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: August 19, 2015
Next Review Date: August, 2016

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

Related policies: None.

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 Pennsylvania developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’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 Pennsylvania 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 Pennsylvania’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 Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

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

Limitations:

All uses of ketamine for primary psychiatric dysfunctions are not considered covered benefits.

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. The National Institute of Mental Health (NIMH) estimates that, in 2012, there were 16 million adults with at least one major episode of depression within the past 12 months. This represents 6.9 percent of US adults. Of this group, current estimates are that 10 percent to 30 percent may be considered to have treatment-resistant depression (Al-Harbi).

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. Treatment-resistant depression (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 with compliance 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.

Newer treatments are being explored for management of treatment-resistant depression. These treatments target different receptors or neurotransmitters than existing antidepressants. The glutamate/N-methyl-D-aspartate (NMDA) receptor system is one of the promising targets. The anesthetic agent ketamine is a nonselective, noncompetitive, high-affinity NMDA receptor antagonist now in clinical trials for treatment of TRD. Ketamine is a nonbarbiturate anesthetic chemically designated dl 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride; ketamine has rapid onset and a variety of pharmacologic impacts, including inhibition of serotonin, norepinephrine and the dopamine transport system.

Package inserts note 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” (Ketalar, ketamine hydrochloride injection, JHP Pharmaceuticals LLC, March 2012, Reference ID 30960500). Bioavailability is near 100 percent when administered intravenously, but with declining absorption when administered intramuscular (IM), intranasally or orally.

Ketamine’s primary indication is as an anesthetic agent. However, early studies have shown depression-response rates as high as 50 percent in small samples when ketamine has been infused on a weekly basis.

**Searches**

AmeriHealth Caritas Pennsylvania 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 July 2015. 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**

A review of current evidence by Matthew et al. noted two proof of concept trials with small numbers of patients demonstrated that after infusion of ketamine there was rapid (within two hours) improvement of depression on the Hamilton Depression scale. 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.

**Summary of clinical evidence**

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<th>Citation</th>
<th>Content</th>
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| Matthew SJ, CNS Drugs (2012) | **Key points:**  
  - The first generation of studies in patients with TRD reported the safety and acute efficacy of a single subanaesthetic dose (0.5 mg/kg) of intravenous ketamine.  
  - A second generation of ketamine studies is 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. |
| Murrough JW, Am. J. Psych (2014) | **Key points:**  
  - Two-site, parallel-arm, randomized controlled trial of a single infusion of ketamine (N = 47) compared to an active placebo control (N = 25).  
  - Depression measured on Montgomery-Asberg Depression Rating Scale (MADRS).  
  - MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval at 24 hours).  
  - Ketamine demonstrated rapid antidepressant effects in an optimized study design, further supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression.  
  - More information on response durability and safety is required before implementation in clinical practice. |
| Intramural Research Program, Zarate CA, NIMH, (2006) | **Key points:**  
  - Seventeen patients in a randomized, placebo-controlled, double-blind, crossover design.  
  - Patients receiving ketamine showed significant improvement in depressive symptoms compared with placebo within 110 minutes.  
  - Approximately 50% of patients maintained the antidepressant response at 72 hours. |
| Am Psychiatric Association, (2010) | **Key points:**  
  - Clinical practice guidelines do not mention ketamine for depression. |
| AHRQ | **Key points:** |
Citation | Content
--- | ---
 | • Early studies are encouraging but still very preliminary.
 | • Concerns about relapse, drug profile safety and ability to administer in a physician office.
| Excellus Blue Cross | Key points:
 | • Investigational.
| Blue Cross of MN. | Key points:
 | • Use of ketamine HCl to treat symptoms of all mental health and substance-related disorders is considered investigative.

Glossary

**Depression** — The most common behavioral health disorder in the U.S., in which the individual may have feelings ranging from sadness to hopelessness. It may be isolated or caused by medication or physical illness.

**Treatment-resistant depression (TRD)** — Depression refractory to multiple attempts at treatment, each of which is of adequate duration and dosage.

**Ketamine** — Anesthetic agent that has been FDA approved 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.” It is used off-label in the treatment of TRB.

Related policies

AmeriHealth Caritas Pennsylvania Utilization Management program description.

References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical trials:**


During the last 9 years several uncontrolled reports have been published, showing a rapid and impressive effect of ketamine in TRD patients (Berman, Cappiello et al. 2000; Zarate, Singh et al. 2006; Mathew, Murrough et al. 2010; Aan Het Rot, Zarate et al. 2012; Mathew, Shah et al. 2012; Murrough, Iosifescu et al. 2013). Recently three placebo-controlled trials showed that a single dose of sub-anesthetic, (0.5 mg/kg) slow intravenous (IV) ketamine improves depressive symptoms dramatically.... The investigators believe that the data presented above allows us to provide ketamine treatment here in the Sheba Medical Center for TRD patients.

**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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<th>CPT codes</th>
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<th>ICD-9 Code</th>
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<td>Major depressive disorder, single episode, unspecified degree</td>
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<td>Major depressive disorder, single episode, severe degree, without mention of psychotic behavior</td>
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<td>296.25</td>
<td>Major depressive disorder, single episode, in partial or unspecified remission</td>
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