INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Ketamine is considered medically necessary and may be covered for:
I. Anesthesia for diagnostic and surgical procedures that do not require skeletal muscle relaxation
II. The induction of anesthesia prior to administration of other anesthesia agents
III. As supplemental anesthesia for low-potency agents, such as nitrous oxide

Ketamine is investigational, and therefore not proven or medically necessary for:
I. Psychiatric disorders (including, but not limited to depression, bipolar disorder, & posttraumatic stress disorder)
II. Chronic pain (including but not limited to nonmalignant pain, Fibromyalgia, neuropathic pain, Complex Regional Pain Syndrome, Reflex Sympathetic Dystrophy)
III. Migraine headaches
**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

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 agents, such as nitrous oxide.¹

**BACKGROUND**

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.

**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 the member specific benefit plan document 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 Coverage Determination Guidelines may apply.

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**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).⁶ 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. 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 min 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**

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.¹² 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 conclude 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.⁴ 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 were not significantly different at any time point. The authors conclude 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 conclude 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. 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 conclude 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. 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 conclude that 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. 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. Pretreatment 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 conclude 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 investigate the use of intravenous, subanesthetic ketamine for chronic migraine (CM) or new daily persistent headache (NDPH) in a retrospective review. 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 conclude 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.

**Technology Assessments**

**Psychiatric Disorders**

Hayes compiled a Medical Technology Directory on ketamine for Mood Disorders dated September 28, 2016. 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 ketamine used as an anesthetic during electroconvulsive therapy to increase antidepressant effects of this treatment in patients with TRD, Hayes assigned a rating of D2. This Rating reflects the mixed results from a small number of studies.

Hayes compiled a Medical Technology Directory on ketamine for Posttraumatic Stress Disorder (PTSD) dated November 21, 2017. 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.

**Chronic Nonmalignant Pain**

Hayes completed a Health Technology Brief on intravenous ketamine for chronic nonmalignant pain and assigned a rating of C, potential but unproven benefit. Some published evidence suggests that safety and impact on health outcomes are at least comparable to standard treatment/testing. However, substantial uncertainty remains about safety and/or impact on health outcomes because of poor-quality studies, sparse data, conflicting study results, and/or other concerns.

**CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)**

Medicare does not have a National Coverage Determination for the use of Ketamine Injection in treatment of depression or pain management. Local Coverage Articles (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual, Chapter 15, Section 50 Drugs and Biologicals. (Accessed October 31, 2017)

**REFERENCES**


**POLICY HISTORY/REVISION INFORMATION**

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