Clinical Policy Title: Ketamine for treatment-resistant depression

Clinical Policy Number: 00.02.13

Effective Date: January 1, 2016
Initial Review Date: August 19, 2015
Most Recent Review Date: January 18, 2017
Next Review Date: January 2018

Policy contains:
- Ketamine.
- Depression.
- Treatment-resistant depression.

Related policies:

CP# 00.02.01 Ketamine (Ketalar®) and intravenous regional sympathetic nerve blockade for treatment of complex regional pain syndrome
CP# 09.02.01 Vagus nerve stimulation (VNS)

ABOUT THIS POLICY: AmeriHealth Caritas Northeast has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Northeast’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Northeast when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Northeast’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Northeast will update its clinical policies as necessary. AmeriHealth Caritas Northeast’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Northeast considers the use of ketamine for treatment-resistant depression (TRD) to be investigational and, therefore, not medically necessary.

Limitations:

All other uses of ketamine for primary psychiatric dysfunctions are not considered medically necessary.

Alternative covered services:

Within plan benefits, physician and behavioral health visits and prescribed medications.

Background
Major depression is one of the most common behavioral health disorders in the United States. In 2015, there were 16 million adults (6.9 percent) with at least one major episode of depression within the past 12 months, and 10 percent to 30 percent were estimated to have TRD (National Institute of Mental Health, 2016; Al-Harbi, 2012).

Treatment of depression typically consists of pharmacotherapy, psychotherapy, or a combination of these two. More severe depression may be treated with electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), or other newer therapies. TRD is depression refractory to multiple attempts at treatment, each of which is of adequate duration and dosage. Individuals at risk for TRD include those who have difficulty complying with pharmacotherapy, have been prescribed ineffective dosage, have genetic predisposition, or have comorbid alcohol or substance abuse. Social determinants of ineffective care play a significant role in the development of TRD, such as poverty or low educational attainment.

**Ketamine hydrochloride:**

Newer treatments are being explored for management of TRD. These treatments target different receptors or neurotransmitters than existing antidepressants, one of which is the glutamate/N-methyl-D-aspartate (NMDA) receptor neurotransmitter system.

The anesthetic agent ketamine is a nonselective, noncompetitive, high-affinity NMDA receptor antagonist with rapid onset and a variety of pharmacologic impacts, including inhibition of serotonin, norepinephrine, and the dopamine transport system. The U.S. Food and Drug Administration (FDA) approved ketamine as the sole anesthetic agent 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 (FDA, 2012). Bioavailability is near 100 percent when administered intravenously (IV), but with declining absorption when administered intramuscularly (IM), intranasally, or orally. Its proposed use as an antidepressant is considered an “off-label” use (ECRI, 2013).

**Searches**

AmeriHealth Caritas Northeast searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

Searches were conducted in November 15, 2016. Search terms were “treatment resistant depression” and “ketamine depression.”
We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Matthew et al. noted two proof-of-concept trials with small numbers of patients that demonstrated rapid (within two hours) improvement of depression on the Hamilton Depression scale after infusion of ketamine. This improvement was sustained for up to a week. Subsequent infusions three times a week demonstrated sustained improvement on the depression scale. However, studies have not been carried out over longer periods of time. Optimal dosage has not been ascertained, and the studies to date have been on very small samples.

**Policy update:**

We identified two new Cochrane reviews (Caddy, 2015; McCloud, 2015) and one new guideline by the Department of Veterans Affairs and Department of Defense (VA/DOD) Working Group (2016). The systematic reviews assessed ketamine and other glutamate receptor modulators for treatment of unipolar depression in adults (Caddy, 2015) and bipolar depression (McCloud, 2015). Limited evidence from placebo-controlled trials of low quality suggests single-dose IV ketamine as an add-on to other mood stabilizers has a rapid, short-term antidepressant effect in persons with TRD. Ketamine was associated with higher rates of confusion and emotional blunting than placebo. However, data on other important effects such as suicidality, cognition, quality of life, costs to healthcare services, and dropouts due to lack of efficacy were rarely reported.

All included studies administered ketamine intravenously, which can pose practical problems in clinical practice. Very few trials were included in the meta-analyses for each comparison, and the majority of comparisons contained only one study. Ketamine's psychotomimetic effects could compromise study blinding. Future research with well-designed randomized controlled trials (RCTs) of longer duration is needed to address difference modes of administration as well as repeat administration.

Given the unresolved safety concerns and duration of effect, the VA/DOD Working Group (2016) recommended against using ketamine to treat major depressive disorder (MDD) outside of research settings. The American Psychiatric Association (2010) reaffirmed their clinical practice guideline on MDD in 2015 and did not mention ketamine as a treatment option. The new information does not change
previous conclusions. Therefore, no policy changes are warranted.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>VA/DOD Working Group (2016) Management of MDD</td>
<td><strong>Key points:</strong> Given the limited information on ketamine’s safety and duration of effect, the Work Group recommends against the use of ketamine to treat MDD outside of a research setting (strong recommendation against).</td>
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<td>Caddy (2015) Cochrane review Ketamine and other glutamate receptor modulators for unipolar depression in adults</td>
<td><strong>Key points:</strong> Systematic review and meta-analysis of 25 RCTs (1,242 total participants), including nine RCTs of ketamine mainly for TRD. Overall quality: low with moderate to high risk of bias and small samples. IV ketamine versus placebo: Ketamine increased the likelihood of response after 24 hours (odds ratio [OR] 10.77, 95% confidence interval [CI] 2.00 to 58.00; three RCTs, 56 participants), 72 hours (OR 12.59, 95% CI 2.38 to 66.73; three RCTs, 56 participants), and one week (OR 2.58, 95% CI 1.08 to 6.16; four RCTs, 131 participants). Effects of ketamine was even less certain at two weeks (OR 0.93, 95% CI 0.31 to 2.83; 51 participants, one RCT). Ketamine caused more confusion and emotional blunting. Insufficient evidence to compare ketamine to other alternatives. Further RCTs (with adequate blinding) are needed to explore different modes of administration of ketamine with longer follow-up that test the comparative efficacy of ketamine and the efficacy of repeated administrations.</td>
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<td>McCloud (2015) Cochrane review Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults</td>
<td><strong>Key points (ketamine results only):</strong> Systematic review and meta-analysis of two placebo-controlled RCTs (33 total participants). Overall quality: very low. IV ketamine versus placebo: 24 hours after infusion, favored ketamine (OR 11.61, 95% CI 1.25 to 107.74; P = 0.03; I² = 0%, two RCTs, 33 participants). Statistical significance disappeared at three days, but the mean estimate still favored ketamine (OR 8.24, 95% CI 0.84 to 80.61; two RCTs, 33 participants). No difference at one week (OR 4.00, 95% CI 0.33 to 48.66; P = 0.28, one RCT; 18 participants). RCTs (with adequate blinding) are needed to explore different modes of administration of ketamine and to study different methods of sustaining antidepressant response, such as repeated administrations.</td>
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<td>Matthew (2012)</td>
<td><strong>Key points:</strong></td>
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Ketamine for unipolar TRD

- A narrative review of early clinical studies.
- First-generation studies reported the safety and acute efficacy of a single subanaesthetic dose (0.5 mg/kg) of IV ketamine.
- Second-generation studies focused on testing alternate routes of drug delivery, identifying methods to prevent relapse following resolution of depressive symptoms and understanding the neural basis.
- There is a paucity of adequately controlled double-blind trials and limited clinical experience outside of research settings.
- Little information exists regarding the impact on cognition of chronically administered ketamine, as reports have generally been limited to small-scale studies of poly-drug abusers.
- Given the potential risks of ketamine, safety considerations will ultimately determine whether this old drug is successfully repositioned as a new therapy for TRD.

American Psychiatric Association (2010, reaffirmed 2015)

Key points:
- Clinical practice guideline does not mention ketamine for depression.

References

Professional society guidelines/other:


Peer-reviewed references:

Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions.


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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