This guideline is used to make coverage determinations as well as to inform discussions about evidence-based practices and discharge planning for behavioral health benefit plans managed by Optum®. When deciding coverage, the member’s specific benefits must be referenced.

All reviewers must first identify member eligibility, the member-specific benefit plan coverage, and any federal or state regulatory requirements that supersede the member’s benefits prior to using this guideline. Other clinical criteria may apply. Optum reserves the right, in its sole discretion, to modify its clinical criteria as necessary using the process described in Clinical Criteria.

This guideline is provided for informational purposes. It does not constitute medical advice.

Optum may also use tools developed by third parties that 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.

Optum may develop clinical criteria or adopt externally-developed clinical criteria that supersede this guideline when required to do so by contract or regulation.

**BENEFIT CONSIDERATIONS**

Before using this policy, please check the member-specific benefit plan document and any federal or state mandates, if applicable.

**DESCRIPTION OF SERVICES**

This review of Ketamine focuses on its utility as a rapid but transient antidepressant, most commonly delivered intravenously.

Ketamine is a selective and potent N-Methyl-D-aspartate (NMDA) receptor antagonist, and a derivative of phencyclidine (PCP). Ketamine works by “disconnecting” the thalamocortical and limbic systems, thereby dissociating the central nervous system from external stimuli, such as pain, sight or sound (Green & Krauss, 2004). Ketamine’s neurophysiologic effects include psychotomimetic, mood-elevating, dissociative, analgesic, and cognitive.

Historically, ketamine has been used for induction and maintenance of general anesthesia, usually in combination with a sedative (Haas & Harper, 1992). More recently, ketamine has been under investigation for its potential antidepressant effects (Brown, 2007).

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1 Optum is a brand used by United Behavioral Health and its affiliates.
Most clinical use of ketamine involves IV, IM, or intranasal administration, with specific dosage levels dependent on the desired therapeutic effect and preferred route (Reves, et al 2010; aan het Rot, et al 2008). Most ketamine studies for depression have used a subanesthetic dose of 0.5 mg/kg, administered via IV infusion over 40-60 minutes.

Initial ketamine infusion is typically administered in a facility setting equipped with appropriate safety monitoring equipment. Ketamine infusion is typically followed by a designated monitoring period, with certain patients requiring regular assessment of clinical status and vital signs. Studies conducted by the National Institute of Mental Health (NIMH) have required patients to be hospitalized for at least 24 hours post-ketamine for vital function monitoring and prudent risk management.

**COVERAGE RATIONALE**

Ketamine Infusion(s) is unproven and not medically necessary for the treatment of major depressive disorder, bipolar depression, and/or suicidal cognition.

A number of clinical trials have shown some benefit of a single intravenous ketamine infusion in patients with treatment resistant unipolar and bipolar depression, but many studies have relatively small sample sizes and poor blinding conditions. Many studies exclude patients who are actively suicidal, have unstable medical conditions, or have a recent history of substance abuse, and therefore safety issues for administration within these populations are not known. Little is also known about ketamine’s safety profile in patients who receive repeated doses.

Ketamine has yet to be cleared by the FDA as a treatment option for depression.

All services must be provided by or under the direction of a properly qualified behavioral health provider.

**CLINICAL EVIDENCE**

**Summary of Clinical Evidence**

A consistent intervention protocol for subanesthetic dosing of ketamine (0.5 mg/kg) when administered intravenously over a 40-minute time period, has been documented. However, little is known about ketamine’s broader incorporation into a well-defined treatment plan, as studies incorporating follow-up therapies after completion of ketamine infusion(s) are generally lacking. With short-term use, subanesthetic ketamine appears to be a relatively safe treatment for depressed patients when given in a controlled setting by properly trained personnel. Short-term side effects, such as perceptual and dissociative disturbances, seem to be well understood and managed.

A number of clinical trials have safely demonstrated the benefit of a single intravenous ketamine infusion in patients with treatment resistant unipolar and bipolar depression. Many studies found that the greatest difference in response between participants receiving ketamine vs. placebo was observed approximately one hour after infusion, with the potential for response to last a number of days. Results from numerous studies have found promising results for the impact of ketamine on suicidal ideation. The most comparable treatment to ketamine infusions for resistant depression and suicidal ideation is electroconvulsive therapy (ECT). At this time, there is a lack of large, well-designed trials comparing these two treatments.

In general, many studies have relatively small sample sizes and note poor blinding conditions; ketamine’s side effects may diminish the placebo effect and confound results. Many studies exclude patients who are actively suicidal, have unstable medical conditions, or have a recent history of substance abuse, and therefore safety issues for administration within these populations are not known. Little is also known about ketamine’s safety profile in patients who receive repeated doses, and longer-term follow-up studies on these individuals are still necessary.

Authors from the reviewed studies have pointed to a number of areas where further research on ketamine for depression is necessary. Many of these needs focus on the long-term safety profile of ketamine in depressed patients, particularly to confirm that no undesirable long-term adverse effects, including abuse or dependence, appear after multiple administrations. Other needs include longer follow-up trials to determine whether ketamine maintains its effect over time and the determination of optimal dosing/treatment schedules.

**Clinical Trials & Studies**

Grunebaum and colleagues (2018) conducted a randomized, controlled clinical trial to examine the acute effect of ketamine on clinically significant suicidal ideation in patients with major depressive disorder. 80 adults with current MDD were randomly assigned either ketamine or midazolam infusions. Reductions in SSI scores were seen after 1 day, and improvement in the Profile of Mood States depression were greater for the ketamine group at day 1. The authors conclude that ketamine demonstrated significant reductions in suicidal ideation within 24 hours when
compared to midazolam. This improvement could be seen for up to 6 weeks in uncontrolled follow-up. Future studies will be needed to assess the long-term safety profile of ketamine in suicidal ideation and depression.

Murrough and colleagues (2015) conducted a single-site, randomized controlled trial of ketamine in patients with mood and anxiety disorders presenting with clinically significant suicidal ideation (SI). A total of 24 patients were randomized to receive either a single IV treatment of ketamine (n = 12) or the anesthetic benzodiazepine agent midazolam (n = 12) as a control condition in addition to standard of care. Eligible participants received 0.5 mg/kg racemic ketamine hydrochloride or 0.045 mg/kg IV midazolam over 40 minutes under double-blind conditions. Subjects were assessed at 24, 48, and 72 hours, and 7 days post-treatment. All participants completed all study visits, with 19 completing a follow-up 5-week safety assessment. The primary efficacy outcome was SI severity at 24 hours post-treatment measured by the 21-item self-report Beck Scale for Suicidal Ideation (BSI). At 24 hours after treatment, BSI score was not significantly different between the treatment groups. However, a significant effect of treatment on BSI score emerged at 48 hours following intervention. The difference was no longer significant at 72 hours or 7 days. The effect was not setting-specific. The treatment was generally safe and well-tolerated, with patients in both groups reporting side effects including headache, dizziness, and anxiety. Five serious adverse events occurred during the study period; none were attributed to study participation. The authors conclude that ketamine may hold promise for the rapid treatment of suicidality, but note several limitations, including small sample size and concomitant medication use.

Wan and colleagues (2015) reported on findings related to the acute neuropsychiatric and general side effects of ketamine and longer-term consequences and overall acceptability in treatment-resistant depression patients. The authors pooled data across 3 clinical trials of 205 IV ketamine infusions in 97 participants with DSM-IV-defined major depressive disorder. Subjects in all studies were washed off psychotropic medication 2-4 weeks prior to randomization. Studies also required participants to have failed to respond to at least 2-3 FDA-approved antidepressant medications. Treatment response was defined as a > 50% improvement in the MADRS. Side effects peaked within the 120-minute period after infusion and largely resolved by the 240-minute and 24-hour time points. Ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms. There were no cases of persistent psychotomimetic and dissociative symptoms. There were no cases of persistent effects or increased substance use in a subgroup of patients with available long-term follow-up information. The authors note several limitations, particularly the efficacy and side-effect profile resulting from the combining of patient-level data from studies utilizing different clinical trial designs. They conclude that the data suggests that subanesthetic doses of ketamine administered to unipolar depressed patients in a controlled research setting presents a low and acceptable level of risk. However, they also note that future studies will be needed to more fully document the longer-term safety profile of ketamine in depression.

Lally and colleagues (2014) conducted a randomized, placebo-controlled, double-blind crossover design study to examine whether a single ketamine infusion could reduce anhedonia levels in patients with treatment-resistant bipolar depression. A total of 36 treatment-refractory individuals with bipolar I or II without psychotic features who were currently experiencing a major depressive episode (MDE) were included. All subjects were inpatients with MADRS scores > 20 at time of screening (mean = 33.92). All subjects had an MDE lasting at least 4 weeks and had failed to respond to at least one adequate antidepressant trial before hospital admission. All participants received on IV infusion of ketamine administered at subanesthetic dose of 0.5 mg/kg, and one infusion of placebo (0.9% saline solution) in a randomized order over a 4-week study period, and with 2 weeks between each infusion. All study team members were blind to the drug condition. The authors found that ketamine, compared with placebo, rapidly reduced the levels of anhedonia in patients; this reduction occurred within 40 minutes of the single ketamine infusion. Post-hoc exploratory simple effects tests revealed that anti-anhedonic effects of ketamine were significant at days 1, 3, 7, and 14 following infusion, suggesting that for some bipolar patients, ketamine may have specific benefits in reducing anhedonia levels, and that these benefits can last up to 2 weeks following a single infusion. After ketamine infusion, it was found that individuals taking lithium experienced greater anti-anhedonic effects than those receiving valproate when the antidepressant effect was controlled for. The authors note the limitation that the experiential difference between receiving ketamine and saline can be dramatic, and subjects likely realized what infusion they were receiving in each session. All, ongoing use of mood stabilizer medication may have masked or enhanced the effect of ketamine.

Price and colleagues (2014) conducted a follow-up from a recent study (Murrough, et al 2013) to test ketamine’s acute effect on explicit suicidal cognition and a performance-based index of implicit suicidal cognition (Implicit Association Test). TRD patients were recruited for a two-site double-blind randomized controlled trial (Murrough, et al 2013). Patients had been randomized to receive a single IV infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg) over 40 minutes. Fifty-seven participants completed measures of explicit suicidal cognition at both baseline and 24-hours postinfusion. Fifty-four participants completed implicit measures of suicidal cognition. Twenty-four house postinfusion, suicidality index scores (calculated by summing z-scores on the Beck Scale for Suicide Ideation, MADRS-SI, and QIDS-SI) were reduced in the ketamine group compared to midazolam. Fifty-three percent of ketamine-treated patients scored zero on all three explicit suicide measures at 24 hours, compared with 24% of the midazolam group. Ketamine also reduced a range of secondary variables previously linked to increased
risk of future suicidal acts, including implicit suicide-relation associations, hopelessness, and state anxiety. Ketamine-specific decreases in explicit suicidal cognition were largest in patients with elevated suicidal cognition at baseline. The authors note several limitations, primarily that generalizability of findings may be limited to patients meeting study enrollment criteria, including absence of imminent suicide risk. It is therefore unclear how findings would apply to patients with more urgent suicide risk levels. A number of financial disclosures among the authors were also reported.

Ghasemi and colleagues (2014) conducted a blind, randomized study to investigate the antidepressant effects of ketamine in comparison with ECT in hospitalized patients experiencing a major depressive episode. Subjects 18-75 scheduled to receive ECT treatment were randomly assigned to the ECT group (n = 9) or the ketamine group (n = 9). In the ECT group, patients underwent ECT on three test days (every 48 hours). Patients in the ketamine group received three infusions of ketamine hydrochloride (0.5 mg/kg IV, over 45 minutes), one infusion every 48 hours. The primary outcome measures were the BD1 and HDRS, and were used to rate overall depressive symptoms at baseline, 24 hours after each treatment, 72 hours, and one week after the last ketamine or ECT treatment. Results found that repeated treatment of ketamine as well as ECT can exert rapid antidepressant effects in patients with MDD. Further analysis interestingly indicated significantly less depressive symptoms in patients who received ketamine vs. those who received ECT at the first treatment, the second treatment, and 72 hours posttreatment. These data suggest that antidepressant effects of ketamine are more rapid and effective than ECT in the early stages of treatment. Limitations of the study were noted, such as using a titration method for ECT, which might result in a non-effective seizure in the first ECT treatment. Researchers also used thiopental as an anesthetic, which has considerable anticonvulsant properties and might also result in slower onset of action. The current study also included a small number of patients, and more studies using a higher number of participants are needed to clarify the efficacy of ketamine treatment in MDD patients.

Ibrahim and colleagues (2012) reported the results of a single-center, inpatient, randomized, double-blind, 4-week, placebo-controlled trial with riluzole or placebo in patients with treatment-resistant depression who received a single ketamine infusion. The objectives of the study were to determine the extent and time course of antidepressant improvement to a single IV dose of ketamine in TRD patients, and to determine whether the addition of riluzole would have an additional benefit in improving depressive symptoms. Subjects were required to have a score of > 22 on the MADRS at screening and on day of ketamine infusion with no greater than a 25% decrease in MADRS total score between these two time points. Patients also had to have previously failed > 2 adequate antidepressant trials and be experiencing a major depressive episode of at least 4 weeks duration. Forty-two patients met study criteria, received a single ketamine infusion, and were subsequently randomized to receive 4 weeks of either riluzole or placebo. Subjects were rated 60 minutes prior to infusion, at 40, 80, 120, and 230 minutes post-infusion, and then daily for the next 28 days following infusion. Rating scales included the MADRS, which was the primary outcome measure. A significant improvement in MADRS scores from baseline was found. The effect size of improvement with ketamine infusion was initially large, and remained moderate throughout the 28-day trial. Overall, 27% of ketamine responders had not relapsed by 4 weeks following a single infusion. The average time to relapse was 13.2 days. The difference between the riluzole and placebo treatment groups was not significant, suggesting that the combination of riluzole with ketamine treatment did not significantly alter the course of antidepressant response to ketamine alone. No serious adverse events occurred during the study. A relatively small sample size and the refractoriness of the patient sample limit the ability of the authors to generalize their findings to all patients with major depressive disorder. The authors note that future studies should examine alternative strategies for the long-term maintenance of antidepressant effects of ketamine.

Murrough and colleagues (2012) sought to characterize the pattern of change in depressive symptoms and durability of response in the context of repeated ketamine infusions among a sample of subjects with treatment-resistant depression. Eligible patients had failed at least two adequate antidepressant medications in the current episode. If a participant was taking antidepressant medication at the time of screening, a washout of > 2 weeks was required before enrollment. The study consisted of two phases. In phase I, participants received up to six IV infusions of ketamine (0.5 mg/kg on a M-W-F schedule over a 12 day period. In phase II, participants who met response criteria (> 50% improvement on MADRS) after the last dose of ketamine in phase I were followed until relapse (< 50% improvement in MADRS score at visit compared with baseline for two consecutive visits) or for the maximum follow-up time of 83 days, whichever came first. Twenty-four participants received at least one ketamine infusion, twenty-two received at least two infusions, and twenty-one received all six scheduled infusions. In phase I, the overall response rate at study end was 70.8%; within 2 hours of the first dose of ketamine, there was a large and statistically mean improvement in MADRS score from baseline to 2 hours across the full study sample. In phase II, the 17 phase I responders were followed for up to 83 days. The median time to relapse was 15 days. Ketamine was associated with a small but significant increase in psychotomimetic symptoms at the peak of infusion, and resulted in a mild, significant increase in dissociative symptoms. The most commonly reported side effects during the 4-hour period after each infusion included feeling strange or unreal (58.3%), abnormal sensations (54.2%), blurred vision (50.0%), and feeling drowsy or sleepy (45.8%). Eight participants experienced elevated blood pressure and/or heart rate. No serious adverse events occurred during the study. Concerns persist, however, with regard to the safety and feasibility of prolonged treatment with ketamine and the optimal number of repeated treatments for safety and efficacy purposes.
As a result, the authors note that more preclinical and clinical research will be required before this treatment strategy can be recommended. Limitations noted by the authors include the open-label design, which limits the interpretation of efficacy. Another is the modest sample size that limits interpretations that can be drawn and generalizability of the sample to the broader population of patients with treatment-resistant depression.

**Systematic Reviews & Meta-Analyses**

Kishimoto and colleagues (2016) conducted a meta-analysis on the efficacy, safety and time trajectories of single-dose infusion of both ketamine and non-ketamine N-methyl-D-aspartate (NMDAR) antagonists. A total of 14 randomized controlled trials were included. Of these, nine were ketamine studies ($n = 234$) and five were non-ketamine NMDAR antagonist studies ($n = 354$). A total of 554 patients with major depressive disorder, and 34 patients with bipolar disorder were included. On average, studies lasted 10 ($\pm 8.8$) days. Results found that ketamine reduced depression significantly more than placebo beginning at 40 minutes after infusion, peaking at day 1, and losing superiority by days 10-12. Ketamine also showed significantly greater response and remission rates when compared to placebo. Non-ketamine NMDAR antagonists were superior to placebo on days 5-8 only, with greater response at day 2 and days 3-5. Some adverse effects were more common with ketamine/NMDAR antagonists than placebo, but were considered by the authors to be transient and clinically insignificant. The authors conclude that a single ketamine infusion has ultra-rapid efficacy for major depressive disorder and bipolar depression, lasting up to 1 week.

Xu and colleagues (2016) conducted a systematic review and meta-analysis of ketamine use in patients with treatment-resistant depression to evaluate antidepressant efficacy, suicidality, safety, and tolerability. The analysis considered all relevant randomized trials in which ketamine was used for treatment of a major depressive episode and compared with placebo. A total of nine trials were identified, representing 201 patients (eight crossover trials and one parallel group design). Of the nine trials, six looked at ketamine dosage of 0.5 mg/kg IV, with the other 3 testing ketamine at lower doses. Results found a reduction in depression severity within 4 hours in all but one trial of low dose ketamine, with treatment effects largest at day 1 (50% response of those in the ketamine group compared with 13% in the placebo group). At day 3, depression severity score reduction was less marked in the very low-dose trials and among those patients with bipolar depression. Response and remission rates were still increased in the ketamine group at day 7, though this analysis excluded the second period of crossover trials. The ketamine treatments were generally well tolerated, with transient, mild-to-moderate dissociative symptoms. Eleven events were reported as serious adverse events in the ketamine group. The authors note that the analysis had a small sample size, and the use of crossover design in all but one trial is a potential limitation. They further note that the safety and efficacy of long-term treatment remain uncertain, and that larger, longer term parallel group trials are needed to study these factors.

Newport and colleagues (2015) conducted a systematic review and meta-analysis of randomized trials of ketamine and other NMDA receptor antagonists in the treatment of depression to critically examine findings for both efficacy and adverse effects of these agents. A total of twelve trials were included in the review ($total \ n = 236$). Findings found that ketamine produced a rapid, yet transient, antidepressant effect. This effect was accompanied by brief psychotomimetic and dissociative effects. Additional findings on ketamine augmentation of electroconvulsive therapy (ECT) found significant reductions in depressive symptoms following initial treatment, but not at conclusion of the ECT course. Aside from ketamine, other NMDA antagonists failed to consistently demonstrate efficacy. The authors conclude that the fleeting nature of ketamine’s therapeutic benefit, coupled with a potential for abuse and neurotoxicity, suggest its use in the clinical setting warrants caution. Absent in the literature are those studies demonstrating that ketamine’s antidepressant effects can be sustained with ongoing infusions, or after transitioning to an alternative maintenance pharmacotherapy. They recommend future research examine three areas: elucidating ketamine’s mechanism of action; understanding the administration profile necessary to provide a sustained therapeutic benefit; and examining ketamine’s safety, particularly with repeated and low-dose administration.

Caddy and colleagues (2015) conducted a systematic review to assess the effects and review the acceptability of ketamine and other glutamate receptor modulators in alleviating the acute symptoms in depression in people with unipolar major depressive disorder. As part of this Cochrane Review, ketamine and other glutamate receptor modulators were compared to placebo (or saline placebo), other pharmacologically active agents, or electroconvulsive therapy (ECT). In total, the authors included 25 studies, with 1,242 total participants. There were nine trials examining ketamine. A total of twenty-one studies were placebo-controlled, and 23 out of 25 were two-arm studies. Eleven of the studies specified at least moderate depression in patients; eight studies specified severe depression. The results found that among all glutamate receptor modulators, only intravenous ketamine proved more efficacious than placebo, though the authors state that quality of evidence was limited by risk of bias and small sample sizes. They found low quality evidence for ketamine increasing the likelihood of response after a period of 24 hours, 72 hours, and one week. Ketamine was found to cause more confusion and emotional blunting when compared with placebo. The authors conclude that there is limited evidence for ketamine’s efficacy over placebo at time points up to one week in terms of response rate. Additionally, they note that despite the promising nature of these preliminary results, confidence in the evidence was limited by risk of bias and small number of participants, and that intravenous...
administration of ketamine can pose practical problems in clinical practice. The authors recommend further RCTs (with adequate blinding) to explore different methods of administration with longer follow-up periods.

McCloud and colleagues (2015) conducted a systematic review to assess the effects of ketamine and other glutamate receptor modulators in alleviating the acute symptoms of depression in people with bipolar disorder. This Cochrane Review identified 5 randomized controlled trials (RCTs) that compared ketamine, memantine, or other glutamate receptor modulators with other active psychotropic drugs or saline placebo in adults with bipolar depression. The authors conclude that the review is severely limited by the small amount of data usable for analysis, finding limited evidence in favor of a single infusion of ketamine over placebo at 24 hour response rate. The authors note that ketamine’s psychotomimetic effects could compromise study blinding, and further RCTs (with adequate blinding) are needed to study methods of sustaining response, including repeat administrations.

Romeo and colleagues (2015) conducted a meta-analysis to determine the efficacy of ketamine on treatment-resistant depression. Studies were included in the analysis if they were randomized, double-blind, and placebo-controlled trials of ketamine. A total of six studies met criteria and were included (n = 103). Separate analyses were conducted for patients suffering from bipolar and unipolar depression. Overall, ketamine was found to have antidepressive efficacy between days 1 and 7 after infusion. In patients with bipolar depression, the maintenance of ketamine’s efficacy over time failed to reach significance after day 3-4. No serious adverse events occurred during the studies. The authors note that the meta-analysis contained a limited number of trials and data, and note that these limitations could explain a poor statistical power.

Parsaik and colleagues (2015) conducted a systematic review and meta-analysis to evaluate ketamine’s role in the treatment of bipolar depression. Eligible studies were those which enrolled subjects of any age with bipolar depression who received treatment with ketamine and that reported primary outcome as change in depression after ketamine therapy. A total of five studies met inclusion criteria for systematic review (n = 125), and three studies met criteria for the meta-analysis (n = 69). Results found significant improvement in bipolar depression among patients who received a single dose of IV ketamine when compared to those receiving placebo. Maximum improvement was seen approximately 40 minutes after infusion. No serious adverse events were reported, with similar side effects seen between study groups. The authors’ conclusions suggest that ketamine can cause a rapid and robust antidepressant response in patient with bipolar depression. They note a major limitation of the systematic review and meta-analysis is the small number of included studies, which prevented assessment of publication bias. The authors suggest that future studies focus on longer-term efficacy of repeated doses of ketamine in patients with bipolar depression.

Reinstatler and Youssef (2015) reviewed the published literature on the efficacy of ketamine for the treatment of suicidal ideation (SI). A total of nine publications met the search criteria for assessing SI after administration of subanesthetic ketamine. There were no studies that examined the effect on suicide attempts or death by suicide. The review found that each study demonstrated a rapid and clinically significant reduction in SI. The earliest significant results were seen after 40 minutes, and the longest results were observed up to 10 days post infusion. The authors encourage additional studies to further investigate ketamine’s mechanism of action, long-term outcomes, and long-term adverse effects (including abuse) and benefits.

Lee and colleagues (2015) conducted a meta-analysis to assess the efficacy of ketamine in comparison with placebo for the reduction of depressive symptoms in patients who meet criteria for a major depressive episode (major depressive disorder or bipolar depression). A total of five studies were included in the quantitative meta-analysis; the authors note that this small number of studies does run the potential risk of publication bias. The results of the analysis signify that ketamine has a significant impact on depressive symptoms in subjects with MDD or bipolar depression. 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), with the effects sustained at 7 days post infusion. Minimal adverse events were noted throughout all studies. Most seriously, psychotomimetic symptoms or transient mild elevations in blood pressure and heart rate were reported. The psychotomimetic effects were short-lived, resolving completely by 60 min post infusion.

Serafini and colleagues (2014) conducted a systematic review on the main pharmacological properties and impact of ketamine in treatment-resistant depression. A total of 24 papers examining a total of 416 patients fulfilled inclusion criteria. Most studies demonstrated that ketamine had a rapid (within hours) antidepressant effect on samples of patients with treatment-resistant depression. The authors conclude that ketamine may be considered a valid and intriguing antidepressant option for the treatment of treatment-resistant depression. They note that the long-term efficacy of ketamine has not been investigated by most studies, and the psychotomimetic properties of ketamine may complicate its application. They suggest that further studies are necessary to evaluate the long-term antidepressant efficacy of ketamine in patients with treatment-resistant depression.

McGirr and colleagues (2014) conducted a systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials to assess the efficacy of ketamine in the treatment of major depressive episodes. The focus was on
clinical remission and response, but changes in clinician-rated depression scores were also examined. The primary outcome measure was clinical remission at 24 hours, 3 days, and 7 days post-treatment. Subjects from collected trials were aged 18-75 with a diagnosis of primary major depressive episode (unipolar or bipolar) who received treatment with ketamine as a single administration (oral, intranasal or parenteral). A total of seven RCTs were included in the meta-analysis, totaling 183 subjects (n = 34 with bipolar depression and 149 with MDD). Ketamine was administered via IV in all but one study, which used intranasal ketamine. Intravenous infusion protocols most commonly used 0.5 mg/kg over 40 min. One study involved an intravenous bolus of 0.27 mg/kg and an additional 0.27 mg/kg infused over 20 min. Ketamine was associated with higher rates of clinical remission relative to comparator (saline or midazolam) at 24 h [OR 7.06, number needed to treat (NNT)=5], 3 days (OR 3.86, NNT=6), and 7 days (OR 4.00, NNT=6), as well as higher rates of clinical response at 24 h (OR 9.10, NNT=3), 3 days (OR 6.77, NNT=3), and 7 days (OR 4.87, NNT=4). A standardized mean difference of 0.90 in favor of ketamine was observed at 24 h based on depression rating scale scores, with group comparisons revealing greater efficacy in unipolar depression compared to bipolar depression (1.07 v. 0.68). Ketamine was associated with transient psychotomimetic effects, but no persistent psychosis or affective switches. Based on the results, the authors suggest that single administrations ketamine are efficacious in the rapid treatment of unipolar and bipolar depression. They note that additional research is required to determine optimal dosing schedules, route, treatment schedules, and the potential efficacy of other glutamatergic agents.

Fond and colleagues (2014) conducted a systematic review and meta-analysis of randomized controlled trials to investigate the efficacy of ketamine’s administration on depressive symptomatology in major depressive disorder, resistant depression and bipolar depression. The study also investigated ketamine’s efficacy as an anesthetic agent in ECT for resistant depression. A total of nine non-ECT studies and four ECT studies were included in the quantitative analysis. In the non-ECT studies, overall, the depression score was significantly improved in patients receiving ketamine compared to controls. Ketamine was found to be effective in studies in which the control group received placebo, as well as in other studies. The results remained significant in all subgroups and sensitivity analyses. Ketamine was effective in drug-free studies, as well as in studies in which patients were under active treatment (antidepressants or mood-stabilizing agents). The authors found “promising results” for suicidal ideation, but suggest they be confirmed in future studies. Depression scores were also significantly improved in patients with major depression receiving ketamine in ECT anesthesia induction compared to those in patients receiving thiopental or propofol. The study noted that more severe cardiovascular events (mostly tachycardia/hypertension requiring treatment) were associated with higher doses of ketamine (0.8 – 1.0 mg/kg) administration. The authors also note that it was not possible to carry out a correlation to highlight a dose effect. Patients with alcohol dependence and substance abuse were excluded in most of the selected studies, as well as those with a history of psychotic episode. The authors suggest that further studies should focus on ketamine’s efficacy in bipolar depression and on the long-term efficacy of repeated doses (e.g., every 2-3 days) to assess whether or not ketamine maintains its effect over time and if no undesirable long-term adverse effects appear.

**Guidelines & Consensus Statements**

**American Psychiatric Association (APA):** In 2017, review on the use of ketamine in the treatment of mood disorders was developed by the APA’s Council of Research Task Force on Novel Biomarkers and Treatments. The review notes that appropriate selection of patients requires consideration of the risk and benefits of treatment in the context of depression severity, duration of current episode, and previous history of and urgency for treatment. Also, there are considerable differences in both the experience and clinical expertise of clinicians currently administering ketamine for treatment of mood disorders. The review states that to ensure patient safety and minimize risk, it is strongly advised that site-specific standard operating procedures be developed and followed for ketamine delivery. The review concludes that although the rapid onset of ketamine infusions for depression has generated much excitement and hope, it is necessary to recognize the major gaps remaining in terms of longer-term efficacy and safety. Future research is necessary to address these unanswered questions and concerns (Sanacora et al 2017).

**Institute for Clinical Systems Improvement (ICSI):** In 2013, the ICSI published a health care guideline for adult depression in primary care. An appendix to the guideline states that there has been a significant interest in using ketamine for patients suffering from treatment-resistant depression (TRD) or acute suicidal thoughts. In some reports, significant patient response has been observed within 2 to 24 hours of ketamine administration. However, poor long-term response, concern about adverse effects, poor bioavailability of oral and intramuscular (IM) formulations, and small study sizes have limited ketamine’s use in the maintenance of depression symptoms. Few studies have followed patients longer than 72 hours after their IV infusion of ketamine. It is also unclear why patients who have demonstrated treatment response at 24 hours post-ketamine infusion may relapse less than 48 hours later. Future studies of ketamine for the treatment of depression are needed. Most sites collaborated with anesthesiologists and monitored patients in the hospital for a minimum of 24 hours after their ketamine infusion due to poor oral and IM bioavailability. The oral and IM formulations also do not provide the rapid response seen with IV administration. Of the studies cited in the appendix, the ICSI ranks them as “low quality evidence”. The authors note that future studies
should also evaluate a way to sustain symptom remission following IV ketamine and evaluate larger groups of patients (Mitchell et al 2013).

**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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**REFERENCES**


Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, Oquendo MA, Mann JJ. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. Am J Psychiatry: April 1, 2018; 175 (4); 327-335.


**HISTORY/REVISION INFORMATION**

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<td>Tech assessment.</td>
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<tr>
<td>06/13/2017</td>
<td>Converted to Behavioral Clinical Policy. Version 1 to UMC as a new policy. Approved</td>
</tr>
<tr>
<td>6/13/2018</td>
<td>Updated references and format. Approved by UMC.</td>
</tr>
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