Harvard Pilgrim Health Care

Medical Policy
Ketamine HCl for Treatment of Psychiatric Disorders and Pain Management

Effective Date: September 1, 2016

Subject: Ketamine Hydrochloride for Treatment of Psychiatric Disorders and Pain Management

Overview: Ketamine hydrochloride is a rapid-acting anesthetic drug that is FDA-approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and to supplement low-potency agents, such as nitrous oxide.

- Common adverse effects include hypertension, tachycardia and psychiatric signs and symptoms.
- Ketamine can also produce a transient respiratory depression, and should be used by or under the direction of physicians experienced in administering procedural anesthetics.[1]

Ketamine hydrochloride is increasingly being used for off label treatment of psychiatric conditions including treatment-refractory unipolar major depression. Ketamine hydrochloride is also increasingly being used for chronic pain management. Use of Ketamine for the treatment of psychiatric disorders and for chronic pain management is an off label use and not an FDA-approved treatment.

Policy and Coverage Criteria:

Harvard Pilgrim considers the off-label use of ketamine hydrochloride to treat any form of depression, psychiatric disorder, or chronic pain including, but not limited to: complex regional pain syndrome, chronic neuropathic pain, fibromyalgia, migraines, and cluster headaches **investigational/experimental and unproven**.

Use of ketamine for the induction of anesthesia or for conscious sedation for minor surgical procedures that do not require skeletal muscle relaxation is considered **medically necessary.**

Exclusions: N/A

Supporting Information:

1. Technology Assessment
   Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and a standard anesthetic drug. The drug can be administered via several routes, resulting in varying degrees of bioavailability: intravenous, up to 100%; intramuscular, 93%; intranasal, 25% to 50%; and oral, 16% to 20%. There has been recent off label use to treat treatment refractory unipolar major depression, however, the benefit is reportedly short lived. Ketamine is potentially neurotoxic and liable to abuse/diversion.

2. Literature Review
   There is an emerging use of ketamine to treat depression in treatment-resistant patients. The research thus far has been promising however, the majority of studies have shortcomings, including: small sample size, poor study design, lack of long-term data, and possibility of bias. Further research is needed to explore the safety, utility and efficacy for the use of ketamine to treat depression.

[1] Regular monitoring of vital signs is required, and resuscitative equipment should be available for use.

Newport et al (2015) conducted a systematic review and meta-analysis of ketamine and other NMDA receptor antagonists in the treatment of major depression. In 7 trials including 147 participants, ketamine produced rapid, yet transient, antidepressant effect, with odds ratios for response and transient remission of symptoms at 24 hours, accompanied by brief psychotomimetic and dissociative effects. In 5 trials including 89 participants, ketamine augmentation of ECT significantly reduced depressive symptoms following an initial treatment but not at the conclusion of the ECT course. The authors concluded that the antidepressant effect of ketamine holds promise for future glutamate-modulating strategies. The fleeting nature of ketamine's therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution.

McGirr et al (2015) conducted a systematic review and meta-analysis to assess the efficacy of ketamine in major depressive episodes. The analysis included data from 7 RCTs employing IV infusion and 1 RCT employing intranasal ketamine. Ketamine was associated with higher rates of clinical remission relative to comparator at 24 h, 3 days, and 7 days, as well as higher rates of clinical response at all 3 times. Ketamine was associated with transient psychotomimetic effects, but no persistent psychosis or affective switches. The authors concluded that single administrations ketamine are efficacious in the rapid treatment of unipolar and bipolar depression. Additional research is required to determine optimal dosing schedules, route, treatment schedules, and the potential efficacy of other glutamatergic agents.

Caddy et al (2015) conducted a review to assess the effects and acceptability of ketamine and other glutamate receptor modulators in comparison to placebo, other pharmacologically active agents, or ECT in alleviating the acute symptoms of depression in people with unipolar major depressive disorder. The review included 9 trials using ketamine. Ketamine proved to be more efficacious than placebo, though the quality of evidence was limited by risk of bias and small sample sizes. There was low quality evidence that treatment with ketamine increased the likelihood of response after 24 hours, 72 hours, and one week. Ketamine caused more confusion and emotional blunting compared to placebo. Ketamine was more effective than ECT at 24 hours and 72 hours, but not at one week or two weeks. The authors concluded that there is limited evidence for ketamine's efficacy over placebo at time points up to one week in terms of response rate. Further RCTs are needed to explore different modes of administration of ketamine with longer follow-up, which test the comparative efficacy of ketamine and the efficacy of repeated administrations.

Fond et al (2014) conducted a systematic review and meta-analysis to determine whether or not ketamine administration significantly improves depressive symptomatology in depression and major depressive disorder (MDD), bipolar depression, resistant depression, and as an anesthetic agent in ECT for resistant depression. The review included 9 non-ECT studies with 192 participants with major depressive disorder and 34 participants with bipolar depression. Depression scores were significantly decreased in the ketamine groups compared to those in the control groups. The authors concluded that the results in the studies are encouraging and further middle and long term efficacy studies are needed.

Ghasemi et al (2014) conducted a blind, randomized study to evaluate the rapid antidepressant effects of ketamine compared with ECT in hospitalized patients with MDD. The study included 18 patients with MDD who were divided into two groups which received either 3 IV infusions of ketamine hydrochloride (0.5 mg/kg over 45 min) or ECT on 3 test days (every 48 hours). Within 24 hours, depressive symptoms significantly improved in subjects receiving the first dose of ketamine compared with ECT group and remained significant throughout the study. The authors concluded that ketamine is as effective as ECT in improving depressive symptoms in MDD patients and have more rapid antidepressant effects compared with ECT.

Lapidus et al (2014) conducted a randomized, double-blind, crossover study to test the safety, tolerability, and efficacy of intranasal ketamine in 20 patients with major depression who had failed at least one prior antidepressant trial. Patients who received ketamine showed significant improvement in depressive symptoms at 24 hours compared to placebo. Response criteria were met in 44% of patients 24 hours after ketamine compared with 6% after placebo. Intranasal ketamine was well tolerated with minimal psychotomimetic or dissociative effects and was not associated with clinically significant changes in hemodynamic parameters.

Price et al (2014) conducted a randomized controlled trial to assess suicidality in symptomatic patients with treatment-resistant unipolar major depression. In the ketamine-treated patients, 53% scored zero on all 3 explicit suicide measures at 24 hours compared with 24% of the midazolam group. Ketamine showed a reduction in implicit associations between self- and escape related words but was not seen in the midazolam group. The authors concluded that IV ketamine produces rapid reductions in suicidal cognition over and above active placebo. Further research is warranted to test ketamine's antisuicidal effects in higher-risk samples.

Szymkowicz et al (2013) assessed the long-term efficacy of repeated IV ketamine infusions in 3 patients with highly treatment-resistant depression via a naturalistic observation study. Patients were administered ketamine at 0.5 mg/kg of ideal body weight over 40 min followed by a saline flush. All three patients responded to the ketamine infusions, but each went through individualized treatments based on their response. The authors concluded that the cases support the therapeutic effect of low-dose repeated IV ketamine for patients with treatment-resistant depression. Further research is needed to define risks, benefits, indications, and contraindications of this treatment.
Murrough et al (2013) conducted a RCT of a single infusion of ketamine compared to an active placebo control to evaluate the rapid antidepressant efficacy of ketamine in 73 patients with treatment-resistant major depression. The ketamine group had greater improvement than the control group 24 hours after treatment. The authors concluded that ketamine demonstrated rapid antidepressant effects, supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression. Further research on response durability and safety are required before implementation in clinical practice.

Codes:

HCPCS code:
J3490 – unclassified drugs

References:

1. Hayes, Inc. Medical Technology Directory. Ketamine for mood disorders. Hayes, Inc. Lansdale, PA. September 22, 2015.
2. Newport, DJ., Carpenter, LL., McDonald, WM., Potash, JB., Tohen, M., Nemeroff, CB., APA Council of Research Task Force on Novel Biomarkers and Treatments. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015; 172(10):950-66.
3. Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lancon, C., Brittner, M., Micoulaud-Franchi, JA., Richieri, R., Courtet, P., Abbar, M., Roger, M., Leboyer, M., Boyer, L. Ketamine administration in depressive disorders: a systematic review and meta-analysis. Psychopharmacology (Berl). 2014; 231(18):3663-76.
4. McGirr, A., Berlim, MT., Bond, DJ., Fleck, MP., Yatham, LN., Lam, RW. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol Med. 2015; 45(4):693.
5. Caddy, C., Amit, BH., McCloud, TL., Rendell, JM., Furukawa, TA., McShane, R., Hawton, K., Cipriani, A. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev. 2015; 9:CD011612.
6. Ghasemi, M., Kazemi, MH., Yoosefi, A., Ghasemi, A., Paragomi, P., Amini, H., Afzali, MH. Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder. Psychiatry Res. 2014; 215(2):355.
7. Szymkowicz, SM., Finnegan, N., Dale, RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. J Affect Disord. 2013; 147(1-3):416-20.
8. Murrough, JW., Iosifescu, DV., Chang, LC., Al Jurdi, RK., Green, CE>, Perez, AM., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., CHarney, DS., Mathew, SJ. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry. 2013; 170(1):1134.
9. Lapidus, KA., Levitch, CF., Perez, AM., Brallier, JW., Parides, MK., Soleimani, L., Feder, A., Iosifescu, DV., Charney, DS., Murrough, JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014; 76(12):970.
10. Price, RB., Iosifescu, DV., Murrough, JW., Chang, LC., Al Jurdi, RK., Iqbal, SZ., Soleimani, L., Charney, DS., Foulkes, AL., Mathew, SJ. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014; 31(4):335-43.
11. Schak, KM., Vande Voort, JL., Johnson, EK., Kung, S., Leung, JG., Rasmussen, KG., Palmer, BA., Frye, MA. Potential risks of poorly monitored ketamine use in depression treatment. Am J Psychiatry. 2016; 173(3):215-218.