Ketamine for the Treatment of Depression and Other Psychiatric Disorders

Policy

Aetna considers ketamine (intranasal, intravenous, oral, or subcutaneous) experimental and investigational for the following indications because its clinical value for these indications has not been established:

- Generalized anxiety and social anxiety disorders
- Depression
- Substance use disorder
- Suicidal ideation.

See also: CPB 0445 - Electroconvulsive Therapy (../400_499/0445.html), CPB 0447 - Complex Regional Pain Syndrome (CRPS) / Reflex Sympathetic Dystrophy (RSD): Treatments (../400_499/0447.html), CPB 0469 - Transcranial Magnetic Stimulation and Cranial Electrical Stimulation (../400_499/0469.html), and CPB 0950 - Esketamine (Spravato) (0950.html).
Background

Major depressive disorder (MDD) has one of the highest morbidities worldwide. As reported in many clinical trials, standard anti-depressants are effective in only approximately 2/3 of patients. Additionally, there is a substantial time-lag in response: 2 to 4 weeks for initial effect, and 6 to 12 weeks for maximal efficacy. Treatment-resistant depression (TRD) is associated with substantial psychosocial dysfunction, morbidity, and mortality, due in part to suicide and under-treated medical co-morbidities. Thus, there is a need for better and more rapid-acting anti-depressants to quickly alleviate the burden of depression for patients (Niciu et al, 2014; Fond et al, 2014). Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist; recent research has suggested that ketamine may be a novel, rapid-acting anti-depressant.

Schoevers and colleagues (2016) reviewed the literature about the dosing regimen, duration, effects and side-effects of oral, intravenous, intranasal and subcutaneous routes of administration of ketamine for TRD and pain. Searches in PubMed with the terms “oral ketamine”, “depression”, “chronic pain”, “neuropathic pain”, “intravenous ketamine”, “intranasal ketamine” and “subcutaneous ketamine” yielded 88 articles. They reviewed all papers for information about dosing regimen, number of individuals who received ketamine, number of ketamine days per study, results and side-effects, as well as study quality. Overall, the methodological strength of studies investigating the anti-depressant effects of ketamine was considered low, regardless of the route of administration. The doses for depression were in the lower range compared with studies that investigated analgesic use. Studies on pain suggested that oral ketamine may be acceptable for TRD in terms of tolerability and side-effects. The authors concluded that oral ketamine, given for longer time periods in the described doses, appeared to be well-tolerated, but few studies had systematically examined the longer-term negative consequences. These researchers stated that the short- and
longer-term depression outcomes as well as side-effects need to be studied with rigorous randomized controlled trials (RCT)s.

Al Shirawi and co-workers (2017) evaluated the effectiveness, tolerability, and safety of oral ketamine as an anti-depressant treatment in adults with TRD. These investigators reviewed retrospective data on 22 patients with TRD, who failed at least 3 adequate anti-depressant treatment trials and 1 adequate trial of repetitive transcranial magnetic stimulation (TMS); subsequently, they received open-label treatment with oral ketamine, commenced at a dose of 50 mg every 3 days, titrated up by 25 mg every 3 days, according to response and tolerability. The primary outcome measure was the Beck Depression Inventory (BDI)-II, which was used to rate subjective mood improvement at baseline and then at each follow-up visit. Data about adverse effects related to ketamine and a self-harm risk assessment were also obtained. Over the course of treatment, 18 % of the patients showed greater than 50 % reduction in the BDI-II scores, 14 % reported partial improvement in mood symptoms, while 45 % had no response to ketamine and 23 % showed a mild worsening in their depressive symptoms. The most frequent adverse effects were acute dissociation, dizziness, blurred vision, numbness and sedation. Neither serious adverse effects, nor any cases of abuse or dependence were observed. The authors concluded that although this case series found oral ketamine to be safe and well-tolerated, the findings also showed rather modest effectiveness of oral ketamine in TRD, with only approximately 30 % reporting some benefit and approximately 70 % reporting no change or worsening of mood. They stated that further investigation of the effectiveness of oral ketamine is needed.

Feifel and associates (2017) described the safety and efficacy of sub-anesthetic ketamine infusions in a TRD patient sample participating in a real-world TRD treatment program within a major university health system. The effects of a sub-
anesthetic dose (0.5 mg/kg) of ketamine infused intravenously over 40 minutes on TRD patients participating in a treatment program at the University of California, San Diego was investigated by retrospectively analyzing the medical charts of 41 adult TRD patients with a diagnosis of MDD or bipolar disorder (BD). Subjects were aged 48.6 years, 78 % white, 36.6 % women, and 82.9 % had MDD. Significant psychiatric co-morbidity existed in 73 %. Average pre-infusion BDI score was 32.6 ± 8.4 (S.D) and dropped to 16.8 ± 3.1 at 24-hour post-infusion (p < 0.001). The 24-hour response (greater than or equal to 50 % reduction from pre-infusion) and remission (BDI less than 13) rates were 53.7 % and 41.5 %, respectively; 3/4 of responders maintained responder status at 7-days. Ketamine infusions were well-tolerated with occasional nausea or anxiety and mild hemodynamic effects during the infusion. The authors concluded that this was the first published study of sub-anesthetic ketamine infusions in a real-world TRD population. They stated that the results suggested that this treatment was effective and well-tolerated in this population. These researchers stated that the main drawbacks of this study were its retrospective nature, lack of control group, and use of self-report depression ratings scales.

Kraus and colleagues (2017) reviewed available literature on efficacy, response rates and safety profile of ketamine for unipolar and bipolar depression -- 12 studies investigating unipolar depression, 7 on BD were included after search in Medline, Scopus and Web of science. Randomized, placebo-controlled or open-label trials reported anti-depressant response rates after 24 hours on primary outcome measures at 61 %. The average reduction of Hamilton Depression Rating Scale (HAM-D) was 10.9 points, BDI 15.7 points and Montgomery-Asberg Depression Rating Scale (MADRS) 20.8 points. Ketamine was always superior to placebo. Most common side effects were dizziness, blurred vision, restlessness, nausea/vomiting and headache, which were all reversible. Relapse rates ranged between 60 % and 92 %. The authors concluded that ketamine constituted a novel,
rapid and efficacious therapeutic option for patients suffering from TRD and exhibited rapid and significant anti-suicidal effects. New administration routes might serve as alternative to intravenous regimes for potential usage in out-patient settings. Moreover, they stated that long-term side effects are unknown and short duration of anti-depressant response need ways to prolong ketamine's efficacy.

The authors stated that this study had several drawbacks. First, all of patients in this series had highly resistant forms of depression, with failure of multiple treatment modalities (multiple anti-depressant medications, neuromodulation, and in most cases cognitive psychotherapy). Second, adherence to the prescribed regimen could not be confirmed for at-home dosing regimens. Third, because this report concerned a series of clinical cases rather than a RCT, standardized clinician ratings of mood symptom were not consistently obtained. Fourth, a series of 22 patients was insufficiently large to assess the incidence of rare but serious adverse effects (medical or psychiatric) ensuing from the treatment.

In a pilot study, George and colleagues (2017) examined the safety and efficacy of subcutaneous ketamine for geriatric TRD. Secondary aims were to examine if repeated treatments were safe and more effective in inducing or prolonging remission than a single treatment. This was a controlled, double-blind, multiple-crossover study with a 6-month follow-up (RCT phase), 16 participants (greater than or equal to 60 years) with TRD who relapsed after remission or did not remit in the RCT were administered an open-label phase. Up to 5 subcutaneous doses of ketamine (0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg) were administered in separate sessions (greater than or equal to 1 week apart), with 1 active control (midazolam) randomly inserted (RCT phase); 12 ketamine treatments were given in the open-label phase. Mood, hemodynamic, and psychotomimetic outcomes were assessed by blinded raters. Remitters in each phase were followed-up for 6 months; 7 of 14 RCT-phase completers remitted with ketamine treatment; 5
remitted at doses below 0.5 mg/kg. Doses greater than or equal to 0.2 mg/kg were significantly more effective than midazolam. Ketamine was well-tolerated. Repeated treatments resulted in higher likelihood of remission or longer time to relapse. The authors concluded that these findings provided preliminary evidence for the safety and efficacy of ketamine in treating elderly depressed. Dose titration was recommended for optimizing anti-depressant and safety outcomes on an individual basis. These preliminary findings need to be validated by well-designed studies.

In a “Consensus statement on the use of ketamine in the treatment of mood disorders” from the American Psychiatric Association (APA), Sanacora and associates (2017) noted that several studies provided evidence of ketamine hydrochloride’s ability to produce rapid and robust anti-depressant effects in patients with mood and anxiety disorders that were previously resistant to treatment. Despite the relatively small sample sizes, lack of longer-term data on efficacy, and limited data on safety provided by these studies, they have led to increased use of ketamine as an off-label treatment for mood and other psychiatric disorders. This review and consensus statement provided a general overview of the data on the use of ketamine for the treatment of mood disorders and highlighted the limitations of the existing evidence. While ketamine may be beneficial to some patients with mood disorders, it is important to consider the limitations of the available data and the potential risk associated with the drug when considering the therapeutic option. The authors concluded that the suggestions provided were intended to facilitate clinical decision making and encourage an evidence-based approach to using ketamine in the treatment of psychiatric disorders considering the limited information that is currently available. This article provided information on potentially important issues related to the off-label therapeutic approach that should be considered to help ensure patient safety.
Short and co-workers (2018) provided the first systematic review of the safety of ketamine in the treatment of depression after single and repeated doses. These investigators searched Medline, PubMed, PsycINFO, and Cochrane Databases and identified 288 articles, 60 of which met the inclusion criteria. After acute dosing, psychiatric, psychotomimetic, cardiovascular, neurological, and other side-effects were more frequently reported after ketamine treatment than after placebo in patients with depression. These findings suggested a selective reporting bias with limited assessment of long-term use and safety and after repeated dosing, despite these being reported in other patient groups exposed to ketamine (e.g., those with chronic pain) and in recreational users. The authors recommended large-scale clinical trials that include multiple doses of ketamine and long-term follow-up to assess the safety of long-term regular use.

Wilkinson and associates (2018) conducted a systematic review and individual participant data meta-analysis examining the effects of a single dose of ketamine on suicidal ideation. Individual participant data were obtained from 10 of 11 identified comparison intervention studies that used either saline or midazolam as a control treatment. The analysis included only participants who had suicidal ideation at baseline (n = 167). A 1-stage, individual participant data, meta-analytic procedure was employed using a mixed-effects, multi-level, general linear model. The primary outcome measures were the suicide items from clinician-administered (the MADRS or the HAM-D) and self-report scales (the Quick Inventory of Depressive Symptomatology-Self Report [QIDS-SR] or the BDI), obtained for up to 1 week after ketamine administration. Ketamine rapidly (within 1 day) reduced suicidal ideation significantly on both the clinician-administered and self-report outcome measures. Effect sizes were moderate to large (Cohen’s d = 0.48 to 0.85) at all time points after dosing. A sensitivity analysis demonstrated that compared with control treatments, ketamine had significant benefits on the individual suicide items of the MADRS, the HAM-D, and the QIDS-SR.
but not the BDI. Ketamine's effect on suicidal ideation remained significant after adjusting for concurrent changes in severity of depressive symptoms. The authors concluded that ketamine rapidly reduced suicidal thoughts, within 1 day and for up to 1 week in depressed patients with suicidal ideation. Ketamine's effects on suicidal ideation were partially independent of its effects on mood, although subsequent trials in trans-diagnostic samples are needed to confirm that ketamine exerts a specific effect on suicidal ideation. They stated that additional research on ketamine's long-term safety and its efficacy in reducing suicide risk is needed before clinical implementation.

In a retrospective, case-series study, Archer and colleagues (2018) reported on the clinical use of ongoing maintenance ketamine infusions in a group of patients with TRD, beyond an acute course of 6 to 8 ketamine infusions. This trial included 11 patients with TRD who received maintenance ketamine infusions, defined as treatments beyond an initial series of up to 8 infusions. Charts were reviewed to collect data on response to treatment and side effects. All 11 patients in this case series were noted to have a reduction in their BDI-II score after an acute course of treatment and a lower median BDI-II during their maintenance treatments than their baseline BDI-II. At the study end-point, 4 patients were continuing maintenance ketamine and 1 patient had transitioned to maintenance intranasal ketamine; 4 patients discontinued ketamine due to loss of effect and 1 due to side effects, and the reason for discontinuation was not noted for the remaining 2 patients. No major adverse events (AEs) were noted in these patients receiving maintenance treatments, and it was well-tolerated overall. The authors concluded that maintenance ketamine treatments may be an effective way of maintaining therapeutic response in some ketamine responders. Moreover, they stated that future research is needed to determine optimal length of treatment in those who respond to ketamine and to track ARs over a longer time.
An UpToDate review on “Unipolar depression in adults: Treatment of resistant depression” (Thase and Connolly, 2018a) does not mention ketamine as a therapeutic option.

Furthermore, an UpToDate review on “Unipolar depression in adults: Management of highly resistant (refractory) depression” (Thase and Connolly, 2018b) lists ketamine as an investigational procedures.

In a systematic review, Rosenblat and colleagues (2019) examined the safety, tolerability, efficacy, and dose range of oral ketamine for bipolar and unipolar depression in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The Medline/PubMed, Embase, and Google Scholar databases were systematically searched for relevant articles, written in English, published prior to July 2018 using relevant keywords for all variants of ketamine, oral, and depression. All clinical studies assessing oral ketamine for bipolar or unipolar depression were included. A total of 13 published articles were identified, of which 2 were proof-of-concept RCTs; 1 was a prospective open-label trial; 5 were retrospective chart reviews; and 5 were case reports. Included articles were qualitatively analyzed to determine anti-depressant safety, tolerability, efficacy, dose range, anti-suicide effects, time to effect, and efficacy in treatment-resistant depression and study bias. Both RCTs demonstrated anti-depressant efficacy with good tolerability; however, significant changes in depressive symptom severity were observed only after 2 to 6 weeks of treatment (p < 0.05). Both RCTs had high risk for bias, due to inadequate intent-to-treat (ITT) analysis and AE monitoring. Rapid antidepressant effects (i.e., within 24 hours), anti-suicide effects, and efficacy in treatment-resistant depression were reported only in retrospective studies. Dosages and frequency of administration were variable (i.e., 0.5 to 7.0 mg/kg thricely-daily to once-monthly), with most studies providing dosages of 1 to 2 mg/kg every 1 to 3 days. No clinically significant AEs were reported. The authors concluded that a small number of
clinical studies assessed the anti-depressant effects of oral ketamine. Initial results suggested that oral ketamine had significant anti-depressant effects with good overall tolerability; however, anti-depressant effects were not as rapid as those associated with intravenous (IV) ketamine. Anti-suicide effects and efficacy in treatment-resistant depression have yet to be demonstrated. These researchers stated that additional well-designed RCTs are needed.

Grabski and associates (2020) noted that esketamine was recently licensed by the Food and Drug Administration (FDA) and European Drug Agency (EDA) for use in TRD, and further research indicates ketamine as a possible treatment in other mental health conditions. While the underlying mechanisms remain unclear, it has been hypothesized that ketamine's acute psychoactive effects may be associated with psychiatric treatment efficacy. These investigators systematically reviewed the evidence for this association. The databases Medline, Embase and PsychInfo were searched up to June 2019. Studies were included if they enrolled adults with a psychiatric diagnosis, assessed acute psychoactive effects using a quantitative measure, and reported on the relationship between acute effects and treatment outcome. They included 21 studies, totaling 891 patients; 17 studies examined patients with depression (TRD [k = 14]), 3 evaluated substance use disorders, and 1 assessed social anxiety disorder. Overall, 41 associations were assessed, of which 26% were significant. The studies reviewed displayed great variability in terms of methodology and quality of reporting. The most commonly assessed effect was dissociation, measured by the Clinician Administered Dissociative States Scale (CADSS). The authors concluded that these findings suggested that the CADSS total was not consistently associated with anti-depressant outcomes. Apart from this, the current literature is too limited to draw definite conclusions on the presence of an association between acute psychoactive effects and mental health outcomes. Moreover, these researchers stated that the field would benefit from consistently employing a priori
hypotheses, more transparent reporting and sufficiently powered statistical analyses. Furthermore, the use of a broader range of assessments tools of acute psychoactive effects during ketamine administration would be beneficial.

Kim and co-workers (2020) noted that suicide is the 2nd leading cause of death in the U.S. among individuals aged 10 to 24 years of age; and severe youth depression is often refractory to the current standards of care. In a systematic review, these researchers examined the current state of evidence for the use of ketamine in children with treatment-resistant mood disorders. They carried out a search utilizing 2 electronic data-bases for English-language studies examining the therapeutic effects and side effect profile of ketamine in youth less than or equal to 19 years of age with a diagnosis of a treatment-resistant mood disorder. Analysis included subjects with TRD with and without psychotic features and with bipolar disorder. Primary outcome measures included the following scales: MADRS, Children's Depression Rating Scale, Children's Depression Rating Scale Revised, Child Bipolar Questionnaire, Overt Aggression Scale, Yale-Brown Obsessive-Compulsive Scale, and Scale for Suicidal Ideation. A total of 4 studies were identified that examined the use of ketamine in youth for the primary purpose of treating a treatment-resistant psychiatric disorder; 3 additional studies that did not meet eligibility criteria were identified and discussed. The authors concluded that ketamine was shown in youth to generally improve depressive symptoms, decrease acute suicidality, and reduce mood lability, although a number of subjects remained resistant to its treatment. Moreover, these researchers stated that these findings substantiated the need for further longitudinal studies examining ketamine's long-term safety, its efficacy, and abuse potential in the youth.

Memon and colleagues (2020) stated that MDD is a common psychiatric disorder with major implications for healthcare system and socioeconomic burden. For chronic and treatment-resistant depression, ketamine has emerged as a
possible therapeutic option. In a systematic review, these researchers examined the evidence for the effectiveness and tolerability of ketamine in patients with MDD. This systematic review was carried out following the guidelines of PRISMA check-list. A total of 8 electronic data-bases were searched by using search terms: (ketamine) AND (trial OR RCT OR clinical-trial) AND (depressive OR depression OR "depressive-disorder"). After a rigorous screening process against the predetermined eligibility criteria, 35 RCTs were included. Quality assessment of included studies was performed by using the Cochrane risk-of-bias tool for RCTs. The majority of the included studies came from the U.S., Iran, and China.

Intravenous ketamine was effective in 70 % (21/30) of the included studies whereas oral and intra-nasal (IN) ketamine were effective in 2 and 3 studies, respectively. The majority of studies (6/8) using ketamine as anesthetic agent during electroconvulsive therapy (ECT) failed to show an improvement compared to the subjects receiving ECT and placebo. The most common reported side effects were nausea, vomiting, dizziness, diplopia, drowsiness, dysphoria, hallucinations, and confusion. The authors concluded that ketamine is an effective therapeutic option for patients with MDD with undesirable effects when administered via oral, IV and IN routes. Augmentation of ECT with ketamine requires further investigation in well-designed studies with adequate sample size. Moreover, these researchers stated that the short-lived anti-depressant effect of ketamine is a potential limitation; further studies administering multiple infusions for acute treatment and maintenance are needed.

Prevention of Emergence Agitation in Children Undergoing Surgery or Imaging Procedures

Ng and colleagues (2019) noted that ketamine is believed to reduce the incidence of emergence agitation in children undergoing surgery or procedure. However, recent RCTs reported conflicting findings. In a meta-analysis, these investigators examined the effect of ketamine on emergence
agitation in children. Medline, Embase, and CENTRAL were systematically searched from their start date until February 2019; RCTs comparing IV ketamine and placebo in children were sought. The primary outcome was the incidence of emergence agitation; secondary outcomes included post-operative pain score, duration of discharge time, and the adverse effects associated with the use of ketamine, namely post-operative nausea and vomiting, desaturation, and laryngospasm. A total of 13 studies (1,125 subjects) were included in the quantitative meta-analysis. The incidence of emergence agitation was 14.7 % in the ketamine group and 33.3 % in the placebo group. Children receiving ketamine had a lower incidence of emergence agitation, with an odds ratio (OR) being 0.23 (95 % confidence interval [CI]: 0.11 to 0.46), certainty of evidence: low. In comparison with the placebo, ketamine group achieved a lower post-operative pain score (OR: -2.42, 95 % CI: -4.23 to -0.62, certainty of evidence: very low) and lower pediatric anesthesia emergence delirium scale at 5 mins after operation (OR: -3.99, 95 % CI: -5.03 to -2.95; certainty of evidence: moderate). However, no evidence was observed in terms of incidence of post-operative nausea and vomiting, desaturation, and laryngospasm. The authors concluded that in this meta-analysis of 13 RCTs, high degree of heterogeneity and low certainty of evidence limited the recommendations of ketamine for the prevention of emergence agitation in children undergoing surgery or imaging procedures. However, the use of ketamine was well-tolerated without any notable adverse effects across all the included trials.

**Treatment of Suicidal Ideation**

Chen et al (2019) stated that increasing evidence suggested that infusion of a sub-anesthetic dose of ketamine exerts anti-depressant and anti-suicidal effects in patients with TRD. In a double-blind, placebo-controlled, randomized, longitudinal study, these researchers used the resting functional connectivity magnetic resonance imaging (fcMRI) to examine
the effects of ketamine on the functional connectivity (FC) of pre-frontal cortex (PFC)-related circuits in patients with TRD. A total of 48 patients with TRD were recruited and randomly divided into 3 groups on the basis of ketamine infusion dose: 0.5 mg/kg (standard-dose), 0.2 mg/kg (low-dose), or normal saline (a placebo infusion). Resting functional MRI data and clinical data were recorded at the baseline and on the 3rd day after ketamine infusion treatment. The standard-dose group showed a reduction in the FC of the left dorsal anterior cingulate cortex (dACC) and right dorsolateral (dl) PFC with the other frontal regions. The low-dose group demonstrated a more pervasive reduction of FC in the bilateral dACC with other frontal and parietal regions. A negative correlation was observed between the reduction in suicidal ideation and the reduction in the FC between the left dACC and right ACC regions in the standard-dose group, whereas a positive correlation was observed between the reduction in suicidal ideation and the increase in the FC between the right dlPFC and left superior parietal region in the low-dose group. The authors concluded that these findings supported the hypothesis that PFC-related circuit modulation was crucial to the anti-depressant and anti-suicidal effects of the ketamine infusion treatment.

Ionescu and co-workers (2019) noted that the extent to which repeated doses of ketamine (versus placebo) reduce depression in the short- and long-term among out-patients with TRD and chronic, current suicidal ideation remains unknown. In a randomized, double-blind, placebo-controlled trial, a total of 26 medicated out-patients with severe MDD with current, chronic suicidal ideation were randomized to 6 ketamine infusions (0.5 mg/kg over 45 mins) or saline placebo over 3 weeks. Depression and suicidal ideation were assessed at baseline, 240 mins post-infusion, and during a 3-month follow-up phase. During the infusion phase, there was no differences in depression severity or suicidal ideation between placebo and ketamine (p = 0.47 and p = 0.32, respectively). At the end of the infusion phase, 2 patients in the ketamine group and 1
in the placebo group met criteria for remission of depression. At 3-month follow-up, 2 patients in each group met criteria for remission from depression. The authors concluded that repeated, non-escalating doses of ketamine did not outperform placebo in this double-blind, placebo controlled study of patients with severe TRD and current, chronic suicidal ideation. This result may support the authors’ previously published open-label data that, in this severely and chronically ill outpatient population, the commonly used dose of 0.5 mg/kg is insufficient. These researchers stated that limitations of this trial included the small sample size (n = 26), uncontrolled outpatient medication regimens, and restriction to out-patients, which may have resulted in lower levels of suicidal ideation than would be observed in emergency or in-patient settings.

In a preliminary study, Zhan et al (2019) examined the anti-suicidal efficacy of repeated ketamine infusions for Chinese depressed suicidal patients, especially distinguished between low suicidal ideation (SI) group and high SI group. A total of 86 unipolar and bipolar depressive patients with current suicidal ideation received 6 ketamine infusions during a 12-day period. Hamilton Depression Rating Scale (HAMD) and Beck Scale for Suicide Ideation (SSI) were measured at baseline, 4 hours and 24 hours after each infusion, and 2-week naturalistically follow-up. A total of 49 (57.0 %) patients found relief of suicidal ideation after 1st infusion and 56 (65.1 %) after 6 infusions. Anti-suicidal response rate in low SI group were higher than high SI group, and anti-suicidal response at 4 hours after 1st infusion was significant predictor of response at 24 hours after 6th infusion. Furthermore, at 24 hours after the 6th infusion, correlation between changes in suicidal ideation and depression was 0.23, accounting for 7.4 % in the variance of suicidal ideation change. The authors confirmed that 6 repeated ketamine infusions for Chinese suicidal depressed patients were effective in generating a rapid response of suicidal ideation, especially low SI achieved more benefits
from ketamine infusions. These researchers stated that the main drawback of this study was that lack of a placebo or other control group, which limited the interpretation of efficacy.

Witt and associates (2020) noted that ketamine may reduce suicidal ideation in TRD. But it is unclear how quickly this occurs and how long it persists. These researchers carried out a systematic review and meta-analysis to determine the short- and long-term effectiveness of ketamine for suicidality. CENTRAL, Embase, Medline, and PsycINFO were searched until December 12, 2018; RCTs of ketamine or esketamine reporting data on suicidal ideation, self-harm, attempted or completed suicide in adults diagnosed with any psychiatric disorder were included. Two reviewers independently extracted data, and certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool. Standardized mean difference was used for continuous outcomes. A total of 25 reports from 15 independent trials, with a total of 572 subjects diagnosed with predominately affective disorders, were included. The evidence was rated moderate-to-low. In most trials, ketamine was administered at 0.5 mg/kg via a single IV infusion over a 30- to 45-min period. Only a single trial of IN esketamine was identified. At 4 hours post-infusion, treatment with ketamine was associated with a significant reduction in suicidal ideation scores (standardized mean difference [SMD] = -0.51, 95 % CI: -1.00 to -0.03), which persisted until 72 hours post-infusion (time-points between 12 and 24 hours: SMD = -0.63, 95 % CI: -0.99 to -0.26; between 24 and 72 hours: SMD = -0.57, 95 % CI: -0.99 to -0.14), but not thereafter. However, there was marked heterogeneity of results. In a single trial of esketamine, marginal effects on suicidal ideation were observed. In terms of actual suicidal behavior, there were virtually no data on effects of ketamine or esketamine. The authors concluded that a single infusion of ketamine may have a short-term (up to 72 hours) beneficial impact on suicidal thoughts. These researchers stated that while confirmation of
these results in further trials is needed, they suggested possible use of ketamine to treat acute suicidality. Means of sustaining any anti-suicidal effect need to be found.

**Adjunctive Ketamine and Electroconvulsive Therapy**

Zheng and colleagues (2019) noted that adjunctive ketamine with electro-convulsive therapy (ECT) has been examined for treating MDD, however, the findings have been inconsistent. These investigators provided an updated meta-analysis on the safety and efficacy of ketamine augmentation of ECT in the treatment of MDD; RCTs reporting on the safety and efficacy of ketamine and ECT were identified and analyzed. A total of 17 RCTs (n = 1,035) compared ketamine alone or ketamine plus other anesthetic drugs (n = 557) with other anesthetic agents (n = 478) in MDD patients who received ECT. Ketamine + other anesthetic drugs was superior in improving depressive symptoms over other anesthetic medications at early study time-point, but not at post-ECT or end of study time-points. Ketamine alone was not more effective in treating depressive symptoms than other anesthetic drugs at early study, post-ECT and end of study time-points. Sensitivity analysis and 19 of the 20 subgroup analyses also confirmed the lack of significance of these findings. A total of 11 RCTs testing the effects of ketamine on neurocognitive functions with various test batteries found mixed results. Ketamine alone significantly increased blood pressure (BP) more than other anesthetic drugs in MDD treated with ECT. The authors concluded that compared to other anesthetic agents, ketamine alone did not appear to improve the efficacy of ECT. However, ketamine + other anesthetic combinations may confer a short-term advantage in improving depressive symptom at the early stages of ECT.

**Ketamine in the Treatment of Generalized Anxiety and Social Anxiety Disorders**
Glue and colleagues (2020) previously reported that ketamine has anxiolytic effects in patients with treatment-resistant generalized anxiety disorder (GAD) and social anxiety disorder (SAD). In a double-blind, psychoactive-controlled, ascending dose study, these researchers attempted to replicate their earlier findings regarding ketamine's anxiolytic activity, using a more robust study design. This trial included 12 patients with treatment-resistant GAD and SAD who were not currently depressed. Ascending doses of ketamine (0.25, 0.5, 1 mg/kg) were administered at weekly intervals, and midazolam 0.01 mg/kg, the control, was randomly inserted into the ketamine dose sequence. Assessments included ratings of anxiety and dissociation, safety and tolerability, and blood samples for ketamine pharmacokinetics and brain-derived neurotrophic factor (BDNF) concentrations. Improvements in anxiety ratings occurred within an hour of ketamine dosing, and persisted for up to 1 week. A dose-response profile was noted for anxiolytic effects, dissociative side effects, and changes in blood pressure and heart rate after ketamine dosing. Midazolam had minor brief effects on anxiety ratings; ketamine was safe and well-tolerated. Ketamine pharmacokinetics were correlated with dissociation ratings. Serum BDNF concentrations declined over time and were similar for all treatments. The authors concluded that ketamine may be a potential therapeutic option for patients with treatment-resistant GAD and SAD.

**Ketamine in the Treatment of Substance Use Disorders**

Ivan Ezquerra-Romano and associates (2018) examined the pre-clinical and clinical research into ketamine's ability to treat addiction. Despite methodological limitations and the relative infancy of the field, results thus far are promising. Ketamine has been shown to effectively prolong abstinence from alcohol and heroin in detoxified alcoholics and heroin dependent individuals, respectively. Moreover, ketamine reduced craving for and self-administration of cocaine in non-treatment seeking cocaine users. However, further RCTs are urgently needed to
confirm ketamine’s efficacy. Possible mechanisms by which ketamine may work within addiction include: enhancement of neuroplasticity and neurogenesis, disruption of relevant functional neural networks, treating depressive symptoms, blocking reconsolidation of drug-related memories, provoking mystical experiences and enhancing psychological therapy efficacy. Identifying the mechanisms by which ketamine exerts its therapeutic effects in addiction, from the many possible candidates, is crucial for advancing this treatment and may have broader implications understanding other psychedelic therapies. The authors concluded that ketamine showed great promise as a treatment for various addictions, but well-controlled research is urgently needed.

Jones and colleagues (2018) stated that despite advances in behavioral and pharmacotherapy interventions, substance use disorders (SUDs) are frequently refractory to treatment. Glutamatergic dysregulation has received increasing attention as one common neuropathology across multiple substances of abuse. These investigators reviewed the literature on the efficacy of ketamine in the treatment of SUDs. A systematic review of the PubMed, Scopus, and ClinicalTrials.gov databases was undertaken to identify completed and ongoing human studies of the effectiveness of ketamine in the treatment of SUDs between January 1997 and January 2018. A total of 7 completed studies were identified; 2 focused on alcohol use disorder, 2 focused on cocaine use disorder, and 3 focused on opioid use disorder. Both cocaine studies found improvements in craving, motivation, and decreased cocaine use rates, although studies were limited by small sample sizes, a homogeneous population and short follow-up. Studies of alcohol and opioid use disorders found improvement in abstinence rates in the ketamine group, with significant between-group effects noted for up to 2 years following a single infusion, although these were not placebo-controlled trials. The authors noted that these findings suggested that ketamine may facilitate abstinence across multiple substances of abuse and warrants broader investigation in addiction.
They concluded with an overview of the 6 ongoing studies of ketamine in the treatment of alcohol, cocaine, cannabis, and opioid use disorders and discussed future directions in this emerging area of research. These researchers stated that further studies are urgently needed.

### CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other CPT codes related to the CPB:</td>
<td></td>
</tr>
<tr>
<td>96365 - 96368</td>
<td>Intravenous infusion administration</td>
</tr>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
<tr>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>Ketamine - no specific code:</td>
<td></td>
</tr>
<tr>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>F10.10 - F19.99</td>
<td>Substance related disorders</td>
</tr>
<tr>
<td>F32.0 - F33.9</td>
<td>Major depressive disorders</td>
</tr>
<tr>
<td>F40.10</td>
<td>Social phobia, unspecified</td>
</tr>
<tr>
<td>F40.11</td>
<td>Social phobia, generalized</td>
</tr>
<tr>
<td>F41.1</td>
<td>Generalized anxiety disorder</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:


Amendment to Aetna Clinical Policy Bulletin Number: 0938 Ketamine for the Treatment of Depression and Other Psychiatric Disorders

There are no amendments for Medicaid.

revised 12/18/2020

Proprietary