Ketalar® (Ketamine) and Spravato® (Esketamine) (for Ohio Only)

Policy Number: CSOH2024D0069.B
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Instructions for Use

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Related Policies

None

Application

This Medical Benefit Drug Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

Coverage Rationale

This policy refers to the following ketamine products:

- Spravato (esketamine)
- Ketalar (ketamine)

Spravato (Esketamine) Nasal Spray

Spravato is proven and medically necessary for the treatment of certain conditions outlined within the InterQual® criteria. For medical necessity clinical coverage criteria, refer to the current release of the InterQual® guideline: Spravato: CP: Specialty Rx Non-Oncology, Esketamine (Spravato).

Ketalar (Ketamine) Injection

Ketamine injection is considered medically necessary and may be covered for the following:

- Anesthesia for diagnostic and surgical procedures that do not require skeletal muscle relaxation; **or**
- The induction of anesthesia prior to administration of other anesthesia agents; **or**
- As supplemental anesthesia for low-potency agents, such as nitrous oxide

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service.

Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3490	Unclassified drugs
S0013	Esketamine, nasal spray, 1 mg

Diagnosis Code	Description
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.8	Other recurrent depressive disorders
F33.9	Major depressive disorder, recurrent, unspecified

Background

Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. The mechanism of action is primarily due to antagonism of NMDA receptors in the central nervous system.[1]

Ketamine for the treatment of psychiatric disorders and pain has been gaining popularity. Studies available currently are of poor design, lacking adequate sample size and duration. Because of this, additional studies are needed to determine the safety and efficacy for the use of ketamine for these indications. Ketamine is not FDA approved for the treatment of any psychiatric disorder and there is not evidence to suggest that it is safer, more effective, or works faster than medications that are FDA approved for the treatment of certain psychiatric disorders.34 Known safety concerns associated with the use of ketamine products include abuse and misuse, psychiatric events, increases in blood pressure, respiratory depression (slowed breathing), and lower urinary tract and bladder symptoms.

Clinical Evidence

Chronic Pain

Schwartzman et al conducted a randomized double-blind placebo - controlled trial to evaluate the effectiveness of intravenous ketamine in the treatment of complex regional pain syndrome (CRPS).[2] Patients were evaluated for 2 weeks or longer before treatment and for 3 months after. All subjects received normal saline with or without ketamine intravenously for 4h (25ml/h) daily for 10 days. The results showed that intravenous ketamine administered in an outpatient setting resulted in statistically significant ($p < 0.05$) reductions in many pain parameters. It also showed that subjects in the placebo group did not experience treatment effect in any parameter. The authors conclude that the results of this study warrant a larger randomized placebo - controlled trial using higher doses of ketamine and a longer follow-up period.

Noppers et al performed a randomized double blind, active placebo-controlled trial to evaluate the analgesic efficacy of ketamine on fibromyalgia pain.[3] Twenty-four fibromyalgia patients were randomized to receive either ketamine or the active placebo, midazolam by intravenous infusion. Visual Analogue Pain Scores (VAS) and ketamine plasma samples were collected after the infusion. In addition, an 8 week follow up collected pain scores derived from the fibromyalgia impact questionnaire (FIQ) were collected weekly. Fifteen minutes after infusion completion, the number of patients showing a reduction in pain

scores > 50% was 8 vs. 3 ($p < 0.05$), at t = 180min 6 vs. 2 (ns), at the end of week-1 2 vs. 0 (ns), and at end of week-8, 2 vs. 2 in the ketamine and midazolam groups, respectively. For VAS and FIQ scores no significant differences in treatment effects were observed in the 2.5-h following infusion or during the 8 - week follow-up. Adverse events were mild to moderate in both study groups. The authors conclude that a short-term infusion of ketamine is insufficient to induce long-term analgesic effects in fibromyalgia patients.

Psychiatric Disorders

Ketamine

McCloud et al assessed the effects of ketamine and other glutamate receptor modulators in alleviating the acute symptoms of depression in people with bipolar disorder.[4] The authors included randomized controlled trials comparing ketamine with other active psychotropic drugs or saline placebo in adults with bipolar depression in their review. Regarding ketamine, the authors concluded that there is limited evidence in favor of a single intravenous dose of ketamine over placebo with regard to response rate in the first 24 hours after treatment. In addition, ketamine did not show any better efficacy regarding remission in bipolar depression. While ketamine may have the potential to have a rapid and transient antidepressant effect, the efficacy of a single intravenous dose is limited.

Coyle et al completed a systematic review of the literature and analyzed data from 21 studies where ketamine was used as an antidepressant.[5] The authors concluded that effectiveness was significantly greater for repeat than single infusion at 4 h, 24 h, and 7 days. For single infusion studies, effect sizes were large and significant at 4 h, 24 h, and 7 days. Effectiveness for open-label and participant-blind infusions was not significantly different at any time point. The authors concluded that single ketamine infusions elicit a significant antidepressant effect from 4 h to 7 days. There were a small number of studies at 12 - 14 days post infusion that failed to reach significance. Results suggest a discrepancy in peak response time depending upon primary diagnosis - 24 h for MDD and 7 days for BD. The authors concluded that further placebo-controlled studies are needed to evaluate the effect of ketamine over time.

Lee et al conducted a meta-analysis to assess the efficacy of ketamine compared to placebo for the reduction of depressive symptoms in patients who meet criteria for a major depressive episode.[6] The authors reviewed two electronic databases for randomized, placebo-controlled trials of ketamine treatment for patients with major depressive disorder or bipolar depression while using a standardized rating scale. The authors included 5 studies in the quantitative meta-analysis. The overall effect size at day 1 was large and statistically significant with an overall standardized mean difference of 1.01 (95% confidence interval 0.69 - 1.34) (Pb.001), with the effects sustained at 7 days after drug administration. The authors concluded that the effect of ketamine on depressive symptoms at days 1 and 7 post administration supports a potential, new and effective pharmacotherapy with rapid onset, efficacy and good tolerability.

Wan et al pooled data from 205 intravenous ketamine infusions in 97 participants with DSM-IV-defined major depressive disorder from 3 clinical trials.[7] They evaluated the safety and tolerability through attrition, adverse events (AEs), hemodynamic changes, and assessments of psychosis and dissociation. The overall antidepressant response rate, defined as a ≥ 50% improvement in Montgomery-Asberg Depression Rating Scale score, was 67%, or 65 of 97 patients. Four of 205 or 1.95% infusions were discontinued due to AEs. The overall attrition rate was 3.1% or 3 of 97 patients. The most frequent AEs within four hours of the infusion were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Protocol-defined hemodynamic changes occurred in ~1/3 of patients. In addition, ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms (all $p < .05$). There were no cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information. The authors concluded that in this group of patients with TRD, ketamine was safe and well tolerated and further research investigating the safety of ketamine in severe and refractory depression is warranted.

Migraine Headache

Lauritsen et al (2016) evaluated the use of intravenous ketamine in patients with refractory migraine treated in the hospital setting.[8] The authors completed a retrospective chart review, which identified six patients with refractory migraine admitted from 2010 through 2014 for treatment with intravenous ketamine. A standard protocol was used to administer ketamine starting with a dose of 0.1 mg/kg/hr and increased by 0.1 mg/kg/hr every 3 to 4 h as tolerated until a target pain score of 3/10 was achieved and maintained for 8 hours or more. Visual Analogue Scale (VAS) scores at time of hospital admission were obtained as well as average baseline VAS scores prior to ketamine infusion. The age range of study patients was 29 - 54 years with a median age of 36.5. Additionally, 83% were women. Pre - treatment pain scores ranged from 9 to 10. All patients achieved a

target pain level of 3 or less for 8 h; the average ketamine infusion rate at target was 0.34 mg/kg/hour (range 0.12-0.42 mg/kg/hr). One patient reported a transient out-of-body hallucination following an increase in infusion rate, which resolved after decreasing the rate. There were no other significant side effects. The authors concluded that IV ketamine was safely administered in the hospital setting to patients with refractory chronic migraine. Treatment was associated with short term improvement in pain severity in 6 of 6 patients with refractory chronic migraine. Prospective placebo-controlled trials are needed to assess short term and long-term efficacy of IV ketamine in refractory chronic migraine.

Pomeroy et al investigated the use of intravenous, subanesthetic ketamine for chronic migraine (CM) or new daily persistent headache (NDPH) in a retrospective review.[9] Upon admission, the mean headache pain rating, using a 0-10 pain scale was an average of 7.1 and decreased to 3.8 at discharge ($p < .0001$). Seventy-two percent (55/77) of patients experienced at least a 2-point improvement in headache pain at discharge. There were some acute responders that maintained this improvement in headache pain at their follow-up office visit, but sustained response did not achieve statistical significance (15/77, 27.3%). The mean duration of infusion was 4.8 days. Overall, patients tolerated ketamine. The authors concluded that subanesthetic ketamine infusions may be beneficial in individuals with CM or NDPH who have failed other treatments. Controlled trials are needed to confirm this.

Etchison et al evaluated the efficacy and safety of low-dose intravenous (IV) ketamine for treatment of acute migraine in the emergency department (ED) in a randomized, double-blind, placebo-controlled trial.[10] 34 subjects were randomized to receive 0.2 mg/kg of IV ketamine or an equivalent volume of normal saline by IV push. Numeric Rating Scale (NRS - 11) pain scores (0 = ”no pain” and 10 = ”worst pain imaginable”), categorical pain intensity scores from 0 to 3 (0 = ”no headache” and 3 = ”severe headache”), functional disability scores from 0 to 3 (0 = ”no disruption of daily activities” and 3 = ”performance of daily activities is severely impaired”), side effects using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) model, and adverse events were assessed at baseline and 30 minutes post-treatment. The primary outcome was between-group difference in NRS - 11 score reduction at 30 minutes and required a 2 - point difference in NRS - 11 scale for statistical significance. The authors found no statistically significant difference or clinically significant difference in NRS - 11 score reduction between the groups after 30 minutes (median NRS - 11 score reduction = 1 (interquartile range [IQR] 0 to 2.25) for ketamine group and 2 (IQR 0 to 3.75) for placebo group. SERDA scores in the ketamine group were significantly greater for generalized discomfort at 30 minutes ($p = 0.008$) and fatigue at 60 minutes ($p = 0.0216$). Authors concluded that ketamine was overall well tolerated; however, 0.2 mg/kg IV ketamine was not efficacious in treating migraine and future studies should be investigated for more effective dosing and routes of administration.

Technology Assessment

Psychiatric Disorders

Hayes compiled a Health Technology Brief on ketamine for treatment-resistant unipolar depression or posttraumatic stress disorder (PTSD) dated November 21, 2017. Regarding treatment-resistant depression (TRD) in adults, Hayes assigned a rating of C, potential but unproven benefit. This rating reflects preliminary positive evidence from a number of studies, and the potential for bias in these results due to shortcomings in study design. For PTSD, Hayes assigned a rating of D2, insufficient published evidence to assess the safety and/or impact on health outcomes or patient management. This rating reflects the small amount of evidence available for this use.[11]

For ketamine used as an adjunct to electroconvulsive therapy to increase antidepressant effects of this treatment in patients with TRD, Hayes assigned a rating of C. This rating reflects a large body of low quality, inconsistent evidence.[12]

Hayes compiled a Medical Technology Directory on ketamine for treatment-resistant bipolar depression (BPD), dated November 19. 2017. Hayes assigned a rating of D2. This rating reflects insufficient evidence regarding the efficacy and safety of ketamine as an add-on to medical treatment for treatment-resistant BPD. This rating also reflects a very-low quality body of evidence limited by a small number of studies, lack of long term follow up, and comparative studies.[13]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Ketamine is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is indicated for the induction of anesthesia prior to the administration of other general anesthetic agents. Ketamine is indicated to supplement low-potency anesthetic agents, such as nitrous oxide.[1]

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Policy History/Revision Information

Date	Summary of Changes
04/01/2024	**Supporting Information** • Updated *Background* and *References* sections to reflect the most current information • Archived previous policy version CSOH2023D0069.A

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]), or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC), or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC), or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC), or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.