Medical Policy

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Title: Intravenous Anesthetics for the Treatment of Chronic Pain and Psychiatric Disorders

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Populations	Interventions	Comparators	Outcomes
Individuals: • With chronic pain syndromes (e.g., neuropathic pain, fibromyalgia)	Interventions of interest are: • A course of intravenous anesthetics (e.g., lidocaine, ketamine)	Comparators of interest are: • Oral pain medications	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Medication use • Treatment-related morbidity
Individuals: • With treatment-resistant depression	Interventions of interest are: • •A course of intravenous ketamine	Comparators of interest are: • Therapy Psychotropic medications	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Medication use

Populations	Interventions	Comparators	Outcomes
			Treatment-related morbidity
Individuals: • With other psychiatric disorders (e.g., obsessive-compulsive disorder, post-traumatic stress disorder)	Interventions of interest are: • A course of intravenous ketamine	Comparators of interest are: • Therapy • Psychotropic medications	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Medication use • Treatment-related morbidity

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 (OCD).

OBJECTIVE

The objective of this evidence review is to determine whether a course of intravenous anesthetics improves the net health outcome in individuals with: (1) chronic pain syndromes (e.g., complex regional pain syndrome, fibromyalgia, chronic headache, chronic neuropathic pain, spinal cord injury), (2) treatment-resistant depression and (3) other psychiatric disorders (e.g., obsessive-compulsive disorder, post-traumatic stress disorder).

BACKGROUND

Intravenous Anesthetic Agents

Courses of intravenous (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 for 1 to 6 hours for up to 10 days.

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 IV administration of anesthetics 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 15 or more days a month for more than 3 months.[3,]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.[4,] 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.[5,] 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 IV ketamine has also been reported for treatment-resistant depression, defined as depression that does not respond adequately to appropriate courses of antidepressant medications.[6,] 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.

POLICY

A. Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of chronic pain, including, but not limited to chronic neuropathic pain, chronic daily headache, fibromyalgia, is considered **experimental / investigational**.

B. Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of psychiatric disorders, including but not limited to treatment-resistant depression, obsessive-compulsive disorder, and post-traumatic stress disorder is considered **experimental / investigational**.

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through September 24, 2024.

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, 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

INTRAVENOUS ANESTHETICS FOR INDIVIDUALS WITH CHRONIC PAIN

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 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 review.

Populations

The relevant population of interest is 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 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.

REVIEW OF EVIDENCE

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.[7,] 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.[8,9,]

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. [10,]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 sypathetic nerve blockade with lidocaine probably does not reduce pain relative to placebo.[11,]

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.[12,] 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.[13,] 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.[14,] 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 diphenydramine (active

control) in patients (N =34) with primarily diabetic neuropathy.[15,] 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[9,], the second examined infusions on 7 days in patients with spinal cord injury[16,], and the third examined a single ketamine infusion in patients with mixed refractory neuropathic pain.[17,]

A double-blind RCT of ketamine for CRPS was reported by Sigtermans et al (2009).[9,] 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.[16,] 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.[17,] 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)[13],	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)[14],	China	1	2015-2017	189 patients with PHN and pain >1 mo with VAS >4	A single 1.5 h infusion of 5 mg/kg lidocaine, injection of 1.5 mg midazolam and 3 mg granisetron, also taking pregabalin and oxycodone	1.5 h infusion of saline, plus midazolam and granisetron, also taking pregabalin and oxycodone
Ketamine						
Sigtermans et al (2009)[9],	Netherlands	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 (2010)[16],	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)[17],	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 mins Saline infusion over a 2-hour period

CRPS: complex regional pain syndrome; IV: intravenous; NR: not reported; 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)[13,]	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)[14,]	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)[9,]	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 et al (2010)[16,]	VAS (100 mm) at 2 weeks	Reduction in NRS Pain Score (SD), %[a]	

Study	Pain Scores (SD), %	Other Clinical Outcomes	AEs
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)[17,]	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	.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 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. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Kim et al (2018)[13,]			2. Did not use active placebo (diphenhydramine)		
Liu et al (2018)[14,]		4. The dose was higher and duration of treatment lower compared to other studies			
Sigtermans et al (2009)[9,]			2. Did not use active placebo (saline)		

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Amr et al (2010)[16,]			2. Did not use active placebo (saline)		
Pickering et al (2020)[17,]				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 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)[13,]						
Liu et al (2018)[14,]						
Sigtermans et al (2009)[9,]						
Amr et al (2010)[16,]					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)[17,]	3. Allocation concealment unclear				1. Power calculations were not reported	

The study limitations stated in this table are those notable in the current 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.[18,] 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.[19,] 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.[20,] 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.[21,] 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)[18,]	Retrospective chart review	Poland	Jan-Nov 2015	Adults with refractory neuropathic pain (N=85)	Lidocaine 5 mg/kg over 30 min once a week; range, 3 to 25 infusions	4 weeks
Vacher et al (2022)[19,]	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)[20,]	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 to 45 min for a total of 369 infusions	NR
Mangnus et al (2021)[21,]	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.

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)[18,]				
N	81		-	-
	NRS: 4.2 (SE not reported)		Not reported	Not reported

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 (%)
Vacher et al (2022)[19,]				
N	74			
	BPI: 6.15-5.88 (p=.106)			
Ketamine				
Patil & Anitescu (2012)[20,]				
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)[21,]				
N	36	18		
	NRS: 2	NRS: 1		

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

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.[22,] 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 time-frames, 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).[23,] 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 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. 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. Additional clinical trials are needed to evaluate the long-term efficacy and safety of repeat courses of IV anesthetics for chronic pain.

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 review.

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 ECT or emergency services for suicidal ideation) were excluded.

REVIEW OF EVIDENCE

Systematic Review
Dean et al (2021) published a systematic review of ketamine and other glutamate receptor modulators in patients with unipolar depression.[24,] 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.[25,] 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.[26,] 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.[27,] 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.[28,] 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).[29,] 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)[27,]	Double-blind, phase 2	U.S.	14	2012-2013	68 patients with TRD and a score >34 on the IDS-CR	IV 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
Ekstrand et al (2022)[28,]	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)[29,]	Open-label, noninferiority RCT	U.S.	5	2017-2022	403 adults with TRD and a score >20 on the MADRS	IV ketamine 0.5 mg/kg twice weekly for 3 weeks	ECT 3 times 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)[27],							
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)[28],							
N				186			
Ketamine				44 (46)			
ECT				57 (63)			
OR (95% CI)				0.51 (0.29 to 0.92)			
Anand et al (2023)[29],							
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.[30,] 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 9. Randomized Controlled Trials with Negative Results

Study; Trial	Countries	Sites	Dates	Design	Participants	Interventions		Outcome Measure	Follow-up	Comment
						Active	*Comparator*			
Ionescu et al (2019)[30,]	U.S.	1	2013-2015	Double-Blind	26 medicated patients with chronic and current suicidal ideation	6 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.

Table 10. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Singh et al (2016)[27,]			2. Did not use an active placebo (saline)		
Ionescu (2019)[30,]			2. Did not use an active placebo (saline)		1. Follow-up was performed at 3 mo, but not earlier time points
Ekstrand et al (2022)[28,]					

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Anand et al (2023)[29,]					

ECT: electroconvulsive therapy.
The study limitations stated in this table are those notable in the current 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)[27,]				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 (2019)[30,]				1. Only 14 of 26 patients completed the study	1. Power calculations were not reported	
Ekstrand et al (2022)[28,]		1. Open-label				
Anand et al (2023)[29,]		1. Open-label				

The study limitations stated in this table are those notable in the current 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.[31,32,33,34,35,] 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)[31,]	U.S.	537 patients with depression	Ketamine 4-8 infusions over 7-28 days	14-31 days after final infusion
Oliver et al (2022)[32,]	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)[33,]	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)[34,]	U.S	215 patients with depression	Ketamine infusion (mean dose 59mg); mean total number of infusions was 18	up to 12 months
Gutierrez et al (2024)[35,]	Canada	71 patients with treatment-resistant depression	IV low dose ketamine (f 0.5 mg/kg) bi-weekly sessions for 4 weeks	4 weeks

Table 13. Summary of Key Observational Study Results

Study	Treatment	Change From Baseline	Response , n (%)	Partial Response , n (%)	Remission, n (%)
McInnes et al (2022)[31,]	Ketamine	PHQ-9: 8.7 (SD, 6.6; 95% CI, 8.1-9.2)	288 (53.6)		155 (28.9)
Oliver et al (2022)[32,]	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)[33,]	Ketamine	MADRS: baseline 32.1 to 15.7 at follow-up; p<.001			
Pfeiffer et al (2024)[34,]	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)[35,]	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; CI: confidence interval; MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; PP: per protocol; SD: standard deviation; SI: suicidal ideation

Section Summary: Intravenous Anesthetics for Patients 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 an 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. 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.

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 review.

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.

REVIEW OF EVIDENCE

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.[36,] 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.[37,] 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)[36,]	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)[37,]	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

NR: not reported; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; SRI: serotonin reuptake inhibitor;

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)[36,]							
N	15						
Ketamine	7 (50)						

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 (%)
Placebo	0						
Feder et al (2021)[37,]							
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)[36,]					1. Follow-up only performed up to 1 week
Feder et al (2021)[37,]					1. Follow-up only performed up to 2 weeks

The study limitations stated in this table are those notable in the current 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)[36,]		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)[37,]		1. Potential unblinding due to dissociative effects of ketamine				

The study limitations stated in this table are those notable in the current 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.[38,] 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)[38,]	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)[38,]	Ketamine	YBOCS: 31.4 vs. 26.9; p=.01	YBOCS: 1 (7.1)[a]	YBOCS: 2 (14.3)[b]	

CI: confidence interval; MADRS: Montgomery-Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; YBOCS: Yale-Brown Obsessive-Compulsive Scale.
[a] YBOCS reduction ≥35%.
[b] YBOCS reduction 25% to 35%.

Section Summary: Intravenous Anesthetics for Patients 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. S 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[39,] 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.[40,] 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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Over 100 trials evaluating IV infusion of ketamine for depression are listed on clinicaltrials.gov.[41,] The majority are completed but not published. Some currently ongoing and unpublished trials that include over 50 participants are listed in Table 20.

Table 20. 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 Sixweek 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

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Each additional hour (list separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
J2002	Injection, lidocaine hcl in 5% dextrose, 1 mg
J2003	Injection, lidocaine hydrochloride, 1 mg

REVISIONS	
01-8-2022	Policy added to the bcbsks.com web site.
12-29-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
01-05-2024	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Diagnosis Box
	Updated References Section
10-01-2024	Updated Coding Section ▪ Removed deleted code J2001 ▪ Added J2002 and J2003 (eff. 10-01-2024)
12-23-2024	Updated Description Section
	Updated Policy Section ▪ Added treatment resistant-depression and post-traumatic stress disorder to section B "Intravenous infusion of anesthetics (e.g., ketamine or lidocaine) for the treatment of psychiatric disorders, including but not limited to treatment-resistant depression, obsessive-compulsive disorder, and post-traumatic stress disorder is considered experimental / investigational."
	Updated Rationale Section
	Updated References Section

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