Policy Number	**SUR702.016**
Policy Effective Date	**02/01/2025**
Policy End Date	**12/31/2025**

Anesthetics for the Treatment of Psychiatric Disorders and Other Selected Indications

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Related Policies (if applicable)
RX501.105: Esketamine Nasal Spray
RX501.063: Compounded Drug Products

Disclaimer

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/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. 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.

Carefully check state regulations and/or the member 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.**

Coverage

Lidocaine

Intravenous infusion of lidocaine **is considered experimental, investigational and/or unproven** for the treatment of:

- Psychiatric disorders, including but not limited to treatment-resistant depression, obsessive-compulsive disorder, or post-traumatic stress disorder;
- Chronic pain, including, but not limited to chronic neuropathic pain, chronic daily headache, or fibromyalgia;

- Pain associated with acute or chronic migraine.

Ketamine
Intramuscular or intravenous administration of ketamine **is considered experimental, investigational and/or unproven** for the treatment of:
- Psychiatric disorders, including but not limited to treatment-resistant depression, obsessive-compulsive disorder, or post-traumatic stress disorder;
- Chronic pain, including, but not limited to chronic neuropathic pain, chronic daily headache, or fibromyalgia;
- Pain associated with acute or chronic migraine.

NOTE 1: Compounded ketamine products (e.g., oral and subcutaneous) are addressed in medical policy RX501.063.

Policy Guidelines

None.

Description

Lidocaine and ketamine have 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. Intramuscular (IM) and intravenous (IV) administration of ketamine have also been investigated for treatment-resistant depression and obsessive-compulsive disorder (OCD).

Lidocaine
Lidocaine, which prevents neural depolarization through effects on voltage-dependent sodium channels, is also used systemically for the treatment of arrhythmias. (1) 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 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 receptor and is a dissociative anesthetic. (2) Respiratory depression may occur with overdosage or a rapid rate of ketamine administration. 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 IM and IV administration of anesthetics 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 15% but varies according to population group. Prevalence is higher in women (21%), among American Indian/Alaska Natives (22%), and among 18- to 44-year-olds (19%). (3) 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. (4)

Chronic daily headache is defined as a headache disorder that occurs 15 or more days a month for more than 3 months. (5) 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. (6) 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. (7) Although fibromyalgia is generally considered 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 IM and IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications. (8) 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

Intravenous 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. IM ketamine does not have off-label or FDA approval for these indications.

Rationale

Medical policies 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, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent 1 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 Migraine Headache Pain and Chronic Pain Syndromes

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with migraine headache pain or 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 migraine 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, QOL, medication use, and treatment-related morbidity.

Follow-up at of least 4 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;
- Consistent with a 'best available evidence approach' within each category of study design, studies with larger sample sizes and longer durations were sought;
- 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 medication classes investigated in RCTs and provided a rank order of various substances. (9) 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 with ketamine were reported by Schwartzman et al. (2009) (N=19) and Sigtermans et al. (2009) (N=60), the latter of which is described below. (10, 11)

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. (12) An update to this Cochrane review similarly found that evidence for use of ketamine for patients with CRPS was of very low certainty; the authors identified moderate-certainty evidence that local sympathetic nerve blockade with lidocaine probably does not reduce pain relative to placebo. (13)

A qualitative systematic review identified 27 studies evaluating lidocaine infusion for chronic neuropathic pain of varying etiologies, including spinal cord injury, peripheral nerve injury, diabetic neuropathy, post-herpetic neuralgia (PHN), and CRPS. (14) In the narrative synthesis, the authors noted that evidence for each etiology was insufficient (owing, in part, to heterogeneity, with significant variability in outcome reporting and results) and underpowered, and that no recommendation for lidocaine infusion in these settings could be made.

Randomized Controlled Trials

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

Lidocaine:

Several RCTs have been performed using IV lidocaine for 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. (15) 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 (p=.001 and p=.009, respectively). In the lidocaine-treated group, there was a significantly greater reduction in pain following the final infusion compared with the placebo group (p=.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.

Liu et al. (2018) randomized 189 patients with PHN to a single 1.5-hour infusion of lidocaine with an injection of midazolam and granisetron. (16) 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 crossover trial by Moulin et al. (2019) found no significant differences between a single infusion of lidocaine (5 mg/kg over 45 minutes) and diphenhydramine (active control) in patients (N=34) with primarily diabetic neuropathy. (17) This study is limited by the short infusion of lidocaine.

Ketamine:
Three double-blind RCTs on ketamine for neuropathic pain were identified. One examined a 4-day infusion in patients with CRPS (11), the second examined infusions on 7 days in patients with spinal cord injury (18), and the third examined a single ketamine infusion in patients with mixed refractory neuropathic pain. (19)

A double-blind RCT of ketamine for CRPS was reported by Sigtermans et al. (2009). (11) Sixty patients were randomized to ketamine or saline, infused over 4 days. The mean ketamine infusion rate was 22 mg/h (normalized to a 70-kg patient) at the end of the treatment phase. Blood samples were collected to assess the plasma concentration of ketamine, and patients were monitored for adverse events. Two patients terminated ketamine infusion early due to psychomimetic effects (e.g., delusions, hallucinations). At baseline, 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. (18) Ketamine or saline were infused for 5 hours over 7 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 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 the infusion. By the third

week after the ketamine infusion, VAS scores had increased to 43 in the ketamine group and were the same as the placebo group. Three patients were reported to have had short-lasting delusions with ketamine infusion.

A third, small, crossover RCT conducted by Pickering et al. (2020) compared a single infusion each of ketamine, ketamine/magnesium, and placebo. (19) The study enrolled 20 patients with refractory neuropathic pain of mixed etiology and assessed patients 5 weeks after each crossover period. The study found no difference between groups in average daily pain intensity based on mean area under the curve (p=.296), nor was there a difference in maximal pain (p=.291) or nightly pain (p=.261). The study also found no difference between interventions in any measure of function or QOL, including Brief Pain Inventory score (p=.527), Hospital Anxiety and Depression Scale (HADS)-Depression (p=.484) or HADS-Anxiety (p=.155) scores. There were no serious adverse events or withdrawals due to adverse events.

Table 1. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Lidocaine						
Kim et al. (2018) (15)	South Korea	1	2015-2016	Patients had PHN or CRPS type II with an 11-point NRS score of 4 or ≥3 months without pain relief from conservative treatment	IV lidocaine 3 mg/kg for 4 weekly treatments of 1 hour each (n=21)	IV saline for 4 weekly treatments of 1 hour each (n=21)
Lui et al. (2018) (16)	China	1	2015-2017	189 patients with PHN and pain >1 month with VAS >4	A single 1.5-hour infusion of 5 mg/kg lidocaine, injection of 1.5 mg midazolam and 3 mg granisetron, also taking pregabalin and oxycodone	1.5-hour infusion of saline, plus midazolam and granisetron, also taking pregabalin and oxycodone
Ketamine						

Sigtermans et al. (2009) (11)	Netherlands	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
Amr (2010) (18)	Egypt	1	Not reported	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)
Pickering et al. (2020) (19)	France	1	2015-2018	20 ketamine-naive patients with refractory neuropathic pain	Ketamine infusion 0.5 mg/kg over a 2-hour period	Magnesium 3 g over 30 minutes Saline infusion over a 2-hour period

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

Table 2. Summary of Key Randomized Controlled Trial Results

Study	Pain Scores (SD), %	Other Clinical Outcomes	AEs
Lidocaine			
Kim et al. (2018) (15)	VAS (100 mm)		
N	42		42
Lidocaine	48.71 (40.59)		3 mild
Saline	19.51 (27.27)		4 mild
p-Value	.011		.698
Liu et al. (2018) (16)	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) (11)	11 point NRS at 1 week	Reduction in NRS Pain Score[a]	
N	60		60
Ketamine	2.68 (0.51)		Nausea: 63%; Vomiting: 47%; 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=.07)	Nausea: p<.001; Vomiting: p=.004; Psychomimetic effects: p<.001; Headache: p=.78
Amr (2010) (18)	VAS (100 mm) at 2 weeks	Reduction in NRS Pain Score (SD), %[a]	
N	40		
Ketamine	22.4 (7.54)		
Placebo	44.0 (6.41)		
p-Value	p <.01	Maintained for 2 weeks after infusion. Ketamine not significantly different from placebo at 3 and 4 weeks after infusion.	
Pickering et al. (2020) (19)	Average daily pain AUC	Brief Pain Inventory pain severity score (SD)	Any adverse event
N	20	20	20
Ketamine	196 (92)	6 (3)	20% (4/20)
Ketamine/magnesium	185 (100)	6 (2)	35% (7/20)
Placebo	187 (90)	6 (2)	10% (2/20)
p-Value	0.296	.527	Not reported

AE: adverse event; AUC: area under the curve; NRS: numeric rating scale; NS: not significant; 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 limitation 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. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kim et al. (2018) (15)			2. Did not use active placebo (diphenhydramine)		
Liu et al. (2018) (16)		4. The dose was higher, and duration of treatment lower compared to other studies			
Sigtermans et al. (2009) (11)			2. Did not use an active placebo (saline)		
Amr (2010) (18)			2. Did not use an active placebo (saline)		
Pickering et al. (2020) (19)				5. Pain reported as area under the curve, mean pain scores not reported	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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) (15)						
Liu et al. (2018) (16)						
Sigtermans et al. (2009) (11)						
Amr (2010) (18)					1. Power calculations were not reported, but significance was obtained	2. Used a Mann-Whitney-U test rather than repeated measures analysis
Pickering et al. (2020) (19)	3. Allocation concealment unclear				1. Power calculations were not reported	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[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); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[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; 5. Other.

Observational Studies

Lidocaine:

A retrospective analysis by Przeklasa-Muszynska et al. (2016) examined the use of 3 to 25 IV infusions of lidocaine (5 mg/kg each over 30 min) in 85 patients (57% women; mean age, 63 years) with neuropathic pain disorders. (20) 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 pain, 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 an NRS ranged from 0 to 10. The mean change from baseline in NRS score was 4.2. Efficacy increased significantly with age (71 to 90 years, p<.05). There was a correlation between treatment efficacy and the number of infusions (6 to10 infusions, p<.01) and the severity of pain (NRS range, 9 to 10; p<.001). There was no correlation between treatment efficacy and the number of years patients had experienced pain symptoms (range, 19 to 30 years; p<.05). Reviewers reported that infusions were not interrupted due to adverse events; however, they did not report whether adverse events occurred.

Vacher et al. (2022) performed a prospective case-series of 74 patients treated with a single lidocaine infusion (3 mg/kg) for chronic pain. (21) Pain questionnaires were administered to patients at the time of infusion and again via telephone follow-up at an average of 63 days (range 30 to 240 days). The primary outcome was the change in Brief Pain Inventory (BPI) pain score. The majority of patients were female (77%). Overall, a single infusion of lidocaine did not significantly improve pain or quality of life.

Ketamine:
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. (22) 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. Aquery 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.

Mangnus et al. (2021) performed a retrospective analysis of data from 48 adult patients with CRPS treated with ketamine infusions at a single center in the Netherlands. (23) The median duration of diagnosis was 5 years. Ketamine infusions were started at 3 mg/hour during a 7-day inpatient stay and were increased twice daily in increments of 1 to 2 mg/hour until patients reached an effective dose. At the end of infusion and at 4 weeks post-infusion, the pain score was significantly reduced from baseline (8 vs. 6; p<.001 and 8 vs. 7; p=.015, respectively). Response (decrease in pain score of ≥2 from baseline) occurred in 62% of patients at the end of infusion but decreased to 48% at 4 weeks.

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
Lidocaine						
Przeklasa-Muszynska et al. (2016) (20)	Retrospective chart review	Poland	Jan-Nov 2015	Adults with refractory neuropathic pain (N=85)	Lidocaine 5 mg/kg over 30 minutes once a week; range 3-25 infusions	4 weeks
Vacher et al. (2022) (21)	Prospective case series	UK	Jun 2018-Jul 2020	Adults with chronic pain (N=74)	Lidocaine 3 mg/kg single infusion	Mean 63 days (range 30-240)
Ketamine						
Patil & Anitescu (2012) (22)	Retrospective chart review	US	2004-2009	Patients with CRPS, refractory headaches, or severe back pain (N=49)	Ketamine 0.5 mg/kg over 30-45 minutes for a total of 369 infusions	NR
Mangnus et al. (2021) (23)	Retrospective chart review	Netherlands	2010-2019	Adult patients with CRPS (N=48)	Ketamine 3 mg/hour increased twice daily in increments of 1 to 2 mg over a 7-day inpatient stay	4 weeks

CRPS: complex regional pain syndrome; NR: not reported; UK: United Kingdom; US: United States.

Table 6. Summary of Key Observational Study Results

Study	Change in Pain Score from Start of Infusion to Discontinuation	Change in Pain Score from Start of Infusion to 4 weeks	Durability	Adverse Events Patient-reported, n (%)
Lidocaine				
Przeklasa-Muszynska et al. (2016) (20)				

N	81		-	-
	NRS: 4.2 (SE not reported)		Not reported	Not reported
Vacher et al. (2022) (21)				
N	74			
	BPI: 6.15-5.88 (p=.106)			
Ketamine				
Patil & Anitescu (2012) (22)				
N	49		29	49
	VAS: 5.9 (0.35)		Pain relief lasted at least 3 weeks in 38% of patients queried	23 (46.9) reported; 35 nonserious
Mangnus et al. (2021) (23)				
N	36	18		
	NRS: 2	NRS: 1		

NRS: numeric rating scale; SE: standard error; VAS: visual analog scale.

Headache (including Migraine)

A small RCT from 1991 found no significant difference between IV lidocaine and placebo for the treatment of acute migraine. (24) No RCTs were identified that evaluate the long-term relief of chronic daily headache following IV infusion of lidocaine. Uncontrolled studies were identified (25, 26), but they do not provide sufficient evidence on the efficacy of IV lidocaine treatment for this condition.

Fibromyalgia

Systematic Review

de Carvalho et al. (2022) conducted a systematic review of 10 clinical trials (2 RCTs; 8 observational) evaluating lidocaine infusions in patients with fibromyalgia. (27) A total of 461 patients were included, and the majority of patients in each study were female (95%-100%). There was a wide range of lidocaine dosage (2-7.5 mg/kg,) the number of infusions, and follow-up timeframes, which ranged from 65.7 to 90 days. Visual analog scores (in mm) ranged from 6.1 to 8.1 at baseline to 1.7 to 4.5 at short-term follow-up. In the studies evaluating long-term follow-up, VAS scores varied from 30% to 35.4%. Adverse events were variable among studies and occurred in 0% to 39.6% of cases.

Randomized Controlled Trial

One notable RCT was not included in the de Carvalho et al. (2022) systematic review. Noppers et al. (2011) 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). (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 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 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.

Section Summary: Intravenous Anesthetics for Individuals with Migraine Headache Pain and Chronic Pain Syndromes

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. None of the RCTs with ketamine infusion used an active control, raising the possibility of placebo effects and unblinding of patients and investigators. A systematic review specific to patients with fibromyalgia found short-term benefit with lidocaine infusions, but long-term efficacy and safety data were limited. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this therapy. No RCTs were identified that evaluate the long-term relief of chronic daily headache (including migraine) following IV infusion of lidocaine. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain.

Intravenous Anesthetics for Individuals with Treatment-Resistant Depression

Clinical Context and Therapy 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 individuals with treatment-resistant depression.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with treatment-resistant depression.

Interventions

The therapy being considered is ketamine. 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 treatment-resistant depression is uncertain. Ketamine is administered as an IV infusion in a medically-supervised setting.

Comparators

The following therapies are currently being used to treat treatment-resistant depression: psychotropic medications and psychotherapy. Long-standing refractory depression in patients who do not benefit from treatment modification or augmentation strategies is referred to as treatment-resistant depression (TRD). The strategy for managing TRD generally involves

modifying current antidepressant therapy or augmenting existing therapies with non-antidepressant medications (such as atypical antipsychotics). For these patients, other strategies such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation, and vagus nerve stimulation techniques have also 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), the Hamilton Rating Scale for Depression (HAM-D), the Patient Health Questionnaire-9 (PHQ-9), and the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR-16).

The 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.

The QIDS-SR-16 is derived from the 30-item Inventory of Depressive Symptomatology and is used to rate the severity of depressive symptoms based on criterion diagnostic domains for depression, including sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance, decrease or increase in appetite or weight, and psychomotor agitation or retardation. The total score ranges from 0 to 27, with the score corresponding to the following classifications:

- 0-5: No depression
- 6-10: Mild depression
- 11-15: Moderate depression

- 16-20: Severe depression
- 21-27: Very severe depression

The PHQ-9 is a self-report on depression-related items used to monitor the severity of depression and response to treatment. Total scores correspond to these classifications:
- 0-4: None
- 5-9: Mild
- 10-14: Moderate
- 15-19: Moderately severe
- 20-27: Severe

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 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;
- Consistent with a 'best available evidence approach' within each category of study design, studies with larger sample sizes and longer durations were sought;
- 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.

Systematic Review

Dean et al. (2021) published a systematic review of ketamine and other glutamate receptor modulators in patients with unipolar depression. (29) Thirty-one trials were included for ketamine; however, the majority of studies investigated ketamine as a single dose, and only 7 studies were included for the response and remission outcome (n=185). While ketamine increased response and remission at 24 hours (odds ratio [OR], 3.94; 95% CI, 1.54 to 10.10) the evidence was graded very low certainty. In a similar analysis of patients with depression in bipolar disorder, Dean et al. (2021) identified 3 trials with ketamine. (30) Ketamine was more effective than placebo at 24 hours (OR, 11.61; 95% CI, 1.25 to 107.74; p=.03); however, the evidence was deemed low certainty and only 33 participants were included from 2 studies. Based on these analyses, evidence is lacking for efficacy beyond the acute treatment period.

Grasso et al. (2024) published a systematic review on changes in cognitive outcomes in patients with unipolar TRD treated with IV ketamine infusions. (31) Fourteen studies were included in the review. All included studies found reduction in depression symptoms after ketamine treatment (ranging from medium to large effect size) with no significant or long-standing adverse effects reported. Authors did note that there were several limitations in their review including the heterogeneity, small sample sizes, and limited external generalizability of populations in the included studies.

Randomized Controlled Trials

Tables 7 through 11 summarize the characteristics and results of identified RCTs. 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. (32) 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. 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. 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.

In a trial comparing ketamine infusion to ECT, Ekstrand et al. (2022) randomized patients hospitalized for depression to 3 times weekly ketamine (0.5 mg/kg) or ECT in an open-label, noninferiority trial. (33) A total of 186 patients received treatment with a maximum of 12 treatment sessions. Previous treatment had included ECT in 37% of ECT recipients and 42% of ketamine recipients. Most patients were experiencing a single severe depressive episode (27% of ECT and 27% of ketamine recipients) or recurrent severe depression (34% of ECT and 33% of ketamine) without psychotic features; 15% of ECT recipients and 19% of ketamine recipients had psychotic symptoms present, and 51% of ECT recipients and 40% of ketamine recipients had previously attempted suicide (median 2 attempts in each group). More patients achieved remission (MADRS ≤10) with ECT than ketamine (63% vs. 46%; OR, 0.52; 95% CI, 0.29 to 0.92). A median of 6 treatment sessions were required for remission. The authors noted that despite being inferior to ECT, ketamine is a potential treatment option for depression. Relapse rates during the 12-month follow-up were similar between treatments (70% with ketamine vs. 64% with ECT). Serious AEs were more common with ECT, but treatment-emergent AEs leading to dropout were more common with ketamine.

Anand et al. (2023) reported another open-label, randomized noninferiority trial comparing ketamine (0.5 mg/kg 3 times weekly) with ECT (3 times weekly) in adults with treatment-resistant moderate or severe depression (lack of response to ≥2 adequate trials of antidepressant therapy and MADRS score >20). (34) Participants were patients experiencing depressive episodes with psychotic features were excluded. Among 403 randomized patients, most (89.1%) were outpatient at the time of randomization. Previous treatment had included ECT and/or ketamine in 11.5% and 7% of ketamine recipients and 10.3% and 3.9% of ECT recipients, respectively. Suicide had previously been attempted in 36.5% of ketamine recipients and 41.4% of ECT recipients. In the primary analysis, 55.4% of participants assigned to ketamine and 41.2% of participants assigned to ECT experienced a response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks (p<.001 for noninferiority). Among participants who

achieved an initial response, relapse (QIDS-SR-16 score >12) occurred in 19% of ketamine and 35.4% of ECT recipients at 1-month follow-up and 34.5% of ketamine and 56.3% of ECT recipients at 6-month follow-up. Patient-reported memory function scores were higher in the ketamine group than the ECT group, and fewer patients in the ketamine group reported cognitive symptoms. Patients in both groups experienced similar improvements in quality-of-life scores. Moderate or severe adverse events were reported in 25.1% of ketamine recipients and 32.4% of ECT recipients; individual events occurred at similar rates with the exception of muscle pain or weakness, which was reported in 0.5% of ketamine recipients and 5.3% of ECT recipients (p=.01).

Table 7. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Design	Countries	Sites	Dates	Participants	Interventions	
						Active	**Comparator**
Singh et al. (2016) (32)	Double-blind phase 2	United States	14	2012-2013	68 patients with TRD a score > 34 on the IDS-CR	IV ketamine (0.5 mg/kg for 40 minutes), 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
Ekstrand et al. (2022) (33)	Open label noninferiority RCT	Sweden	6	NR	186 adult inpatients with depression	IV ketamine 0.5 mg/kg 3 times weekly up to 12 treatments	ECT
Anand et al. (2023) (34)	Open-label, noninferiority RCT	United States	5	2017-2022	403 adults with TRD and a score >20 on the MADRS	IV ketamine 0.5 mg/kg twice	ECT 3 times weekly for 3 weeks

						weekly for 3 weeks	

ECT: electroconvulsive therapy; IDS-CR: Inventory of Depressive Symptomatology–Clinician Rated; IV: intravenous; MADRS: Montgomery-Asberg Depression Rating Scale; NR: not reported; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; SRI: serotonin reuptake inhibitor; TRD: treatment-resistant depression.

Table 8. Summary of Key Randomized Controlled Trial Results

Study	YBOCS Response to Day 7[1], n (%)	Change in MADRS to Day 15, Mean (SD)	Change in MADRS to Day 29, Mean (SD)	Remitters (MADRS < 10), n (%)	Drug-related Adverse Events, n (%)	Change in CAPS-5 at Day 15, Mean (SD)	Response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks, n (%)
Singh et al. (2016) (32)							
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		<.001	NR	NS			
Ekstrand et al. (2022) (33)							
N				186			
Ketamine				44 (46)			
ECT				57 (63)			
OR (95% CI)				0.51 (0.29 to 0.92)			
Anand et al. (2023) (34)							
N							
Ketamine				74 (37.9)			108 (55.4)
ECT				37 (21.8)			70 (41.2)
Difference, % (95% CI)				16.2 (7.0 to 25.4)			14.2 (3.9 to 24.2)

p-value for noninferiority				--			<.001

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; ECT: electroconvulsive therapy; ITT: intent to treat; MADRS: Montgomery-Asberg Depression Rating Scale; NR: not reported; OR: odds ratio; NS: not significant; QIDS-SR-16: 16-item Quick Inventory of Depressive Symptomatology - Self-Report; 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. (35) The study found no significant difference in HAM-D between the saline and ketamine groups at the end of infusion (6 infusions over 3 weeks) or after 3 months of follow-up. Limitations of the study included possible insufficient power due to difficulties in recruitment and a high drop-out rate. Review of clinicaltrials.gov shows a large number of small studies that have not been published or followed with larger trials.

Table 9a. Randomized Controlled Trials with Negative Results

Study; Trial	Countries	Sites	Dates	Design	Participants	Interventions	
						Active	*Comparator*
Ionescu et al. (2019) (35)	United States	1	2013-2015	Double-Blind	26 medicated patients with chronic and current suicidal ideation	6 ketamine infusions (0.5 mg/kg for 45 minutes) over 3 weeks	Saline at the same schedule

Table 9b. Randomized Controlled Trials with Negative Results

Study; Trial	Outcome Measure	Follow-up	Comment
Ionescu et al. (2019) (35)	HAM-D	End of infusion and at 3 months 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 months follow-up.

HAM-D: Hamilton Rating Scale for Depression.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Singh et al. (2016) (32)			2. Did not use an active placebo (saline)		
Ionescu et al. (2019) (35)			2. Did not use an active placebo (saline)		1. Follow-up was performed at 3 months, but not

					earlier time points
Ekstrand et al. (2022) (33)					
Anand et al. (2023) (34)					

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 11. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Singh et al. (2016) (32)				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		
Ionescu et al. (2019) (35)				1. Only 14 of 26 patients completed the study	1. Power calculations were not reported	

Ekstrand et al. (2022) (33)		1. Open-label				
Anand et al. (2023) (34)		1. Open-label				

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[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); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[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; 5. Other.

Observational Studies

Numerous observational studies have evaluated ketamine for use in depression and selected studies are summarized in Tables 12 and 13. (36-40) Ketamine has generally been found to be effective for depression and suicidality in these observations; however, the inherent limitations of observational study design prohibit firm conclusions regarding the effectiveness and safety of ketamine infusions.

Table 12. Summary of Key Observational Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
McInnes et al. (2022) (36)	U.S.	537 patients with depression	Ketamine 4-8 infusions over 7-28 days	14-31 days after final infusion
Oliver et al. (2022) (37)	U.S.	424 patients with treatment-resistant depression or suicidal ideation	Ketamine 0.5 mg/kg for 6 infusions followed by as needed booster infusions thereafter	Up to 52 weeks
Zhou et al. (2022) (38)	China	111 patients with treatment-resistant depression	Ketamine 0.5 mg 3 times weekly for a total of 6 doses	26 days

Pfeiffer et al. (2024) (39)	U.S.	215 patients with depression	Ketamine infusion (mean dose 59 mg); mean total number of infusions was 18	Up to 12 months
Gutierrez et al. (2024) (40)	Canada	71 patients with treatment-resistant depression	IV low dose ketamine (0.5 mg/kg) bi-weekly sessions for 4 weeks	4 weeks

IV: intravenous; U.S.: United States.

Table 13. Summary of Key Observational Study Results

Study	Treatment	Change From Baseline	Response, n (%)	Partial Response, n (%)	Remission, n (%)
McInnes et al. (2022) (29)	Ketamine	PHQ-9: 8.7 (SD, 6.6; 95% CI, 8.1-9.2)	288 (53.6)		155 (28.9)
Oliver et al. (2022) (30)	Ketamine	Mean PHQ scores significantly decreased after week 1 (p<.001; results reported graphically)	50% of patients had responded by day 36		20% were in remission by 30 days
Zhou et al. (2022) (31)	Ketamine	MADRS: baseline 32.1 to 15.7 at follow-up; p<.001			
Pfeiffer et al. (2024) (39)	Ketamine	Mean improvement in PHQ9 scores at weeks 6, 12, and 26: mean improvement in PHQ-9 scores was 4.6 (SD = 6.8), 4.4 (SD = 6.5), and 4.7 (SD = 6.7) respectively	At week 6, 26% had a 50% improvement in PHQ-9 score		At week 6, 5% had PHQ-9 score ≤ 5
Gutierrez et al. (2024) (40)	Ketamine	BDI-II and MADRS: statistically significant reduction in SI comparing the baseline to treatment endpoint scores	CGI-S scale: 54.93% of patients responded to treatment	CGI-S scale: 23.94% achieved remission	CGI-S scale: 23.94% achieved remission

BDI-II: statistically significant reduction in SI comparing the baseline to treatment endpoint scores; CGI-S scale: Clinical Global Impression Scale-Severity; CI: confidence interval; MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; SI: suicidal ideation.

Additional literature was reviewed specific to IV ketamine. (41-45) Although results are promising, many questions still need be addressed and many issues resolved in terms of therapeutic strategy and long-term risks and management. Evidence for long-term efficacy, safety, and tolerability of intravenous ketamine in TRD is insufficient.

Section Summary: Intravenous Anesthetics for Individuals with Treatment-Resistant Depression
Two double-blind trials have been published that compared multiple ketamine infusions with saline for TRD. There is a possibility of publication bias due to the lack of publication of many other small trials. Systematic reviews in unipolar depression and depression in patients with bipolar disorder have identified numerous studies evaluating ketamine infusion. However, the studies are generally limited to a single ketamine infusion. 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. An RCT comparing ketamine infusion to ECT in hospitalized patients with depression found improved remission rates with ECT, whereas another RCT comparing ketamine infusion with ECT in a predominantly outpatient, less severely ill sample found that ketamine was noninferior to ECT in inducing response with numerical improvements in quality of life and adverse effects. Multiple observational studies have demonstrated efficacy of ketamine infusions in depression, but limited conclusions can be made based on the observational study design. Additional literature was reviewed and although results are promising, many questions still need be addressed and many issues to be resolved, in terms of therapeutic strategy and long-term risks and management. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. High-quality clinical trials, several of which are in progress, are needed to evaluate the long-term safety and efficacy of IV ketamine use for depression.

Intravenous Anesthetics for Individuals with Other Psychiatric Disorders
Clinical Context and Therapy 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 individuals with other psychiatric disorders (e.g., obsessive-compulsive disorder [OCD], post-traumatic stress disorder [PTSD]).

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with psychiatric disorders (e.g., OCD, PTSD).

Interventions
The therapy being considered is ketamine. 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 IV infusion in a medically supervised setting.

Comparators
The following therapies are currently being used to treat psychiatric disorders: psychotropic medications and psychotherapy.

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 Clinically Administered Post-Traumatic Stress Disorder (PTSD) Scale (CAPS-5), and the Yale-Brown Obsessive-Compulsive Scale (YBOCS).

The CAPS-5 is the gold standard in assessment of PTSD symptoms. The CAPS-5 is a structured interview performed by clinicians or researchers that is used to diagnose PTSD and assess PTSD symptoms. Scores for each item range from 0 (absent) to 4 (extreme/incapacitating); total scores range from 0 to 120.

The YBOCS is a 10-item clinician-administered scale that is the most widely used rating scale for OCD. The YBOCS rates 5 dimensions related to obsessions and compulsions: time spent or occupied; interference with functioning or relationships; degree of distress; resistance; and control (i.e., success in resistance). Each item is scored on a 4-point scale with 0 representing no symptoms and 4 representing extreme symptoms. Total scores of the YBOCS correspond to the following indicated classifications:

- 0-7: Subclinical
- 8-15: Mild
- 16-23: Moderate
- 24-31: Severe
- 32-40: Extreme

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 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.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with short-term outcomes (<24 h) were excluded.
- Studies examining a single infusion in an inpatient setting (e.g., in conjunction with ECT or emergency services for suicidal ideation) were excluded.

Randomized Controlled Trials

Tables 14 through 17 summarize the characteristics and results of identified RCTs. Rodriguez et al. (2013) performed a double-blind, placebo-controlled trial in patients with serotonin reuptake inhibitor (SRI)-resistant OCD to compare the effects of ketamine (0.5 mg/kg given over 40 minutes on 2 occasions at least 1 week apart) with saline placebo. (46) Patients had failed or refused treatment with at least 1 trial of SRI therapy and/or cognitive behavioral therapy. The mean age of patients was 34.2 years and the mean YBOCS score was 28.2. A significant carryover effect was detected with ketamine, and these patients did not return to their baseline disease severity; therefore, data from each phase of the crossover trial were not combined and results were presented only for the first-phase data (ketamine first [n=8] and saline first [n=7]). A higher proportion of patients treated with ketamine achieved treatment response (≥35% reduction in YBOCS score; 50% vs. 0%; p<.05). The authors noted the small sample size and unblinding due to adverse effects of ketamine.

Feder et al. (2021) performed a double-blind trial comparing IV ketamine with IV midazolam, each administered 3 times weekly over 2 weeks, in adult patients with PTSD. (47) The primary outcome measure was change in PTSD symptom severity, assessed using the CAPS-5, from baseline to 2 weeks. The mean duration of PTSD was 14.9 years. Thirteen (43.3%) patients were receiving concomitant psychotropic medications, and 17 (56.7%) were receiving concomitant psychotherapy. At week 2, the mean CAPS-5 total score was lower in the ketamine group compared to the midazolam group (difference, 11.88 points; p=.004). The most common adverse events that occurred more frequently with ketamine included nausea or vomiting (33% vs. 20%), headache (33% vs. 20%), and fatigue (20% vs. 7%). The authors noted the potential for unblinding in the ketamine group due to the higher rate of dissociative symptoms.

Table 14. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	**Design**	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
						Active	*Comparator*
Rodriguez et al. (2013) (46)	Double-blind, crossover RCT	U.S.	1	2010-2012	15 adult patients with SRI-resistant OCD and near-constant obsessions	IV ketamine (0.5 mg/kg) given over 40 min on 2 occasions at least 1 week apart	Saline infusion given over 40 min on 2 occasions at least 1 week apart
Feder et al. (2021) (47)	Double-blind RCT	U.S.	1	2015-2020	30 adult patients with chronic PTSD	IV ketamine 0.5 mg/kg 3 times per week over 2 consecutive weeks	IV midazolam 0.045 mg/kg 3 times per week over 2

							consecutive weeks

IV: intravenous; min: minute(s); OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; SRI: serotonin reuptake inhibitor; U.S.: United States.

Table 15. Summary of Key Randomized Controlled Trial Results

Study	YBOCS Response to Day 7[1], n (%)	Change in MADRS to Day 15, Mean (SD)	Change in MADRS to Day 29, Mean (SD)	Remitters (MADRS < 10), n (%)	Drug-related Adverse Events, n (%)	Change in CAPS-5 at Day 15, Mean (SD)	Response (≥50% reduction in QIDS-SR-16 score from baseline) after 3 weeks, n (%)
Rodriguez et al. (2013) (46)							
N	15						
Ketamine	7 (50)						
Placebo	0						
Feder et al. (2021) (47)							
Ketamine						NR	
Midazolam						NR	
Difference (p value)						-11.88 (.004)	

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; ITT: intent to treat; NR: not reported; OR: odds ratio; NS: not significant; SD: standard deviation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

[1]YBOCS reduction ≥35%.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Rodriguez et al. (2013) (46)					1. Follow-up only performed up to 1 week
Feder et al. (2021) (47)					1. Follow-up only performed up to 2 weeks

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Rodriguez et al. (2013) (46)		1. Potential unblinding due to dissociative effects of ketamine				4. Data from second phase of crossover not included due to carryover effect of ketamine
Feder et al. (2021) (47)		1. Potential unblinding due to dissociative effects of ketamine				

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

Observational Studies

Observational studies have evaluated ketamine in psychiatric disorders and selected studies are summarized in Tables 18 and 19. (48) Ketamine has generally been found to be effective for OCD in these observations; however, the inherent limitations of observational study design prohibit firm conclusions regarding the effectiveness and safety of ketamine infusions.

Table 18. Summary of Key Observational Study Characteristics

Study	Country	Participants	Treatment Delivery	Follow-Up
Sharma et al. (2020) (48)	India	14 patients with SRI-resistant OCD	Ketamine 0.5 mg/kg over 40 min either twice weekly or 3 times weekly	2-3 weeks

OCD: obsessive-compulsive disorder; SRI: serotonin reuptake inhibitor.

Table 19. Summary of Key Observational Study Results

Study	Treatment	Change from Baseline	Response, n (%)	Partial Response, n (%)	Remission, n (%)
Sharma et al. (2020) (48)	Ketamine	YBOCS: 31.4 vs. 26.9; p=.01	YBOCS: 1 (7.1)[a]	YBOCS: 2 (14.3)[b]	

YBOCS: Yale-Brown Obsessive-Compulsive Scale.

[a] YBOCS reduction ≥35%.

[b] YBOCS reduction 25% to 35%.

Section Summary: Intravenous Anesthetics for Individuals With Other Psychiatric Disorders

One double-blind placebo-controlled trial and case series were identified in OCD, and 1 double-blind trial was identified that compared multiple ketamine infusions with midazolam in chronic PTSD. There is a possibility of publication bias due to the lack of publication of many other small trials. One double-blind, crossover RCT in patients with SRI-resistant OCD found that ketamine infusion provided higher frequency of YBOCS response at day 7 compared to placebo; however, unblinding was suspected and only data from the first phase were analyzed because of a carryover effect of ketamine. A case series also found significant improvements in YBOCS at 2 to 3 weeks, but only 1 patient demonstrated YBOCS response. A single l RCT in patients with chronic PTSD (N=30) found that ketamine infusion produced significantly greater improvements in a PTSD symptom scale at 2 weeks compared to midazolam. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. 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.

Intramuscular Ketamine for Individuals with Migraine Headache Pain, Chronic Pain Syndromes and Psychiatric Disorders

In 2021, Kazi et al. published a narrative review to discuss the evidence supporting the use of injectable (intravenous, intramuscular [IM], or subcutaneous) medications for patients in the emergency department (ED) who fail to improve sufficiently after treatment with first-line medication. (49) The results for these second-line interventions for migraine in the ED narrative review state that most data published to date demonstrate no role for propofol and ketamine.

In 2008, Castrillon et al. aimed to investigate the effects of local intramuscular injection of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine on chronic myofascial pain and mandibular function in temporomandibular disorder patients. (50) Fourteen myofascial temporomandibular disorder pain patients (10 women and 4 men) were recruited. The subjects completed 2 sessions in a double-blinded randomized and placebo-controlled trial. They received a single injection of 0.2 mL ketamine or placebo (buffered isotonic saline [NaCl], 155 mmol/L) into the most painful part of the masseter muscle. The primary outcome parameters were spontaneous pain assessed on an electronic visual analog scale and numeric rating scale. In addition, numeric rating scale of unpleasantness, numeric rating scale of pain relief, pressure pain threshold, pressure pain tolerance, completion of a McGill Pain Questionnaire and pain drawing areas, maximum voluntary bite force and maximum voluntary jaw opening were obtained. Paired t tests and analysis of variance were performed to compare the data. The results suggested that peripheral NMDA receptors do not play a major role in the pathophysiology of chronic myofascial temporomandibular disorder pain. Although there was a minor effect of ketamine on maximum voluntary jaw opening, local administration may not be promising treatment for these patients.

In 2022 from Ahuja et al., a retrospective descriptive cohort study of real-world depression, anxiety, and safety outcomes of intramuscular ketamine treatment was published. (51) This study aimed to evaluate the clinical characteristics, treatment patterns, clinical outcomes, and adverse events of patients receiving IM ketamine treatment. Adults with any psychiatric diagnosis who received ketamine treatment only by IM administration from January 2018 to June 2021 were included. A total of 452 patients were included in the cohort. The authors concluded that IM ketamine is being utilized to treat psychiatric outpatients with multiple mental illnesses not limited to depression. Average depression and anxiety levels significantly improve throughout IM ketamine treatment and do not regress to baseline during patients' maintenance treatment phase. However, the authors report several limitations which include that the change in in patients' depression, suicidal ideation and anxiety symptoms must be interpreted cautiously. The fact that this study had no control group limits the ability to make causal links between IM ketamine treatment and symptom improvement. Furthermore, patients received open-label treatment, thus the possible placebo effect of ketamine treatment was not evaluated. Prospective studies are recommended to confirm the long-term effectiveness and safety of IM ketamine.

<u>Section Summary: Intramuscular Ketamine for Individuals with Migraine Headache Pain, Chronic Pain Syndromes and Psychiatric Disorders</u>

The evidence for IM Ketamine for migraine headache pain, chronic pain syndromes and psychiatric disorders includes a narrative review, a double-blinded randomized and placebo-controlled trial, and a recent retrospective cohort study. Evidence suggests that IM ketamine may be effective, however, the narrative review failed to demonstrate a role for ketamine, the double-blinded randomized and placebo-controlled trial was a small sample study (N=14) and long-term data is still needed to effectively evaluate the efficacy and safety of IM ketamine.

Summary of Evidence

For individuals who have migraine headache pain or chronic pain syndromes (e.g., neuropathic pain or fibromyalgia) who receive a course of IV anesthetics (e.g., lidocaine, ketamine), the evidence includes systematic reviews, several randomized controlled trials (RCTs), and observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life (QOL), medication use, and treatment-related morbidity. Several RCTs have been performed using IV lidocaine for post-herpetic neuralgia (PHN), complex regional pain syndrome (CRPS), and diabetic neuropathy. These 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 in some settings. Neither of the RCTs used an active control, raising concerns about placebo effects. A third trial found no benefit from a single infusion of ketamine or ketamine/magnesium. Overall, the intense treatment protocols, the severity of adverse events, and the limited treatment durability raise questions about the net health benefit of this therapy. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain. No RCTs were identified that evaluate the long-term relief of chronic daily headache (including migraine) following IV infusion of lidocaine or ketamine. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive a course of IV ketamine, the evidence consists of systematic reviews, RCTs, and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, 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 treatment-resistant depression. Additionally, 2 open-label randomized trials comparing ketamine infusion to electroconvulsive therapy (ECT) were identified. There is a possibility of publication bias due to the lack of publication of many other small trials. Systematic reviews in patients with unipolar depression or depression related to bipolar disorder have identified numerous studies evaluating the efficacy of ketamine infusion. While the analyses indicate depression improvement in the short-term, there is limited evidence beyond a single infusion. 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 an active control, raising the possibility of placebo effects and unblinding of patients and investigators. The open-label randomized trials comparing ketamine with ECT produced mixed results, with the first trial indicating ketamine was not noninferior to ECT in inducing remission

and the second trial indicating ketamine was noninferior to ECT in inducing response. These divergent findings may be attributable to differences in the populations studied, as the first trial was conducted in severely ill inpatients and the second trial was conducted in a less severely ill, predominantly outpatient sample. Large observational studies in patients with depression indicate improvement on depression rating scales following ketamine infusions; however, these studies lack a control group, and no firm conclusions on the effectiveness or safety of serial ketamine infusions can be drawn from this evidence. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other psychiatric disorders (e.g., obsessive-compulsive disorder [OCD], post-traumatic stress disorder [PTSD]) who receive a course of IV ketamine, the evidence consists of RCTs and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, medication use, and treatment-related morbidity. One double-blind placebo-controlled trial and case series for OCD treatment, and 1 double-blind trial comparing multiple ketamine infusions with midazolam in chronic PTSD were identified. There is a possibility of publication bias due to the lack of publication of many other small trials. One double-blind, crossover RCT in patients with serotonin reuptake inhibitor-resistant OCD (N=15) found that ketamine infusion provided a higher frequency of Yale-Brown Obsessive-Compulsive Scale (YBOCS) response at day 7 compared with placebo; however, unblinding was suspected and only data from the first phase were analyzed because of a carryover effect of ketamine. A case series (N=14) identified only 1 patient who demonstrated prespecified significant YBOCS response after 2 to 3 weeks. A single RCT in patients with chronic PTSD (N=30) found that ketamine infusion produced significantly greater improvements in a PTSD symptom scale at 2 weeks compared to midazolam. Common side effects of ketamine infusion include headache, anxiety, dissociation, nausea, and dizziness. The intense treatment protocols, the severity of adverse events, and the short treatment durability limit the clinical utility of the treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have migraine headache pain, chronic pain syndromes (e.g., complex regional pain syndrome, fibromyalgia, headache, neuropathic pain, spinal cord injury) and psychiatric disorders (e.g., treatment-resistant depression, OCD, PTSD) who receive intramuscular (IM) ketamine, the evidence consists of a narrative review, a double-blinded randomized and placebo-controlled trial, and a recent retrospective cohort study. The evidence suggests that IM ketamine may be effective, however, the narrative review failed to demonstrate a role for ketamine, the double-blinded randomized and placebo-controlled trial was a small sample study (N=14), and long-term data is still needed to effectively evaluate the efficacy and safety of IM ketamine. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Society of Regional Anesthesia and Pain Medicine et al.

In 2018, the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine and the American Society of Anesthesiologists issued a joint consensus guideline on the use of intravenous (IV) ketamine for treatment of chronic pain. (52) The guideline found:

- Weak evidence supporting use of IV ketamine for short-term improvement in patients with spinal cord injury pain
- Moderate evidence supporting use of IV ketamine for improvement in patients with chronic regional pain syndrome up to 12 weeks
- Weak or no evidence for immediate improvement with IV ketamine use for other pain conditions, including mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache and spinal pain

American Psychiatric Association

In 2017, the American Psychiatric Association (APA) published an evidence review and consensus opinion of the use of ketamine in treatment-resistant depression. (53) The APA 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."

Ongoing and Unpublished Clinical Trials

Over 100 trials evaluating IV infusion of ketamine for depression are listed on clinicaltrials.gov. (54) The majority are completed but not published. Some currently ongoing and unpublished trials that include over 50 participants are listed in Table 20.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05339074	Maintenance Ketamine Infusions for Treatment-Resistant Bipolar Depression: An Open-Label Extension Trial	60	Feb 2026
NCT05045378	Low-dose Ketamine Infusion Among Adolescents with Treatment-resistant Depression: a Randomized, Double-blind Placebo-control Study	54	Dec 2026
NCT05973851	A Randomised, Controlled Trial to Investigate the Effect of a Six week Intensified Pharmacological Treatment for Major Depressive Disorder Compared to Treatment as Usual in Subjects Who Had a First-time Treatment Failure on Their First-line Treatment	418	Jun 2026

NCT06034821	Rapid Reversal of Suicidal Depression: Comparative Effectiveness of ECT vs. KETAMINE Over the Lifespan (REaKT-SD)	1500	Mar 2030
NCT04032301	Characterization of Comorbid Post-traumatic Stress Disorder and Major Depressive Disorder Utilizing Ketamine as an Experimental Medicine Probe	108	Apr 2025
Unpublished			
NCT02461927	Ketamine for The Rapid Treatment of Major Depression and Alcohol Use Disorder	65	Oct 2023

NCT: national clinical trial.

Coding

Procedure 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, or device 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 Codes	96365, 96366, 96374
HCPCS Codes	J2002, J2003, J2004, [Deleted 10/2024: J2001]

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

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 <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2025	Document updated with literature review. The following editorial refinement was made to Coverage: Added “post-traumatic stress disorder” as an example of psychiatric disorder in both lidocaine and ketamine sections. Added references 1-8, 13, 14, 31, 34, 39, and 40; others removed.
11/15/2023	Document updated with literature review. The following changes were made to Coverage: 1) Added intramuscular administration of ketamine is considered experimental, investigational and/or unproven 2) Note 1 was added to refer for information on compounded ketamine products (e.g., oral and subcutaneous), and 3) Coverage was divided into 2 separate categories, Lidocaine and ketamine. Added references 13, 15-16, 21-23, 25-26, 28-40 and 44; one reference removed. Title changed from: Intravenous Anesthetics for the Treatment of Pain and Psychiatric Disorders.
04/15/2022	Reviewed. No changes.
05/15/2021	Document updated with literature review. Coverage unchanged. References 8, 9, 11, and 19-23 added, others updated, and some removed.
08/15/2020	Reviewed. No changes.

09/01/2019	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".
04/15/2018	Document updated with literature review. Coverage unchanged. References 17 and 20 added.
04/15/2017	Reviewed. No changes.
04/01/2016	Document updated with literature review. The following condition was added to the EIU listing in Coverage; Chronic daily headache. Otherwise coverage unchanged.
04/01/2015	Reviewed. No changes.
04/15/2014	Document updated with literature review. Coverage unchanged.
08/15/2012	New Medical Document