**Reduction in NRS Pain Score (SD), %[a]**	**AEs**
		Measured	Targeted			
Kim et al. (2018) (10)						
N					42	42
LIT group					48.71 (40.59)	3 mild
Control group					19.51 (27.27)	4 mild
p					0.011	0.698
Wallace et al. (2000) (8)						
N	16	16		16		
Means (SD), μg/mL	488 (98)	• 1.6 • 2.4 • 3.4 • 1 • 2 • 3 • 8 (50%) reported pain to cold stimuli • Significantly decreased response to stroking and cold allodynia				
Range, μg/mL	329-700	• 0.8-1.8 • 1.4-3.9				

		• 2.4-4.8				

AE: adverse event; LIT: lidocaine infusion therapy; NRS: numeric rating scale: SD: standard deviation.

[a] Measured from baseline to after the final infusion.

Kim et al. (2018) published a prospective, randomized, double-blind, placebo-controlled trial evaluating 43 patients with postherpetic neuralgia (PHN) or CRPS who were randomized to lidocaine or placebo (saline) in 4 weekly infusions. (10) The groups did not differ significantly at weeks 1 and 2 in a reduction in pain; however, there were between-group differences after weeks 3 and 4 (respectively, p=0.001 and p=0.009). In the lidocaine-treated group, there was a significantly greater reduction in pain following the final infusion compared with the placebo group (p=0.011). However, this difference in the percentage of pain reduction was not reported at follow-up assessments in 1 and 4 weeks after the final infusion, suggesting only a temporary analgesic effect.

Wallace et al. reported on a randomized, double-blind, placebo-controlled study of 16 patients with CRPS types I and II. (8) While IV lidocaine significantly reduced the pain response to cool stimuli, mechanical pain relief was not significantly improved.

The purpose of the gaps table (see Table 3) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following the table and provides the conclusions on the sufficiency ofevidencesupporting the position statement.

Table 3. Relevance Gaps

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kim et al. (2018) (10)	4. Patients with PHN and CRPS were included		2. Did not use active placebo (diphenhydramine)	4. Did not measure plasma concentration of lidocaine during infusions	
Wallace et al. (2010) (8)					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CRPS: complex regional pain syndrome; PHN: postherpetic neuralgia.
[a]Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3.Studypopulation is unclear; 4. Study population not representative of intended use.

[b]Intervention key: 1. Not clearly defined; 2.Versionused unclear; 3. Delivery not similar intensity ascomparator; 4. Not the intervention of interest.

[c]Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity asintervention; 4. Not delivered effectively.
[d]Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e]Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Fibromyalgia

Vlainich et al. (2011) reported on a randomized, double-blind trial of IV lidocaine plus amitriptyline versus amitriptyline monotherapy in 30 patients with fibromyalgia. (11) 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).

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. (7) None of these patients responded to IV lidocaine alone.

Headache (including Migraine)

A small RCT from 1991 found no significant difference between IV lidocaine and placebo for the treatment of acute migraine. (12) No RCTs were identified that evaluate the long-term relief of chronic daily headache following IV infusion of lidocaine. Uncontrolled studies were identified (13, 14), but they do not provide sufficient evidence on the efficacy of IV lidocaine treatment for this condition.

Chronic Neuropathic Pain

A Cochrane review by Challapalli et al. (2005) 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 than placebo and with similar effectiveness as other analgesics. (15) 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. (16) Although AEs were reported as not significantly different from other active controls (amitriptyline, carbamazepine, gabapentin, and morphine), the severity and nature of the AEs could not be assessed. As indicated in an accompanying editorial by Rathmell and Ballantyne (2005), “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 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 AEs and the short duration of action, the health benefits of IV lidocaine remain unclear for chronic pain.

Tremont-Lukats et al. (2006) reported results of a randomized, double-blinded, placebo-controlled pilot trial in 32 subjects with ongoing neuropathic pain. (18) 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 AEs.

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. (5) The authors reported no significant differences in pain reduction over placebo on VAS.

Wu et al. (2002) evaluated the effects of IV lidocaine on 31 patients with post amputation pain in a randomized, double-blind, active placebo controlled, crossover trial. (9) 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 post herpetic neuralgia, Baranowski et al. (1999) reported IV lidocaine provided significant pain reduction over placebo; however, the pain was not eliminated. (4) Medrik-Goldberg et al. (1999) evaluated 30 patients with sciatica in a randomized, double-blind, 3-arm crossover trial. (6) 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 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. (19) 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 numeric rating scale (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.

In a retrospective analysis by Carroll et al. (2007), 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 post treatment numeric rating scale for pain (range, 0-10). Mean pain reduction, measured on the NRS, during infusion was 2.34 (95% CI, 2.83 to 1.85, p<0.001). (20)

Spinal Cord Injury

Finnerup et al. (2005) reported on a randomized, double blind crossover trial of IV lidocaine in 24 patients with spinal cord injury-related neuropathic pain. (21) In this trial, spontaneous and evoked pain were significantly reduced as measured on a visual analog scale (VAS), as administered before infusion and 25 to 35 minutes after infusion initiation. Mostly mild AEs (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 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 they noted, long-term treatment with lidocaine is usually not suitable.

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. (3) However, the duration of this reduction lasted only 45 minutes.

Tables 4 and 5 summarize the characteristics and results of selected RCTs on spinal cord injury.

Table 4. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Finnerup et al. (2005) (21)	Denmark		2002-2003	24 adults with neuropathic pain from trauma, spinal cord disease, or cauda equine with median pain intensity of 3 on 10-point NRS	23 patients received lidocaine 5 mg/kg over 30 minutes; 1 patient had adverse events and received only 4.75 mL/kg in 28.5 minutes	NR
Attal et al. (2000) (3)	France		NR	16 patients with poststroke or SCI pain	Patients received lidocaine 5 mg/kg or saline for 30 minutes[a]	3 wk after second infusion, patients received mexiletine 200 mg/day

NR: not reported; NRS: numeric rating scale; SCI: spinal cord injury.

[a] Two treatments were performed in separate sessions 3 weeks apart.

Table 5. Summary of Key Randomized Controlled Trial Results

Study	Effect on Spontaneous Pain (VAS)[a]	Proportion With VAS Score Decrease≥50%, n/N	Median Difference in Pain Reduction (95% CI)	Responders to Treatment, n	Patient-Reported Pain Relief During Treatment, n
Finnerup et al. (2005) (21)					
N	24		24	24	24
Lidocaine	NR			11	19
Placebo	NR			2	4
Between group comparison	Significantly greater reduction in pain for lidocaine vs placebo (p<0.01)		Overall: 36% (18% to 50%) Group with evoked pain: 40% (13% to 58%) Group without evoked pain: 35% (9% to 59%)	p=0.008	p<0.01
Attal et al. (2000) (3)					
N	16	16			
Lidocaine, mean (SD)	Preinjection: 61 (18) Postinjection 31 (28)	• End of injection: 10/16 • 30 min[a]: 7/16 • 60 min[a]: 4/16			
Placebo, mean (SD)	Preinjection: 61 (17) Postinjection 46 (24)	• End of injection: 6/16 • 30 min[a]: 4/16 • 60 min[a]: 3/16			

CI: confidence interval; min: minutes; N: number; NR: not reported; VAS: visual analog scale.
[a]Length of time afterendof injection.

Section Summary: Lidocaine for Migraine Headache Pain and Chronic Pain Syndromes

The evidence for IV anesthetics in patients with migraine, CRPS, fibromyalgia, chronic headache, chronic neuropathic pain, or spinal cord injury includes several randomized controlled trials, 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 for Migraine Headache Pain and Chronic Pain Syndromes

A systematic review by Hocking and Cousins (2003) on 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. (22) 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 *N*-methyl-D-aspartate (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. (2017) 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). (23) 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 by Wertli et al. (2014) evaluated the efficacy of all agent classes investigated in RCTs and provided a rank order of various substances. (24) 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 in further detail below. (25, 26)

These 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, although the effects were not sustained beyond 4 to 11 weeks' posttreatment. (27)

Tables 6 and 7 summarize the characteristics and results of selected RCTs.

Table 6. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparators
Sigtermans et al. (2009) (26)	NL	1	2006-2008	Patients were diagnosed with CRPS type I	30 patients randomized to ketamine infused over 4 days (titrated up to 30 mg/hour for a 70-kg patient)	30 patients randomized to saline infused over 4 days

CRPS: complex regional pain syndrome; NL: Netherlands.

Table 7. Summary of Key Randomized Controlled Trial Results

Study	Mean Change in NRS Pain Score, Baseline to End of Week 11	Differences in Pain Reduction	Side Effects During Infusion, %

	(SD)		
Sigtermans et al. (2009) (26)			
N	60	60	60
Ketamine	7.20 (1.16) to 2.68 (0.51)		• Nausea: 63 • Vomiting: 47 • Psychomimetic effects: 93 • Headache: 37
Placebo	6.87 (1.43) to 5.45 (0.48)		• Nausea: 17 • Vomiting: 10 • Psychomimetic effects: 17 • Headache: 33
		Maintained until week 11; at week 12, ketamine's treatment effect no longer significant (p=0.07)	• Nausea: p<0.001 • Vomiting: p=-0.004 • Psychomimetic effects: p<0.001 • Headache: p=0.78

N: number; NRS: numeric rating scale.

A large double-blind RCT of ketamine for CRPS is the aforementioned European report by Sigtermans et al. (26) 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 ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, numeric rating scale 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. 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.

No relevance, study design, and conduct gaps were identified for this set of RCTs.

Fibromyalgia

Noppers et al. (2011) reported on a randomized, double-blind, active placebo-controlled trial that was conducted in Europe using a 30-minute infusion of 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% than in the placebo group (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 Pain

A study by Eichenberger et al. (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.

Tables 8 and 9 summarize the characteristics and results of selected observational studies.

Table 8. Summary of Key Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Patil & Anitescu (2012) (30)	Retrospective chart review	U.S.	2004-2009	Patients with CRPS, refractory headaches, or severe back pain	Ketamine 0.5 mg/kg over 30-45 minutes	NR
Webster & Walker (2006) (31)	Retrospective	U.S.	2002-2004	Patients with severe neuropathic pain treated with prolonged IV ketamine	Ketamine 100 mg/mL; mean duration of infusion treatment, 16.4 days (range, 5-55 days)	NR

CRPS: complex regional pain syndrome; IV: intravenous; NR: not reported.

Table 9. Summary of Key Observational Comparative Study Results

Study	Decrease in VAS From Start of Infusion to Discontinuation	Global Pain Relief From Baseline to EOT	Adverse Events
Patil & Anitescu (2012) (30)			
N	49	49	49
Patient-reported, n (%)			23 (46.9) reported; 35 nonserious
Mean reduction in VAS (SE)	5.9 (0.35)		
Webster & Walker (2006) (31)			
N	13	13	13
Patient-reported, n (%)	11 (85)	• Improvement: 8 (62) • No improvement: 3 (23) • Decrease in relief: 2 (15) • Irritation from delivery: 5 (38) • Fatigue: 4 (31) • Dizziness: 3 (23) • Confusion: 2 (15) • Spinal pain: 2 (15)	
Mean VAS score	• 7.7 at baseline • 4.8 at EOT (p=0.003)		

EOT: end of treatment; VAS: visual analog scale.

Patil and Anitescu (2012) retrospectively analyzed data from 49 patients with severe refractory pain who had undergone 369 outpatient ketamine infusions during a 5-year period at a U.S. academic medical center. (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. Adverse events, which included confusion and hallucination, were considered minimal.

Webster and Walker (2006) published a retrospective analysis describing 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 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

Amr (2010) 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. (32) 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 the 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.

Kvarnstrom et al. (2004) assessed the effect of subanesthetic levels of IV ketamine or lidocaine on pain after spinal cord injury. (33) 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. AEs were common with both active treatments; ketamine produced 39 AEs in 9 of 10 subjects. They included somnolence, dizziness, out-of-body sensation, changes in hearing and vision, paresthesia, and other “unpleasant experiences.”

Section Summary: Ketamine for Migraine Headache Pain and Chronic Pain Syndromes 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.

Intravenous Anesthetics for Psychiatric Disorders

Clinical Context and Test Purpose

The purpose ofa course of IV anesthetics (e.g., lidocaine, ketamine)is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with psychiatric disorders (e.g., depression, obsessive-compulsive disorder).

The question addressed in this medical policy is: Doesa course ofIVanesthetics improve the net health outcome in individuals withpsychiatric disorders (e.g., depression, obsessive-compulsive disorder)?

The following PICOTS were used to select literature to inform this policy.

Patients

The relevant population of interest is individuals withpsychiatric disorders (e.g., depression, obsessive-compulsive disorder).

Interventions

The therapy being considered isa course of IV anesthetics (e.g., lidocaine, ketamine).

Comparators

The following therapy is currently being used to treat psychiatric disorders:psychotropic medication.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity.

Timing

Though not completely standardized, follow-up forpsychiatric disorderssymptoms would typically occur in the months to years after starting treatment.

Setting

Patients withpsychiatric disordersare actively managed by psychiatrists and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with apreferencefor prospective studies;
- To assesslonger termoutcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Clinical Studies

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

Section Summary: Intravenous Anesthetics for Psychiatric Disorders

Current evidence does not support the utility of IV anesthetic injections for patients with psychiatric disorders.

Summary of Evidence

For individuals who have migraine headache pain or chronic pain syndromes (e.g., complex regional pain syndrome, fibromyalgia, headache, neuropathic pain, spinal cord injury) who receive a course of intravenous (IV) anesthetics (e.g., lidocaine, ketamine), the evidence includes several randomized controlled trials. 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, 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.

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.

Practice Guidelines and Position Statements

American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine

The practice guidelines on managing chronic pain from the American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine (2010) discussed various treatments for chronic pain. (34) Use of ionotropic *N*-methyl-D-aspartate receptor antagonists and topical agents for neuropathic pain was addressed; IV infusion of lidocaine or ketamine was not.

American Headache Society

The American Headache Society position statement (2018) on integrating new preventive and acute migraine treatments into clinical practice does not mention IV anesthetic use for treatment of acute migraine. (35)

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 10.

Table 10: Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02299440	Evaluation of the Effects of Ketamine in the Acute Phase of Suicidal Ideation: a Multicenter Randomized Double-blind trial.	156	April 2019
Unpublished			
NCT01371110	Intravenous Ketamine in the Treatment of Obsessive-Compulsive Disorder.	3	Jun 2015 (terminated)
NCT01920555	Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in Treatment-Resistant Depression (TRD).	99	Feb 2017 (completed)
NCT02106325	A Randomized, Double-Blinded Controlled Trial of an N-Methyl D-Aspartate Antagonist as a Rapidly-Acting Antidepressant in Depressed Emergency Department Patients.	28	Mar 2017 (completed)

NCT: national clinical trial.

Contract:

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coding:

CODING:

Disclaimer for coding information on Medical Policies

Procedure and diagnosis codes on Medical Policy documents are included only as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, device or diagnosis codes in a Medical Policy document has **no** relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a medical policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT/HCPCS/ICD-9/ICD-10 Codes
The following codes may be applicable to this Medical policy and may not be all inclusive.
CPT Codes
96365, 96366, 96374
HCPCS Codes
J2001
ICD-9 Diagnosis Codes
Refer to the ICD-9-CM manual
ICD-9 Procedure Codes
Refer to the ICD-9-CM manual
ICD-10 Diagnosis Codes
Refer to the ICD-10-CM manual
ICD-10 Procedure Codes
Refer to the ICD-10-CM manual

Medicare Coverage:

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

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Policy History:

Date	Reason
8/15/2020	Reviewed. No changes.
9/1/2019	Document updated with literature review. The following statements were added to Coverage: 1) Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for psychiatric disorders (e.g., depression, obsessive-compulsive disorder) is considered experimental, investigational and/or unproven; and 2) Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of pain associated with acute or chronic migraine headache is considered experimental, investigational and/or unproven. Added references: 1-2, 10, and 35. Title changed from “Intravenous Anesthetics for the Treatment of Chronic Pain”.
4/15/2018	Document updated with literature review. Coverage unchanged. References 17 and 20 added.
4/15/2017	Reviewed. No changes.

4/1/2016 Document updated with literature review. The following condition was added to the EIU listing in Coverage; Chronic daily headache. Otherwise coverage unchanged.

4/1/2015 Reviewed. No changes.

4/15/2014 Document updated with literature review. Coverage unchanged.

8/15/2012 New Medical Document

Archived Document(s):

Title:	Effective Date:	End Date:
Intravenous Anesthetics for the Treatment of Pain and Psychiatric Disorders	09-01-2019	08-14-2020
Intravenous Anesthetics for the Treatment of Chronic Pain	04-15-2018	08-31-2019
Intravenous Anesthetics for the Treatment of Chronic Pain	04-15-2017	04-14-2018
Intravenous Anesthetics for the Treatment of Chronic Pain	04-01-2016	04-14-2017
Intravenous Anesthetics for the Treatment of Chronic Pain	04-01-2015	03-31-2016
Intravenous Anesthetics for the Treatment of Chronic Pain	04-15-2014	03-31-2015
Intravenous Anesthetics for the Treatment of Chronic Pain	08-15-2012	04-14-2014