5.01.16	Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders		
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Section:	5.0 Prescription Drug	**Page:**	Page 1 of 17

Policy Statement

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) is considered **investigational** for the treatment of chronic pain, including, but not limited to:

- Chronic neuropathic pain
- Chronic daily headache
- Fibromyalgia

Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) is considered **investigational** for the treatment of psychiatric disorders, including but not limited to:

- Depression
- Obsessive-compulsive disorder

Policy Guidelines

- N/A

Description

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

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

IV lidocaine is approved by the U.S. Food and Drug Administration for systemic use in the acute treatment of arrhythmias and locally as an anesthetic; IV lidocaine for the treatment of chronic pain or psychiatric disorders is considered off-label use.

Ketamine hydrochloride injection is approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia before the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide. IV ketamine for the treatment of chronic pain or psychiatric disorders is an off-label use.

Rationale

Background

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. Treatment protocols for the initial cycle may include infusion of subanesthetic doses of one to six hours for up to ten days.

Lidocaine

Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. Adverse 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 events may include arrhythmias, seizures, loss of consciousness, confusion, or even death. Lidocaine should only be given intravenously to patients with normal conduction on electrocardiography and normal serum electrolyte concentrations to minimize the risk of cardiac arrhythmias.

Ketamine

Ketamine is an antagonist of the *N*-methyl-d-aspartate receptor and a dissociative anesthetic. It is the sole anesthetic agent approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Respiratory depression may occur with overdosage or too rapid a rate of administration of ketamine. Ketamine is a schedule III controlled substance. Psychological manifestations vary in severity from pleasant, dream-like states to hallucinations and delirium; further, these manifestations can be accompanied by confusion, excitement, aggression, or irrational behavior. The occurrence of adverse events with IV anesthetics may be reduced by the careful titration of subanesthetic doses. However, the potential benefits must be carefully weighed against the potential for serious, harmful adverse events.

Indications

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

Chronic daily headache is defined as a headache disorder that occurs more than 15 days a month for at least 3 months. Chronic daily headache includes chronic migraine, new daily persistent headache, hemicranias continua, and chronic tension-type headache.

Neuropathic pain is often disproportionate to the extent of the primary triggering injury and may consist of thermal or mechanical allodynia, dysesthesia, and/or hyperalgesia. Allodynia is pain that occurs from a stimulus that normally does not elicit a painful response (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 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 *N*-methyl-d-aspartate receptors in the peripheral and central nervous system. Sympathetic ganglion blocks with lidocaine have been used to treat sympathetically maintained chronic pain conditions, such as complex regional pain syndrome (previously known as reflex sympathetic dystrophy). Test infusion of an anesthetic has also been used in treatment planning to assess patient responsiveness to determine whether medications, such as oral mexiletine or oral ketamine, may be effective. A course of IV lidocaine or ketamine, usually at subanesthetic doses, has also been examined. This approach for treating chronic neuropathic pain differs from continuous subcutaneous or IV infusion of anesthetics for managing chronic pain conditions, such as terminal cancer pain, which is not discussed herein.

Fibromyalgia is a chronic state of widespread pain and tenderness. Although fibromyalgia is generally considered to be a disorder of central pain processing or central sensitization, others have proposed that the nerve stimuli causing pain originates mainly in the muscle, causing both widespread pain and pain on movement. There are focal areas of hyperalgesia, or tender points, which tend to occur at muscle-tendon junctions. Biochemical changes associated with fibromyalgia include alterations in *N*-methyl-d-aspartate receptors, low levels of serotonin, suppression of dopamine-releasing neurons in the limbic system, dysfunction of the hypothalamic-pituitary-adrenal axis, and elevated substance P levels. Fibromyalgia is typically treated with neuropathic pain medications such as pregabalin, non-narcotic pain relievers, or low doses of antidepressants.

The use of IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications. Particularly challenging are patients with treatment-resistant depression with suicidal ideation. Several studies are ongoing to test the efficacy of IV ketamine in patients with suicidal ideation who present to the emergency department.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function- including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, two 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 Individuals with Chronic Pain

Clinical Context and Test Purpose

The purpose of a 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 chronic pain syndromes (e.g., complex regional pain syndrome [CRPS], fibromyalgia, headache, neuropathic pain, spinal cord injury).

The question addressed in this evidence review is: Does a course of IV anesthetics improve the net health outcome in individuals with chronic pain syndromes?

The following PICOs were used to select literature to inform this review.

Patients

The relevant populations of interest are individuals with chronic pain syndromes (e.g., CRPS, fibromyalgia, headache, neuropathic pain, spinal cord injury).

Interventions

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

Comparators

The following therapy is currently being used to treat chronic pain syndromes: oral pain medication.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity.
Follow-up of at least four weeks is of interest to monitor for outcomes.

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;
- To assess long-term outcomes 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.
- Studies with short-term outcomes (<24 h) were excluded.

Neuropathic Pain

Systematic Reviews

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.[1,] Sixteen studies on bisphosphonates, calcitonin, *N*-methyl-d-aspartate analogues, analgesics, vasodilators, steroids, anticonvulsive agents, and radical scavengers were analyzed. Of these, only bisphosphonates, *N*-methyl-d-aspartate analogues (ketamine), and vasodilators showed better long-term pain reduction than placebo. The 2 RCTs on ketamine were reported by Schwartzman et al (2009) (n=19) and Sigtermans et al (2009) (n=60), the latter of which is described below.[2,3,]

The same 16 studies were selected by O'Connell et al (2013) in a Cochrane overview of interventions for CRPS, which found low-quality evidence that a course of IV ketamine may be effective for CRPS-related pain; the effects of such a course were not sustained beyond 4 to 11 weeks posttreatment.[4,]

Randomized Controlled Trials

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

Lidocaine

Several RCTs have been performed using intravenous lidocaine for postherpetic neuralgia (PHN), CRPS, and diabetic neuropathy. These trials have failed to show a durable effect of lidocaine infusion on chronic pain.

Kim et al (2018) published a prospective, randomized, double-blind, placebo-controlled trial evaluating 43 patients with PHN or CRPS who were randomized to lidocaine or placebo (saline) in 4 weekly infusions.[5] The groups did not differ significantly at weeks one and two in a reduction in pain; however, there were between-group differences after weeks three and four (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 one and four weeks after the final infusion, suggesting only a temporary analgesic effect.

Liu et al (2018) randomized 189 patients with PHN to a single 1 1/2 hour infusion of lidocaine with an injection of midazolam and granisetron.[6] Patients were also taking pregabalin and oxycodone as needed. The control group received saline with midazolam and granisetron. The study was double-blind with allocation concealment and an independent assessor. Pain scores decreased from baseline in both groups, but there was no significant difference in scores between the lidocaine and placebo groups. However, patients treated with a lidocaine infusion had a greater change in the 36-item Short Form Health Survey score (maximal at 1 week), and had a greater reduction in analgesic use (relative risk: 6.2 [95% confidence interval : 2.24 to 17.16]), with 26.6% of patients in the lidocaine group either decreasing or stopping use of analgesics compared to 2.2% of controls. Side effects were generally mild and did not differ between the groups. The main limitation of this study is the short infusion of lidocaine.

A randomized 4-week cross-over trial by Moulin et al (2019) found no significant differences between a single infusion of lidocaine (5 mg/kg over 45 minutes) and diphenydramine (active control) in patients (n=34) with primarily diabetic neuropathy.[7] This study is limited by the short infusion of lidocaine.

Ketamine

Two double-blind RCTs on ketamine for neuropathic pain were identified. One examined four days infusion in patients with CRPS[3], the second examined seven days infusion in patients with spinal cord injury.[8]

A double-blind RCT of ketamine for CRPS was reported by Sigtermans et al (2009).[3] Sixty patients were randomized to ketamine or saline, infused over four days. The mean ketamine infusion rate was 22 mg/h (normalized to a 70-kg patient) at the end of the treatment phase. Blood samples were collected to assess the plasma concentration of ketamine, and patients were monitored for adverse events. Two patients terminated ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, numeric rating scale (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 deduced treatment assignment (slightly better than chance); 93% of patients in the ketamine group correctly deduced treatment assignment due primarily to psychomimetic effects.

Amr (2010) published results from a double-blind, randomized, placebo-controlled study of 40 patients with neuropathic pain secondary to spinal cord injury.[8] Ketamine or saline were infused for five hours over seven days. All patients received gabapentin (300 mg) 3 times daily. Visual analog scale (VAS) scores for pain were similar in the ketamine and saline 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 four-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.

Table 1. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	***Comparator***
Lidocaine						
Kim et al (2018)[5,]	South Korea	1	2015-2016	Patients had PHN or CRPS type II with an 11-point NRS score of 4 or ≥3 mo without pain relief from conservative treatment	IV lidocaine 3 mg/kg for 4 weekly treatments of 1 h each (n=21)	IV saline for 4 weekly treatments of 1 h each (n=21)
Liu et al (2018)[6,]	China	1	2015-2017	189 patients with post-herpetic neuralgia and pain > 1mo with VAS >4	A single 1 1/2 h infusion of 5 mg/kg lidocaine, injection of 1.5 mg midazolam and 3 mg granisetron, also taking pregabalin and oxycodone	1 1/2 h infusion of saline, plus midazolam and granisetron, also taking pregabalin and oxycodone
Ketamine						
Sigtermans et al (2009)[3,]	NL	1	2006-2008	Patients were diagnosed with CRPS type I	30 patients randomized to ketamine infused over 4 d (titrated up to 30 mg/h for a 70-kg patient)	30 patients randomized to saline infused over 4 d
Amr[8,]	Egypt	1		40 patients with neuropathic pain secondary to spinal cord injury. Baseline mean VAS of 84	Ketamine infusion (80 mg) over a 5-hour period daily for 7 days, with gabapentin during and after infusion. (n=20)	Saline infusion over the same time period, with gabapentin during and after infusion. (n=20)

CRPS: complex regional pain syndrome; IV: intravenous; NL: Netherlands; NRS: numeric rating scale; PHN: postherpetic neuralgia; VAS: visual analog score.

Table 2. Summary of Key Randomized Controlled Trial Results

Study	Reduction in Pain Scores (SD), %	Reduction in NRS Pain Score (SD), %[a]	AEs
Lidocaine			
Kim et al (2018)[5,]	VAS (100 mm)		
N	42		42
lidocaine	48.71 (40.59)		3 mild
saline	19.51 (27.27)		4 mild
p-Value	0.011		0.698
Liu et al (2018)[6,]	VAS (10 cm) at 2 weeks	SF-36 at 1 week	
N	183		
Lidocaine	2.74	80.09 (7.64)	
Placebo	2.94	30.28 (7.07)	
p-Value	NS		
Ketamine			
Sigtermans et al (2009)[3,]	11 point NRS at 1 week		
N	60		60
Ketamine	2.68 (0.51)		Nausea: 63; Vomiting: 47;

Study	Reduction in Pain Scores (SD), %	Reduction in NRS Pain Score (SD), %[a]	AEs
			Psychomimetic effects: 93; Headache: 37
Placebo	5.45 (0.48)		Nausea: 17; Vomiting: 10; Psychomimetic effects: 17; Headache: 33
p-Value		Clinically significant difference (2 points) maintained until week 4. Statistical difference 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
Amr et al (2010)[8,]	VAS (100 mm) at 2 weeks		
N	40		
Ketamine	22.4 (7.54)		
Placebo	44.0 (6.41)		
p-Value	p <0.01	Maintained for 2 weeks after infusion. Ketamine not significantly different from placebo at 3 and 4 weeks after infusion.	

AE: adverse event; NRS: numeric rating scale: SD: standard deviation; SF-36: 36-item Short-Form health survey; VAS: visual analog score.
[a] Measured from baseline to after the final infusion.

The purpose of the limitations tables (see Tables 3 and 4) is to display notable limitations identified in each study. The primary limitations of the RCTs are the lack of active control for the psychomimetic effects of ketamine.

Table 3. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kim et al (2018)[5,]			2. Did not use active placebo (diphenhydramine)		
Liu et al (2018)[6,]		4. The dose was higher and duration of treatment lower compared to other studies			
Sigtermans et al (2009)[3,]			2. Did not use an active placebo (saline)		
Amir et al (2010)[8,]			2. Did not use an active placebo (saline)		

The study imitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 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.

Table 4. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Kim et al (2018)[5,]						
Liu et al (2018)[6,]						
Sigtermans et al (2009)[3,]						
Amir et al (2010)[8,]					1. Power calculations were not reported, but significance was obtained	2. Used a Mann-Whitney-U test rather than repeated measures analysis.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Case Series

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.[9,] 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 the 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 minimal.

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.[10,]These disorders included: trigeminal neuralgia (n=18), chemo-induced peripheral neuropathy (n=6), PHN (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 events occurred.

Tables 5 and 6 summarize the characteristics and results of selected observational studies.

Table 5. Summary of Key Observational Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Patil & Anitescu (2012)[9]	Retrospective chart review	U.S.	2004-2009	Patients with CRPS, refractory headaches, or severe back pain (n=49)	Ketamine 0.5 mg/kg over 30-45 min for a total of 369 infusions	NR

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

Table 6. Summary of Key Observational Study Results

Study	Decrease in VAS From Start of Infusion to Discontinuation	Durability	Adverse Events Patient-reported, n (%)
Patil & Anitescu (2012)[9]			
N	49	29	49
	5.9 (0.35)	Pain relief lasted at least 3 weeks in 38% of patients queried	23 (46.9) reported; 35 nonserious

VAS: visual analog scale.

Fibromyalgia

Noppers et al (2011) also reported on a randomized, double-blind, active placebo-controlled trial conducted in Europe using a 30-minute infusion of ketamine (n=12) or midazolam (n=12).[11] Baseline VAS pain scores were 5.4 in the ketamine group and 5.8 in the midazolam group. At 15 minutes after termination of the infusion, significantly more patients in the ketamine group showed a reduction in VAS score for pain exceeding 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 scores measured weekly over eight weeks. In this well-conducted study, a short infusion of ketamine (30 minutes) did not have a long-term analgesic effect on fibromyalgia pain.

Vlainich et al (2011) reported on a randomized, double-blind trial of IV lidocaine plus amitriptyline vs amitriptyline monotherapy in 30 patients with fibromyalgia.[12] Infusion of lidocaine or saline was given once a week for four weeks. Pain intensity decreased in both groups during treatment; however, there was no significant difference between the treatment groups (VAS, 4.1 for combined treatment vs 4.0 for monotherapy).

Section Summary: IV Anesthetics for Individuals With Chronic Pain

Several RCTs have been performed using IV lidocaine or ketamine for PHN, CRPS, and diabetic neuropathy. Trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients. Neither of the RCTs with ketamine infusion used an active control, raising the possibility of placebo effects and unblinding of patients and investigators. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain.

Psychiatric Disorders

Clinical Context and Test Purpose

The purpose of a 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 evidence review is: Does a course of IV anesthetics improve the net health outcome in individuals with psychiatric disorders?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with psychiatric disorders (e.g., depression, obsessive-compulsive disorder).

Interventions
The therapy being considered is ketamine, which is an on-competitive N-Methyl-D-aspartate receptor antagonist. Ketamine is approved by the U.S. Food and Drug Administration as an anesthetic and use for psychiatric conditions is off-label. The mechanism for its effects in psychiatric disorders is uncertain. Ketamine is administered as an I.V. infusion in a medically-supervised setting.

Comparators
The strategy for managing treatment-resistant depression generally involves modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics). Modification strategies include the use of a higher dose, switching to a new antidepressant, or adding on to existing therapy. An adequate trial of antidepressant therapy is usually a minimum of six weeks. An additional four to six weeks may be required for patients who show partial response.

Long-standing refractory depression in patients who do not benefit from treatment modification or augmentation strategies is referred to as treatment-resistant depression (TRD). For these patients, other strategies such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation techniques have been used. Depression-focused psychotherapy may be added to pharmacotherapy, but is generally not considered stand-alone therapy for refractory depression.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Commonly used scales are the Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D).

MADRS is commonly used to evaluate the efficacy of antidepressants by assessing the severity of depression. It contains 10 items and the total score ranges from 0 to 60. The following cut-offs were proposed to classify the level of depression severity:

- 0-6: No depression (absence of symptoms)
- 7-19: Mild depression
- 20-34: Moderate depression
- 35-60: Severe depression

HAM-D is a 17-item rating scale to determine the severity level of depression in a patient before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥24: Severe depression

Inventory of Depressive Symptomatology–Clinician Rated 30 items
Though not completely standardized, follow-up for psychiatric disorders symptoms would typically occur in the months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for double-blind RCTs;
- To assess long-term outcomes 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.
- Studies with short-term outcomes (<24 h) were excluded.
- Studies examining a single infusion in an inpatient setting (e.g., in conjunction with electroconvulsive therapy or emergency services for suicidal ideation) were excluded

Clinical Studies

Singh et al (2016) reported an industry-sponsored phase 2 multi-center double-blind trial of ketamine (0.5 mg/kg) either 2 or 3 times per week for 4 weeks, followed by 2 weeks of open-label treatment, and then a 3-week ketamine-free phase (see Table 7).[13,] Two control groups received saline infusions over the same intervals. Ketamine infusion resulted in significantly greater improvement in the MADRS compared to saline during the weeks of infusion (see Table 8). Thirty of the 33 patients in the placebo group withdrew from the study for lack of efficacy, compared to 3 of 35 who withdrew due to lack of efficacy in the ketamine groups. Although the analysis was intent-to-treat with the imputation of missing values, the lack of active control and high drop-out rate are limitations of the study (see Tables 10 and 11). The most common adverse events (>20%) were headache, anxiety, dissociation, nausea, and dizziness. By the third withdrawal week, only 9 of 33 ketamine patients remained in the study with diminishing benefits shown on the MADRS. Thus, the benefit observed during the infusion phase does not appear to have been maintained after the end of infusions.

Table 7. Summary of Key RCT Characteristics

Study; Trial	Design	Countries	Sites	Dates	Participants	Interventions	
						Active	Comparator
Singh et al (2016)[13,]	Double-blind phase 2	U.S.	14	2012-2013	68 patients with TRD a score ≥ 34 on the IDS-CR	I.V. ketamine (0.5 mg/kg for 40 min), either 2 (n=18) or 3 (n=17) times a week for 4 weeks, followed by 2 weeks of open-label and then a 3-week ketamine-free phase	Saline infusion either 2 (n=17) or 3 (n=16) times per week over the same interval.

IDS-CR: Inventory of Depressive Symptomatology–Clinician Rated; RCT: randomized controlled trial; TRD: treatment-resistant depression

Table 8. Summary of Key RCT Results

Study	Change in MADRS to Day 15 Mean (SD)	Change in MADRS to Day 29 Mean (SD)	Remitters (MADRS < 10) at Day 15 n (%)	Drug-related Adverse Events n (%)
Singh et al (2016)[13,]				
N	67 ITT	67 ITT	58	68
Ketamine 2	-18.4 (12)	-21.2 (12.9)	6 (37.5)	13 (72.2)
Ketamine 3	-17.7 7.3)	-21.1 (11.2)	3 (23.1)	10 (58.8)
Saline 2	-5.7 (10.2)	-4.0 (9.1)	1 (7.7)	6 (37.5)
Saline 3	-3.1 (5.7)	-3.6 (6.6)	0 (0)	5 (31.3)
p-Value	<0.001	NR	NS	

ITT: intent to treat; MADRS: Montgomery-Asberg Depression Rating Scale; NR: not reported; NS: not significant; RCT: randomized controlled trial; SD: standard deviation.

Trials that have found no benefit of ketamine infusion are described in Table 9. Ionescu et al (2019) reported a double-blind trial in 26 patients with chronic and current suicidal ideation.[14,] The study found no significant difference in HAM-D between the saline and ketamine

groups at the end of infusion (six infusions over three weeks) or after three months of follow-up. Limitations of the study included possible insufficient power due to difficulties in recruitment and a high drop-out rate (see Tables 10 and 11). Review of clinicaltrials.gov shows a large number of small studies that have not been published or followed with larger trials.

Table 9. RCTs with Negative Results

Study; Trial	Countries	Sites	Dates	Design	Participants	Interventions		Outcome Measure	Follow-up	Comment
						Active	*Comparator*			
Ionescu et al (2019)[14],	U.S.	1	2013-2015	Double-Blind	26 medicated patients with chronic and current suicidal ideation	Six ketamine infusions (0.5 mg/kg for 45 min) over 3 weeks	Saline at the same schedule	HAM-D	End of infusion and at 3 mo after infusion	No significant difference in HAM-D between groups at the end of infusion. 2 patients in each group were in remission at 3 mo follow-up.

HAM-D: Hamilton Rating Scale for Depression; RCT: randomized controlled trial.

Table 10. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Ionescu (2019)[14],			2. Did not use an active placebo (saline)		1. Follow-up was performed at 3 mo, but not earlier time points
Singh et al (2016)[13],			2. Did not use an active placebo (saline)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 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.

Table 11. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Ionescu (2019)[14],				1. Only 14 of 26 patients completed the study	1. Power calculations were not reported	
Singh et al (2016)[13],				1. 91% of patients in the control group withdrew due to lack of efficacy. Only 27% of ketamine patients remained in the study at the end of the withdrawal phase		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: IV Anesthetics for Patients With Psychiatric Disorders
Two double-blind trials have been published that compared ketamine infusion with an infusion of saline for TRD. There is a possibility of publication bias due to the lack of publication of many other small trials. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT (n=68) found a significantly greater improvement in a depression scale during the 4 week infusion period, but the effect diminished over 3 weeks post-infusion. The trial did not use active control, raising the possibility of placebo effects and unblinding of patients and investigators. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine for psychiatric disorders.

Summary of Evidence
For individuals who have chronic pain syndromes (e.g., neuropathic pain or fibromyalgia) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence includes several RCTs. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Several RCTs have been performed using IV lidocaine or ketamine for PHN, CRPS, and diabetic neuropathy. Trials have failed to show a durable effect of lidocaine infusion on chronic pain. Two trials with a total of 100 patients provide limited evidence that courses of IV ketamine may provide temporary relief (2 to 4 weeks) to some chronic pain patients. Neither of the RCTs with ketamine infusion used active control, raising the possibility of placebo effects. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have psychiatric disorders (e.g., TRD, obsessive-compulsive disorder) who receive a course of IV ketamine, the evidence consists of RCTs. The relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, medication use, and treatment-related morbidity. Two publications of double-blind trials were identified that compared repeated ketamine infusion with an infusion of saline for TRD. There is a possibility of publication bias due to the lack of publication of many other small trials. One study with 26 patients found no significant difference in a depression scale at the end of infusion. A larger RCT (n=68) found a significantly greater improvement in a depression scale during the 4 week infusion period, but the effect diminished over 3 weeks post-infusion. The trial did not use active control, raising the possibility of placebo effects and unblinding of patients and investigators. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this procedure. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine for psychiatric disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

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.[15] Use of ionotropic *N*-methyl-d-aspartate receptor antagonists and topical agents for neuropathic pain was addressed; intravenous infusion of lidocaine or ketamine was not.

The American Psychiatric Association (2017) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression.[16] The Association noted that "while ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the treatment option."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

Around 100 completed or ongoing trials evaluating intravenous infusion of ketamine for depression are listed on clinicaltrials.gov. Most of these studies are phase 1 with fewer than 20 patients and many are completed but not published. Some currently ongoing and unpublished trials that include over 40 are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02556606	Ketamine for Treatment-Resistant Late-Life Depression	72	Sep 2020
NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Jun 2021
NCT03666390	A Double-blind, Randomized-controlled Trial Using a Low Dose of Ketamine vs Active Placebo in Treating Severe Depression and Suicide	48	Dec 2021
NCT03674671	Investigations on the Efficacy of Ketamine in Depression in Comparison to Electroconvulsive Therapy	240	Dec 2021
NCT03113968	ELEKT-D: Electroconvulsive Therapy (ECT) vs Ketamine in Patients With Treatment-Resistant Depression (TRD)	400	Apr 2022
NCT03237286	Testing a Synergistic, Neuroplasticity-Based Intervention for Depressive Neurocognition	150	Oct 2023
Unpublished			
NCT01920555	Double-Blind, Placebo-Controlled Trial of Ketamine Therapy in Treatment-Resistant Depression (TRD)	99	Feb 2017 (completed)
NCT02659085	A Randomized Controlled Non-inferiority Trial Comparing Ketamine With ECT in Patients With Major Depressive Disorder	200	Dec 2018
NCT02299440	Evaluation of the Effects of Ketamine in the Acute Phase of Suicidal Ideation: a Multicenter Randomized Double-blind Trial	156	Mar 2019 (completed)
NCT02360280	Intravenous Sub-anesthetic Ketamine Treatment in Treatment-Resistant Depression	62	Mar 2019 (completed)

NCT: national clinical trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
	96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
	96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
HCPCS	J2001	Injection, lidocaine HCl for intravenous infusion, 10 mg

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/31/2015	BCBSA Medical Policy adoption
07/01/2016	Policy revision without position change
08/01/2017	Policy revision without position change
01/01/2018	Policy revision without position change
01/01/2019	Policy revision without position change
02/01/2020	Annual review. Policy statement and literature updated. Policy title changed from Intravenous Anesthetics for the Treatment of Chronic Pain to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance

with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.