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Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

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Abstract

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for their competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of ketamine and esketamine in adults with treatment-resistant depression. The authors also provide guidance for the implementation of these agents in clinical practice, with particular attention to practice parameters at point of care. Areas of consensus and future research vistas are discussed.

The majority of individuals with major depressive disorder who are treated with monoamine-based antidepressants fail to achieve full symptomatic and functional recovery with the index treatment (1). Remission rates in major depression are reportedly less than 15% among patients with two prior conventional treatment or augmentation failures, that is, with treatment-resistant depression (TRD) (2–7). Despite the efficacy of manual-based psychotherapy (e.g., cognitive-behavioral therapy) in major depression, its efficacy as a monotherapy in TRD is not well established (8).

In March 2019, intranasal esketamine, co-initiated with a conventional antidepressant, was approved by the U.S. Food and Drug Administration (FDA) for adults with TRD (9). The European Medicines Agency granted regulatory approval for intranasal esketamine for TRD in December 2019, and additional approvals are expected in other parts of the world. In August 2020, the FDA updated the approval of intranasal esketamine to include adults with major depression and suicidal ideation and behavior (10). The development and regulatory approvals of esketamine for mood disorders occurred pari passu with extraordinary media, public, clinical, and scientific interest in ketamine and related agents (11).

Although increasing access to and availability of treatments such as ketamine and esketamine for persons with TRD is welcome, legitimate concerns have been raised with respect to long-term efficacy, safety, tolerability, patient selection, and risk for precipitating

substance use disorder, as well as appropriate personnel and settings for competent and safe administration of ketamine (12–15). These concerns are amplified by the rapid increase in the numbers of practitioners and community-based clinics in the United States that have expanded their scope of practice to include ketamine for TRD (16).

Our overarching aims in this review are twofold: to provide practitioners with a synthesis of the current knowledge as it relates to ketamine's pharmacology, efficacy, tolerability, and safety; and to review the clinical aspects related to administration of ketamine at point of care. This article is not meant to be an exhaustive review of the literature, which has been done in several recent systematic reviews and meta-analyses of ketamine and esketamine (17–20).

KETAMINE PHARMACOLOGY

Pharmacodynamics

The key pharmacodynamic targets of ketamine and its proposed clinical effects are summarized in Table 1. The prevailing view with respect to ketamine's mechanism of action in TRD is that ketamine facilitates synaptogenesis and synaptic potentiation (21–23). Ketamine exhibits high affinity for the phencyclidine site of the *N*-methyl-D-aspartate receptor (NMDAR) (24, 25). Antagonism of NMDARs on fast-spiking γ-aminobutyric acid (GABA)-ergic interneurons inhibits interneuron tonic firing with a consequent glutamate surge (26).

The glutamate surge activates the ionotropic AMPA receptor (AMPAR), setting in motion a series of intracellular signaling cascades, resulting in an increase in brain-derived neurotrophic factor (BDNF)-TrkB-ERK activity as well as PI3-AKT-mammalian target of rapamycin (mTOR) activation (27, 28). Indirect evidence supporting this pathway includes the observation that pretreatment with the AMPAR antagonist NBQX (2,3-dioxo-6-nitro-7-sulfamoyl-benzo[f] quinoxaline) attenuates antidepressant-like behavioral effects with ketamine (28–30).

Recent studies also suggest that ketamine's mechanism of action may involve effects on the subgenual anterior cingulate cortex (sgACC) (31, 32). Overactivity in the sgACC is a replicated pathological feature of major depressive disorder, and reduction of activity in the sgACC is associated with response to conventional antidepressant treatments (31, 33). Studies in nonhuman primates showed that glutamatergic overactivation of the sgACC led to anhedonic behavior that could be reversed by injection of ketamine directly into the sgACC (32). Consistent with this finding, patients with major depression show hyperactivation of the sgACC during receipt of monetary reward that was reversed by ketamine (31).

In addition to effects on glutamate-GABA systems, evidence suggests that other low-affinity targets may also be relevant to ketamine's mechanism of action in TRD (34). For example, ketamine is reported to activate human-recombinant μ, κ, and δ opioid receptors (35). It is also observed that μ opioid receptors and NMDAR co-localize in the CNS, which may account for the increase in glutamatergic signaling reported with morphine (36, 37). Animal data indicate that the opioidergic system is necessary, but not sufficient, for the

antidepressant action of ketamine in rodents (38). Williams et al. observed that pretreatment with naltrexone (50 mg), a nonselective pure opioid antagonist with differential affinity for the μ opioid receptor, attenuated the antidepressant and anti–suicidal ideation effects of a single intravenous infusion of ketamine (0.5 mg/kg) in adults (N=30) with TRD (39, 40). This interesting proof-of-concept study implicates opioidergic systems as a direct and/or indirect target of ketamine treatment in TRD.

The findings of this elegant study need to be considered along with results of a separate small (N=5) open-label pilot study (41) in which adults with major depressive disorder and current alcohol use disorder received pretreatment with injectable naltrexone (380 mg) once every 2–6 days prior to repeat intravenous ketamine infusion (0.5 mg/kg per day). Despite pretreatment with naltrexone, significant antidepressant effects as well as reductions in craving for alcohol consumption were reported. Moreover, a separate post hoc analysis indicated that allelic variation of the μ opioid receptor does not attenuate the anti–suicidal ideation effect of ketamine treatment in TRD (42).

Taken together, the available evidence has not excluded the potential for misuse and/or gateway activity with ketamine or esketamine among patients receiving these treatments for TRD. Indeed, there is an urgent need to refine the potential role of opioid receptors in ketamine's antidepressant effect and safety profile (43). Ketamine's putative effects on other low-affinity targets (e.g., σ receptors, voltage-gated sodium channels, and L-type voltage-dependent calcium channels) are comprehensively reviewed elsewhere (34).

Pharmacokinetics

Ketamine is available in multiple formulations, of which the intravenous and intranasal routes have the most compelling evidence of efficacy in TRD. As summarized in Table 2, the bioavailability of ketamine differs as a function of route of delivery, and a gradient of bioavailability is observed (i.e., intravenous > intramuscular > subcutaneous > intranasal > oral) (34). Ketamine's plasma protein binding is approximately 10%–15%. The elimination half-lives are approximately 2–4 hours for racemic ketamine and 5 hours for esketamine (44). The bioavailability is approximately 100% for intravenous ketamine and approximately 30%–50% for intranasal esketamine. The dosing equivalence of intravenous ketamine and intranasal esketamine is not definitively established. However, as intravenous racemic ketamine comprises an equal molar ratio of *S*- and *R*-ketamine, it is estimated that 0.5 mg/kg of ketamine approaches the bioavailability of approximately 56 mg of esketamine (34).

Ketamine is highly lipophilic and is metabolized primarily through CYP3A4 and CYP2B6 to its principal metabolite, norketamine. CYP3A4 demethylates esketamine at a faster rate than it does *R*-ketamine, and CYP2B6 metabolizes both isomers with equal efficiency (34). The differential efficiency may account for the observation that the ratio of *S*- to *R*-ketamine in individuals with treatment-resistant bipolar depression receiving intravenous racemic ketamine (0.5 mg/kg over 40 minutes) was reported as 0.84 (44). *R*/*S*-norketamine is subsequently converted to hydroxynorketamine and dehydronorketamine (34).

Reports from rodent studies indicate that ketamine has mild and likely clinically insignificant induction and/or inhibitory effects on CYP3A4 (45–48). It is unlikely that

the effects described here would be clinically meaningful when ketamine is coprescribed with other agents that are substrates of CYP3A4. Concomitant administration of other drugs that are CYP3A4 and/or CYP2B6 inhibitors or inducers may have effects on the areas under the curve (AUC) and peak serum concentrations (C_{max}) for circulating ketamine and norketamine, but the clinical significance is not determined (49).

KETAMINE AND ESKETAMINE EFFICACY IN TRD

The most studied and compelling formulations and routes of delivery of ketamine in TRD are intranasal esketamine coadministered with a newly initiated antidepressant, or intravenous racemic ketamine administered as monotherapy or adjunctively with preexisting psychotropic regimens. Replicated short-term randomized controlled studies have unequivocally established the rapid and significant efficacy of both formulations and routes of delivery in adults with TRD (17–20,50). A legitimate criticism, as it relates to interpreting the effect sizes reported with single or repeat-dose ketamine in TRD, is the possibility that nonspecific effects such as functional unblinding (e.g., by patients experiencing dissociation or euphoric responses) and expectancy may inadvertently inflate the efficacy of ketamine (51, 52).

The short-term efficacy of intravenous racemic ketamine has invited the need in most cases for repeated dosing to sustain the therapeutic benefit (53). Studies ranging from 0.1–1.0 mg/kg suggest that higher dosing (i.e., 0.5–1.0 mg/kg) is superior in efficacy at the group level when compared with lower dosing (i.e., 0.1–0.2 mg/kg) 1 day after administration (54). The upper dosing limit for intravenous racemic ketamine in TRD is not established, but evidence from single-dose studies indicates efficacy at doses of 0.5 mg/kg as well as 1.0 mg/kg, with no evidence of superiority of 1.0 mg/kg over 0.5 mg/kg (54). It is also reported that some treatment-emergent adverse events with ketamine (e.g., elevation in blood pressure) are dose dependent (55). Experience with intravenous ketamine administration in adults with TRD receiving care at a community-based clinic also indicates that higher doses of intravenous ketamine are associated with higher rates of treatment-related adverse events (e.g., dissociation) when compared with lower dosing (i.e., 0.75 mg/kg and 0.5 mg/kg, respectively) (56). Clinicians administering ketamine should be aware of the greater propensity to adverse events and potential safety concerns when relatively higher doses of intravenous ketamine are administered.

The ideal frequency of intravenous administration has also not been established in adults with TRD. For example, results from a multicenter double-blind study in adults (N=67; ages 18–64 years) with TRD indicated that acute antidepressant efficacy at day 15 did not differ between twice weekly and thrice weekly intravenous administration (0.5 mg/kg) (57).

An initial pilot study demonstrated the antidepressant efficacy and tolerability of intranasal racemic ketamine given as a single administration (50 mg) (58). Thus far, intranasal racemic ketamine has not been definitively established as safe and effective in adults with TRD. Intranasal esketamine was studied in several registration trials prior to regulatory approval. The trial designs for intranasal esketamine studies were unique insofar as intranasal esketamine was co-initiated with a conventional antidepressant and compared with a placebo

co-initiated with an antidepressant as the comparator. The effective doses of intranasal esketamine were 56 mg and 84 mg, administered twice weekly for 4 weeks, followed by weekly administration for 4 weeks and every 1–2 weeks thereafter.

A meta-analysis of the efficacy of intranasal esketamine augmentation in TRD (five trials, N=774 patients) reported significant improvement (19). The endpoints in the intranasal esketamine studies were efficacy at 4 hours and at days 8 and 28. The overall standardized mean difference for the Montgomery-Åsberg Depression Rating Scale score change was 0.36 (95% CI=0.24, 0.49, $p<0.0001$). The pooled risk ratios for response and remission were 1.4 and 1.45 (both at $p<0.0001$), respectively. It was further reported that the number needed to treat was 6 for response and 7 for remission. The clinically significant results in that study were apparent despite the high placebo response (i.e., placebo co-initiated with a conventional antidepressant) in the esketamine development program. Nevertheless, it should be highlighted that a secondary subgroup analysis of the intranasal esketamine data indicated that placebo-subtracted differences in some subgroups with intranasal esketamine were not significant (e.g., those with <3 previous antidepressant failures) (59).

In addition to acute efficacy, relapse prevention was established with intranasal esketamine in combination with a conventional antidepressant. Intranasal esketamine combined with a conventional antidepressant decreased the risk of relapse by 51% among persons who had achieved stable remission and 70% among those who achieved a stable response with acute therapy (60). However, it was subsequently noted that one of the participating sites had a 100% relapse rate in the placebo arm, which accounted for a significant overall effect in the positive relapse prevention study result (61). This observation needs to be placed in a broader context, however, as the study was not designed primarily with a view to evaluating site-specific placebo-drug differences.

The efficacy of intranasal esketamine in adults ≥65 years old is not yet established. In one study in adults ≥65 years old, intranasal esketamine was flexibly dosed at 28–84 mg twice weekly and co-initiated with a new antidepressant (62). The overall efficacy of adjunctive intranasal esketamine was not significantly greater than placebo in that study at the prespecified endpoint (i.e., day 28). In addition to this negative study, another study reported non-significant differences between adjunctive intranasal esketamine and placebo co-initiated with a conventional antidepressant (63). Notwithstanding, preliminary evidence does suggest that ketamine may be safe and effective in older populations with TRD (64).

Given the absence of an adequately designed head-to-head trial, the relative efficacies of intranasal esketamine and intravenous racemic ketamine are not known (65). Nevertheless, a single study suggested that twice- or thrice-weekly intravenous racemic ketamine (0.5 mg/kg) may be superior to intranasal esketamine co-initiated with an antidepressant (the numbers needed to treat were 2 and 6, respectively, for response at week 2) (57). A recent meta-analysis comparing intranasal and intravenous ketamine formulations was unable to identify a significant difference between formulations as well as routes of delivery in efficacy at 24 hours, 7 days, and 28 days (17). A separate meta-analysis concluded that intravenous ketamine may be superior in efficacy and have lower dropout rates (66).

However, it is difficult to draw definitive conclusions from these analyses given the heterogeneity across component studies.

Ketamine's efficacy in TRD using oral, intramuscular, and subcutaneous formulations has also been preliminarily reported. Of these formulations, the oral formulation has relatively more studies in TRD with evidence suggesting efficacy alter repeat dosing, with insufficient data on efficacy within 24 hours (67). Oral ketamine has been commonly prescribed off-label for its analgesic effect and is often compounded into capsules or mixed with juice to increase its palatability (68). Oral ketamine has extensive first-pass metabolism, resulting in a bioavailability of 10%–20% (sublingual ketamine has a bioavailability of approximately 30%) (69, 70). Similar to oral ketamine, the efficacy of subcutaneous and intramuscular ketamine in TRD has not been established with adequately powered, replicated randomized double-blind placebo-controlled studies.

KETAMINE AND SUICIDALITY

Rapid reduction of suicidal ideation with ketamine has been reported (71, 72). Results from systematic reviews and meta-analyses have also reported anti–suicidal ideation effects of ketamine/esketamine with both single and repeat dosing (166). The reduction in suicidal ideation has been reported to endure for up to 7 days from the previous administration (73). Repeat-dose studies also indicate that reduction in suicidal ideation may persist for up to 6 weeks in persons receiving repeat-dose intravenous racemic infusion (0.5 mg/kg) (74). Available evidence also suggests that the reduction in suicidal ideation observed with ketamine may be in part independent of its effect on overall depressive symptoms (18, 75).

A limitation, however, is the lack of evidence demonstrating reduction in suicide completion and whether a more persistent reduction in suicidal ideation is observed beyond 6 weeks for either esketamine or ketamine (74). Of the two formulations, esketamine has been subjected to a more rigorous assessment of its acute antisuicidality effects. For example, although two phase 3 studies and one phase 2 study in adults with major depression at imminent risk for suicide who underwent randomized assignment to intranasal esketamine (84 mg) or placebo co-initiated with conventional antidepressants showed rapid improvement in depressive symptoms as measured by the Montgomery-Åsberg Depression Rating Scale (the primary outcome measure), the studies did not find significant reductions in suicidal ideation compared with placebo at 24 hours after administration and/or 25 days later (76). Notwithstanding the failure to detect a difference in suicidal ideation, the studies provided the basis for the FDA approval of esketamine for the treatment of major depressive disorder with suicidal ideation or behavior (77, 78). No data are available on the effect of maintenance esketamine or ketamine with suicidality as the primary outcome.

KETAMINE TOLERABILITY AND SAFETY

Treatment-emergent adverse events with ketamine and esketamine in major depression may be categorized as psychiatric (e.g., dissociation, psychotomimetic), neurologic/cognitive, hemodynamic, genitourinary, and abuse liability (79). The categories of side effects observed with ketamine and esketamine in major depression are, in some cases, identical

with differences in the percentage and severity of events. The differences in the frequency and severity of adverse events are a function of the heterogeneity in ketamine formulation, route of delivery, patient population, concomitant medications, and methodological aspects (e.g., safety assessments) of study designs. A limitation of adverse event reporting is that most adverse events with intravenous ketamine are not systematically reported and are likely subject to reporting bias insofar as there is relatively less data as it relates to long-term ketamine exposure. This is in contradistinction to the safety and tolerability data for esketamine in TRD, where the data collection was systematic and included both short- and long-term data.

Psychiatric Adverse Events

Dissociation.—The most common psychotomimetic effects reported with ketamine in TRD are dissociation, perceptual disturbances, abnormal sensations, derealization, and depersonalization (79). Approximately 72% of studies with intravenous racemic ketamine in TRD report dissociation, compared with 36% in non-intravenous racemic ketamine studies, most likely reflecting differences in plasma levels rather than route of administration (79). It is a replicated finding that the percentage of individuals with TRD reporting dissociation decreases with subsequent administration. Dissociation usually peaks within 40 minutes after administration and usually resolves within 1–2 hours. The most commonly used scale to assess the severity of dissociation in TRD is the Clinician-Administered Dissociative States Scale (CADSS).

Although results are mixed with respect to whether dissociation correlates with acute or sustained antidepressant effects, dissociation is neither necessary nor sufficient for antidepressant response (80, 81). Moreover, there is no evidence that adults with treatment-resistant major depression or bipolar disorder differ in their propensity for dissociation (82). Consensus exists that the CADSS, which has been repurposed as a ketamine safety measure, does not provide sufficient coverage of psychotomimetic experiences with ketamine and likely underestimates the frequency of dissociation (83). Unfortunately, a tool specifically validated for measuring dissociation in adults with TRD receiving ketamine is not available at this time for point-of-care implementation.

Psychotomimetic.—In this discussion, psychotomimetic is defined as the induction of psychosis and is differentiated from dissociation. Ketamine has long been reported to carry a risk of induction of psychosis, especially in individuals with a preexisting vulnerability. Ketamine, for example, can induce psychotic phenomena in individuals with schizophrenia (84, 85). Nevertheless, it remains possible that selected individuals with a primary psychotic disorder may safely and effectively benefit from ketamine administration (86). It was also reported that individuals with a history of psychosis are more vulnerable to dissociation, but not psychosis, with ketamine administration. Despite the greater propensity for dissociation in those with a history of psychosis, the duration of dissociation did not endure beyond the 40-minute time point (87).

Neurologic/Cognitive

For adults with TRD, no replicated and persistent deficits in cognitive functions in persons treated with racemic ketamine have been reported (88–90). It has been reported that the multidomain cognitive impairment assessed in healthy volunteers (N=24) 40 minutes after esketamine administration (84 mg) was no different from that assessed in the placebo group at 120 minutes (91). Also, 1-year exposure to intranasal esketamine in adults with TRD has not been reported to result in impairment in cognitive function (91).

The most common neurologic side effects are dizziness, drowsiness, and light-headedness. It is not known whether long-term exposure to ketamine results in cellular or molecular evidence of neurotoxicity. Preclinical studies have reported the presence of excitotoxic lesions, including Olney lesions, hyperphosphorylation of tau, and a loss of parvalbumin-containing GABAergic neurons with repeated exposure to ketamine (34). It remains unknown whether such lesions are possible in individuals with TRD receiving maintenance ketamine treatment.

Hemodynamic

Ketamine exhibits cardiac-stimulating effects via central mechanisms (55). The most common hemodynamic adverse event associated with ketamine use in major depression is an increase in heart rate and blood pressure, followed by palpitations, arrhythmias, chest pain, and hypotension (55, 92). It is observed that ketamine-associated blood pressure elevations in adults with TRD are dose dependent (55, 93).

Increases in systolic and diastolic blood pressure are reported in 10%–50% of patients and are usually observed within 20–50 minutes of treatment administration and usually resolve within 2–4 hours. It is also reported that blood pressures exceeding 180/100 mmHg and/or heart rate ≥110 beats per minute affect 20%–30% of persons receiving ketamine (usually intravenous in TRD) (55, 79). It is reported that up to 20% of individuals receiving ketamine for TRD in a community-based clinic may require (depending on clinic-level protocols) pharmacological treatment for intravenous ketamine-induced hypertension (56). The rates of hypertension reported in the esketamine development program in TRD revealed relatively low rates of blood pressure elevations, which were usually transient and asymptomatic, with 2.1% of patients requiring antihypertensive treatment, compared with 1.2% in the placebo group (94). For most individuals, hemodynamic changes are asymptomatic, and they do not usually attenuate with subsequent administration of ketamine.

Genitourinary

Lower urinary tract symptoms in persons receiving ketamine affect approximately 20%–40% of individuals who use ketamine recreationally (95, 96). Lower urinary tract symptoms include nocturia, painful hematuria, dysuria, urinary urgency, and incontinence. Improvement in lower urinary tract symptoms is reported in the majority of individuals upon ketamine discontinuation, although for approximately 5% of individuals, symptoms may persist or progress (97).

The underlying pathology subserving lower urinary tract symptoms includes disruption of the urine–bladder epithelium interface, destruction of the neuromuscular junction at the level of the bladder, nitric oxide synthase–mediated inflammation, and immunoglobulin E–mediated inflammation (98). Bladder cystoscopy reveals bladder wall inflammation. Further investigation also reveals ureter thickening, stenosis, vesico-ureteral reflux, and, in some cases, hydronephrosis (97, 99).

A dose-response relationship is reported between ketamine exposure and probability of experiencing lower urinary tract symptoms, indicating that long-term exposure to ketamine, which is generally required for many individuals with major depression, may be cause for concern in some cases. It is reassuring that a long-term study with intranasal esketamine did not identify a significant percentage of individuals experiencing genitourinary symptoms (100, 101). Other than discontinuation of ketamine, there is no established treatment for ketamine-associated kidney-ureter bladder pathology (167). It is reassuring that, thus far, no evidence of genitourinary toxicity has been reported with repeated-dose esketamine in TRD (98).

Abuse Liability

Ketamine is an abusable substance and, as such, is classified as a schedule III agent in the United States. In healthy volunteers, intravenous racemic ketamine at doses typically administered for TRD (i.e., 0.4–0.8 mg/kg) is associated with increased liking for ketamine, providing the basis for concern about potential misuse and/or sensitization to other drugs of misuse (102–107). Moreover, both intravenous racemic ketamine and esketamine are reported to increase drug liking in recreational polydrug users (34, 108). It is also speculated that evidence reviewed above, in the pharmacodynamics section, suggests that ketamine's effects on opioidergic systems may presage sensitization of drug reward substrates, increasing the possibility of gateway activity (15).

Nevertheless, there is no evidence that racemic ketamine or esketamine administered as single or repeated doses has increased the risk for substance use disorders. For adults who completed the open-label 1-year safety study with intranasal esketamine, there were no reports of new-onset drug or alcohol misuse; however, the status of the study subjects after completion of the study is not known (101). Early clinical studies of opioids for chronic pain also did not identify a public health risk with respect to misuse and diversion, which provides the basis for a cautionary approach with ketamine in adults with TRD (109).

KETAMINE IMPLEMENTATION AT POINT OF CARE

All clinicians are encouraged to consult country-specific regulatory requirements with respect to guidance on ketamine implementation in adults with TRD. In the United States, the product monograph or package insert for esketamine requires the implementation of a Risk Evaluation and Mitigation Strategy. Thus, clinicians administering esketamine should consult the product monograph, which provides specific requirements for implementation.

Patient Selection

The evidence with respect to the efficacy, safety, and tolerability of ketamine and esketamine is best established in adults with treatment-resistant major depressive disorder (59, 79). Preliminary evidence from small controlled trials provides preliminary support for the efficacy of intravenous racemic ketamine in adults with treatment-resistant bipolar disorder, obsessive-compulsive disorder, and posttraumatic stress disorder (56, 110–114). Consequently, individuals with TRD as part of major depressive disorder would be appropriate candidates with respect to the evidence base supporting intravenous ketamine and esketamine. Box 1 summarizes patient selection and monitoring.

The high rate of TRD in persons with bipolar disorder, as well as preliminary evidence supporting the safety and efficacy of ketamine, would justify consideration of ketamine as an investigational treatment in bipolar disorder (115). The evidence to date supporting ketamine in obsessive-compulsive disorder and posttraumatic stress disorder is highly preliminary, and use of ketamine in these disorders should be considered investigational and limited to centers with expertise in assessing and managing these conditions. As described earlier, the safety of ketamine administration in patients with TRD and a history of affective psychosis is not yet established, and therefore the treatment is to be used with caution in such patients (116). Preliminary evidence suggests that persons with psychotic depression or a primary psychotic disorder may safely benefit from treatment with intravenous ketamine or esketamine (86, 117).

Most studies in adults with TRD have defined TRD as insufficient response to at least two antidepressants during the index episode. An important observation with respect to ketamine's efficacy in adults with TRD is the possibility of attenuated efficacy in individuals with greater degrees of treatment resistance in some, but not all, studies (59, 118–120). It is not known whether esketamine's efficacy is attenuated in adults with greater degrees of treatment resistance. Available studies suggest that ketamine and esketamine may be considered in patients who have had at least two prior treatment failures.

It is not known whether failure to respond to ECT or repetitive transcranial magnetic stimulation (rTMS) affects subsequent response to ketamine (168). In a study comparing adults with TRD who were nonresponders to ECT (N = 17) and adults with TRD who were ECT-naive (N=23) receiving a single dose of intravenous racemic ketamine (0.5 mg/kg), overall, the two groups exhibited similar depressive symptom reduction, with a trend toward favoring ECT-naive patients that did not reach statistical significance (121).

Adults with TRD are a heterogeneous group with respect to phenomenology, patterns of comorbidity, and prior history. Clinicians and patients are especially interested in whether, a priori, they would be more (or less) likely to safely benefit from ketamine administration (122–125). However, no biomarker or biosignature (e.g., pharmacogenomics) or phenomenological presentation has proven to reliably predict outcome with ketamine in TRD (114, 126–128).

The efficacy and safety of ketamine and esketamine in adults with major depression and psychotic features has not been well characterized, but preliminary evidence suggests that

it maybe an appropriate strategy in some cases (116, 117, 129). Similarly, adults with major depression and comorbid substance use disorders (including alcohol use disorder) have not been sufficiently studied with respect to ketamine's efficacy and safety profile. It remains a testable hypothesis that some individuals with TRD and comorbid substance use disorders may safely benefit from ketamine. Preliminary evidence suggests that single-dose intravenous racemic ketamine, in combination with manual-based psychosocial treatment, may attenuate alcohol and cocaine craving and consumption (130, 131).

Current psychiatric comorbidities need not be exclusionary as long as major depressive symptoms are the principal focus of clinical concern. However, patients with dementia experiencing TRD have not been sufficiently studied with respect to ketamine administration. Moreover, patients reporting hypersensitivity to ketamine in the past should be excluded from receiving ketamine for TRD. Other individuals who also should be excluded from receiving ketamine treatment are those with uncontrolled hypertension, central aneurysmal disease, significant valvular disease, a recent (within 6 weeks) cardiovascular event (e.g., myocardial infarction), or New York Heart Association class III heart failure (50).

Most patients with TRD will likely receive ketamine or esketamine in combination with their existing psychiatric medication. Intranasal esketamine, as part of its clinical development program, was co-initiated with a concomitant oral antidepressant (i.e., sertraline, escitalopram, duloxetine, venlafaxine). Less evidence is available on combining esketamine with other antidepressants, which will undoubtedly happen in real-world practice. Similarly, intravenous ketamine will likely be prescribed as an adjunctive treatment to the patient's existing regimen. It is also not known whether any particular combination of conventional antidepressant with intravenous racemic ketamine is uniquely effective.

Clinicians need to be aware of potential pharmacodynamic and/or pharmacokinetic drug-drug interactions when administering ketamine in combination with other agents. Concomitant medications that are of potential concern, but not necessarily contraindicated, are nonselective monoamine oxidase (MAO) inhibitors and reversible inhibitors of monoamine oxidase-A (132). Preliminary evidence suggests that in some cases, ketamine may be safely coadministered with MAO inhibitors, but the data on the safety of this combination remain limited (132, 133).

A relative contraindication also exists for psychostimulants and other agents with vasopressor activity. Preliminary evidence suggests, but has not established, attenuated antidepressant efficacy with ketamine coadministered with naltrexone, suggesting that naltrexone should be discontinued prior to ketamine treatment (13). As ketamine and esketamine depend on CYP3A4 and CYP2B6 for biotransformation, concomitant use of other agents that are inducers or inhibitors of these enzymes may have effects on the bioavailability of ketamine. Nevertheless, no clinically significant drug interactions have been reported in the coadministration of ketamine or esketamine with conventional antidepressants, second-generation antipsychotics, lithium, or anticonvulsants that are FDA approved in the treatment of bipolar disorder.

The available evidence suggests that concomitantly administered benzodiazepines may attenuate and/or delay antidepressant response to ketamine (45, 134–137). In addition, lamotrigine, which reduces glutamate release, may in theory interact with ketamine administration. For example, it remains uncertain whether lamotrigine attenuates the dissociative effects of ketamine (138, 139). It is also unknown whether lamotrigine affects the efficacy of ketamine in major depression.

Ketamine Dosing and Frequency

It is recommended that intravenous ketamine be started at 0.5 mg/kg and infused over 40 minutes; doses may be lowered in cases of intolerability with the proviso that efficacy at lower doses may be inferior. For persons who are overweight or obese, dosing ketamine based on ideal body weight is recommended. Parenthetically, preliminary evidence, from some but not all studies, suggests that individuals who are obese may exhibit higher response rates to ketamine (122, 140–142, 169). The differential efficacy in persons in higher body mass index (BMI) categories in some cases may be a function of higher ketamine dosing and/or differential pharmacokinetics or pharmacodynamics in persons of higher weight.

There remains a lack of sufficient evidence to guide dose optimization with intravenous ketamine (54). Upon completion of four to six intravenous infusions, a post-follow-up assessment should be conducted to determine overall efficacy of the intervention. Although the preponderance of data suggest that most individuals with TRD who respond to intravenous ketamine do so after one to two infusions, the possibility remains that there are patients who may not respond to intravenous ketamine until after a higher number of infusions (i.e., four to six infusions). It is generally recommended that if an individual exhibits minimal response (i.e., ≤20% improvement from baseline in total depression symptom severity) after four to six ketamine treatments, then the individual can be deemed nonresponsive and subsequent treatments would not be warranted. For adults with TRD, intranasal esketamine should start at 56 mg on day 1 and increase (as per clinician discretion and patient agreement) to 56–84 mg twice weekly for weeks 1–4, and then 56–84 mg once weekly for the following 4 weeks and every 1–2 weeks thereafter. The recommended dosage of esketamine for the treatment of depressive symptoms in adults with major depressive disorder and acute suicidal ideation or behavior in the United States is 84 mg twice per week for 4 weeks. Evidence of therapeutic benefits with esketamine should be determined after week 4 (19). If minimal response to esketamine treatment is observed after 4 weeks, it would be recommended that treatments be discontinued.

The frequency of intravenous ketamine administration where the therapeutic objective is prevention of relapse or recurrence also has not been ascertained and should be determined on an individual basis. Moreover, it is unknown whether the maintenance intravenous ketamine dose should be identical to the dosing established as efficacious during the acute phase.

Notwithstanding the administration of intravenous ketamine as a maintenance treatment, practitioners should bear in mind that there is insufficient evidence guiding dosing, frequency, and long-term safety and tolerability. It is our opinion that maintenance

ketamine treatment with periodic evaluation of need for ongoing treatment on a monthly to bimonthly basis is warranted in selected cases. Evaluation of the relative benefits and risks of maintenance intravenous ketamine, as well as consideration of patient preference and availability of alternative treatment options, should be an ongoing process. In contradistinction to intravenous ketamine, maintenance data do support the efficacy and safety of intranasal esketamine administered approximately weekly to biweekly in adults with TRD (100, 101). The effectiveness of ketamine maintenance treatment will need to be considered along with the probability of tolerance, as well as of relapse or recurrence, in patients on an individual basis.

It remains unknown whether intravenous ketamine or intranasal esketamine is more effective, safer, better tolerated, and/or more cost-effective for adults with TRD. Unfortunately, there have been no rigorous head-to-head comparative studies of the efficacy, tolerability, and safety of both formulations in TRD. Meta-analysis of outcomes comparing disparate routes of administration of ketamine in TRD also fail to adequately inform the decision (17). A major limitation with such comparisons is that whereas a novel antidepressant is often co-initiated with intranasal esketamine, intravenous ketamine is often administered as a monotherapy or as an adjunct to an existing antidepressant.

A related and pragmatic issue is whether some adults with TRD may begin treatment with the intravenous route, followed by transition to intranasal esketamine as a maintenance treatment strategy for those who responded acutely. It is also unknown whether nonresponse or intolerability to intravenous ketamine in TRD predicts outcome with intranasal esketamine or vice versa. Electing either formulation over the other will be influenced by patient preference, personnel, experience, and clinical infrastructure. Clinicians should be aware of the fact that the rigor of evidence supporting esketamine in the short and long term is superior to that for intravenous ketamine. The relative cost-effectiveness of ketamine (available as a generic drug) and esketamine (available only as a branded drug) is another factor that might be considered (143). Although intravenous ketamine is generic, there are additional costs in its administration, often uninsured, that need to be considered with respect to its cost-effectiveness.

Strategies to Prolong Ketamine's Efficacy

Various strategies have been attempted to prolong the efficacy of ketamine in TRD (e.g., lithium, riluzole), but none have been proven effective in replicated randomized controlled studies (139, 144–146). Although not necessarily a strategy to prolong efficacy per se, repeated dosing appears to sustain benefits longer than single dosing (20, 53, 100, 147).

For example, results from meta-analysis indicate that single-dose ketamine administration is effective for 3–7 days (20, 147). Repeated-dose intravenous racemic ketamine has demonstrated efficacy for up to 2–3 weeks (20, 147). Original studies and meta-analyses indicate that most patients relapse within 1 month (median, 18 days) of administration, inviting the need for repeated ketamine administrations (20, 53, 147). Esketamine has demonstrated relapse prevention with repeated dosing as part of the development program for this product (60).

Setting, Personnel, and Monitoring

Ketamine should be administered in a general or specialty setting that has personnel with expertise in the assessment, diagnosis, management, and follow-up of persons with mood disorders. When intravenous ketamine is being administered, at least one member at the point of care should have advanced cardiac life support training (ACLS). The product monograph for esketamine does not explicitly require personnel with ACLS training at the site of implementation. The setting personnel should be able to monitor cardiovascular, hemodynamic, and respiratory function; electrocardiography and measurement of oxygen saturation are essential. Although doses of ketamine greater than 0.5 mg/kg have not demonstrated superior efficacy, safety, or tolerability, capnography should be considered for patients receiving higher doses (e.g., 1.0 mg/kg).

Settings that intend to provide ketamine to multiple patients simultaneously should have sufficient personnel to safely oversee both the psychiatric and physical safety aspects of the administration of ketamine or esketamine intravenously or intranasally. As ketamine administration in some individuals may amplify sensory experiences and/or result in dissociation or psychotomimetic effects, a comfortable and adaptable environment is highly recommended during administration.

Before patients are scheduled for ketamine administration as well as upon completion of ketamine treatment, a psychiatric assessment should be conducted to confirm diagnosis and eligibility as well as response and tolerability after intervention. The psychiatric assessment should be conducted by a psychiatrist or a health care provider with expertise in the assessment and evaluation of adults with mood disorders. Prior to ketamine administration, evaluation of depression symptom severity is a minimum expectation. Although no depression metric is specifically validated for ketamine administration or other rapid-onset treatments, reasonable options include, but are not limited to, the Patient Health Questionnaire–9, the Beck Depression Inventory, and the 16-item Quick Inventory of Depressive Symptomatology–Self-Report.

In addition, the assessment of anxiety (e.g., the Generalized Anxiety Disorder Scale), psychosocial function, self-rated cognitive function (e.g., the Perceived Deficits Questionnaire, 5-item), and well-being (e.g., the five-item World Health Organization Well-Being Index) is encouraged (148, 149). Prior to receiving ketamine treatment, all patients should have a physical examination, with measurement of vital signs, cardiorespiratory stability, and BMI. Although mandatory toxicology screening would not be required for all individuals receiving intravenous ketamine or esketamine, it may be considered in cases where concerns about substance misuse are present.

A survey of treatment-emergent adverse events is encouraged. From a safety perspective, all patients should be asked about the presence and severity of dissociative symptoms when intravenous ketamine or esketamine is administered. Although the CADSS has been the most frequently used measure of dissociation in clinical research, its utility at point of care and in clinical practice is not well established, and it cannot be considered, at this time, a standardized safety metric.

According to the Risk Evaluation and Mitigation Strategy established for esketamine, all patients should be monitored for a minimum of 2 hours before discharge from the clinic. Although it is unknown what the minimum adequate duration is for monitoring adults with TRD receiving intravenous ketamine, a similar period of up to 2 hours should be considered. All patients should be monitored for hemodynamic stability, normalization of respiratory functions, clear sensorium, and attenuation of dissociation and any other psychiatric adverse events. Patients should be notified that they should not operate a motor vehicle until they have had at least one night of sleep; patients are required to arrange for reliable transportation from clinic to home.

For patients receiving maintenance ketamine treatment, safety should focus on evidence of drug or alcohol misuse, subjective cognitive complaints, genitourinary pathology (e.g., hematuria), and change in concomitant medication. All individuals receiving ketamine or esketamine for major depression should be queried with respect to suicidal ideation and suicidal behavior as part of the eligibility assessment. Individuals who are discontinuing ketamine or esketamine treatment for major depression should have a transition-of-care plan in place for ongoing surveillance of depressive symptoms, including suicidal ideation and behavior.

Ketamine's Positioning in the Algorithmic Treatment of TRD

Other somatic treatment considerations in adults with TRD are second-generation antipsychotics, combined antidepressants, combination with other agents (e.g., lithium), and neurostimulation (e.g., ECT). Ketamine has been demonstrated to be efficacious in adults with TRD after two prior conventional antidepressants. The recent indication in the United States of esketamine for adults with major depression experiencing suicidal ideation or behavior suggests that not all individuals considered for esketamine, and possibly racemic ketamine, will meet criteria for TRD.

Taken together, results from meta-analyses suggest superiority of intravenous ketamine or esketamine when compared with second-generation antipsychotics (19, 143, 150, 151). However, there have not been studies comparing ketamine or esketamine with second-generation antipsychotics head-to-head in TRD, and there have been significant differences in trial designs, eligibility criteria, and use of concomitant medication. The wider availability, ease of administration, lack of requirement for a Risk Evaluation and Mitigation Strategy, and lower cost of second-generation antipsychotics suggests that they will be prioritized in many cases (143).

It has not been empirically established which somatic treatment is preferred in adults with TRD. Studies under way are seeking to determine the relative efficacies of ECT and ketamine in TRD (152–157). Moreover, the relative efficacies of ketamine or esketamine in combination with second-generation antipsychotics, combined antidepressants, and other treatments in TRD have not yet been established in randomized controlled trials. Of the second-generation antipsychotics, only the combination of olanzapine with fluoxetine has been proven efficacious in adults with TRD, but it is limited by significant weight gain and metabolic liability.

The efficacy of other pharmacological strategies, such as combined antidepressants, lithium, or thyroxine, in adults with TRD has insufficient evidence. A pragmatic approach until such data are available is to consider ketamine or esketamine, or ECT or rTMS, for adults with TRD. It is also recognized that the efficacy of ECT may be more compelling than that for rTMS in adults with TRD (158). Preliminary evidence suggests that nonresponse to neurostimulation treatment may not predict nonresponse to ketamine or esketamine in adults with TRD (159). Indeed, patient preference, as well as cost, access, and availability, would also inform treatment selection for adults with TRD.

Ketamine combined with psychosocial interventions is a promising treatment avenue, especially for individuals with substance use disorders. It remains a testable hypothesis whether, in some cases, manual-based psychotherapy could be conceptualized as a maintenance treatment in persons with TRD who respond acutely to ketamine (160, 161).

CONCLUSIONS

The opportunity and hope provided by intravenous ketamine and intranasal esketamine exist alongside the urgent need to clarify the long-term efficacy of these agents as well as significant unanswered questions with respect to safety. It was observed in the esketamine development program that suicides occurred in persons upon discontinuation of the treatment. Postdiscontinuation surveillance of patients who have received ketamine or esketamine treatment would provide a fuller characterization of unintended safety events (e.g., sensitization to other drugs of misuse) (162). Debates as to the safety and efficacy of intravenous ketamine and esketamine in TRD would be informed by familiarity with the totality of the data, which is growing exponentially (51, 163). Data obtained by the FDA Adverse Event Reporting System between March 2019 and March 2020 indicate that esketamine has an unequivocal potential for serious adverse events (164). For example, the reporting odds ratios were significant for dissociation, sedation, “feeling drunk,” suicidal ideation, and completed suicide (164). This finding underscores the need for a fuller understanding of any potential safety concerns associated with esketamine (or ketamine) in the treatment of adults with TRD.

Toward the goal of personalized medicine, future research can be expected to provide information on whether any biomarkers (e.g., pharmacogenomics) or other clinical aspects, perhaps augmented with advanced computational models, will be predictive of outcome with ketamine. Moreover, the efficacy of ketamine combined with manual-based psychotherapies in adults with TRD and other mental disorders is a promising avenue that will be informed by rigorous clinical trials (165). A consensus exists with respect to current knowledge and future vistas for ketamine and esketamine (Box 2 and Box 3). In the interim, these agents should be administered only at centers with the appropriate infrastructure and multidisciplinary personnel with expertise in the assessment and treatment of adults with mood disorders.

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BOX 1.

Implementation checklist for ketamine and esketamine in clinical practice

Patient Selection

- Diagnosis of confirmed treatment-resistant depression. Rule out psychosis and other conditions that would significantly affect the risk-benefit ratio.
- Discontinuation and/or holding of contraindicated medications.

Setting, Personnel, Monitoring

- Physical examination is suggested; measurement of body mass index; vital signs monitoring during treatment and posttreatment surveillance; consider urine drug screen if history suggests contributory.
- Setting should have expertise in the assessment, diagnosis, and management of mood disorders.
- Setting should be equipped with appropriate cardiorespiratory monitoring and be capable of psychiatric and medical safety (e.g., hemodynamic instability, respiratory suppression).
- Depressive symptom measurement to be conducted. Additional scales are encouraged to assess anxiety, cognitive function, well-being, and psychosocial function.
- Safety assessments at each visit include cardiorespiratory surveillance and assessment of dissociation and psychotomimetic effects.
- Patients should be monitored until stable (and according to Risk Evaluation and Mitigation Strategies [REMS] where applicable) after treatment to assure cardiorespiratory stability, clear sensorium, and attenuation of dissociative and psychotomimetic effects.
- Patients should arrange for reliable transportation for each appointment and should be instructed not to operate motor vehicles or hazardous machinery without at least one night of sleep.

BOX 2.

Esketamine and ketamine for treatment-resistant depression (TRD): Consensus

- Evidence supports the rapid-onset (i.e., within 1–2 days) efficacy of esketamine and ketamine in TRD.
- Efficacy in TRD is best established for intranasal esketamine and intravenous ketamine; there is insufficient evidence for oral, subcutaneous, or intramuscular ketamine in TRD.
- Intranasal esketamine demonstrates efficacy, safety, and tolerability for up to 1 year in adults with TRD.
- Evidence for long-term efficacy, safety, and tolerability of intravenous ketamine in TRD is insufficient.
- Safety concerns with respect to ketamine and esketamine include, but are not limited to, psychiatric (e.g., dissociation, psychotomimetic), neurologic/cognitive, genitourinary, and hemodynamic effects.
- Esketamine is FDA approved for major depressive disorder with suicidal ideation or behavior but has not been proven to reduce suicide completion.
- Esketamine and ketamine should be administered only in settings with multidisciplinary personnel including, but not limited to, those with expertise in the assessment of mood disorders. A Risk Evaluation and Mitigation Strategy (REMS) is required in some countries administering esketamine (e.g., the United States).

BOX 3.

Esketamine and ketamine in TRD: Future research vistas

- Comparative effectiveness data are needed (e.g., intravenous ketamine versus intranasal esketamine; esketamine or ketamine versus neurostimulation; esketamine or ketamine versus second-generation antipsychotics).
- A data commons and/or access to large public or private databases that provide the opportunity to assess serious but infrequent adverse events would provide a fuller understanding of the effectiveness and safety of esketamine and ketamine.
- Integrated measures (e.g., phenomenology, pharmacogenomics) should be used to identify ketamine response predictors as well as safety and tolerability predictors.
- Strategies to prolong the efficacy of esketamine and ketamine in adults with TRD are urgently needed (e.g., pharmacologic, manual-based psychosocial).
- More thorough characterization is needed of the long-term efficacy, safety, and tolerability of intravenous ketamine, as well as the possibility of withdrawal and/or tachyphylaxis/therapeutic tolerance.
- Characterization of the efficacy, tolerability, and safety of administration in less restrictive treatment environments (e.g., in physicians' offices or self-administration at home under certain conditions) is needed.
- Characterization of the relative efficacy, tolerability, and safetyof oral, subcutaneous, and intramuscular formulations is needed.
- Further empirical study is needed on the risk for predisposing alcohol and other substance use disorders, as well as withdrawal-emergent suicidality, with esketamine and ketamine.
- Research is needed on the efficacy, safety, and tolerability of esketamineand ketamine inadultswith non-treatment-resistant major depression as well as other mental disorders (e.g., major depressive disorder with psychosis, bipolar depression, posttraumatic stress disorder, substance use disorders).
- Integration of esketamine and ketamine with manual-based psychosocial treatments needs to be better characterized across mental disorders.
- The mechanism of action and tolerability of ketamine (e.g., role of opioidergic system), needs to be refined.
- The safety, tolerability, and efficacy of other ketamine derivatives (e.g., *R*-ketamine, *2R*/*6R*-hydroxynorketamine) remains to be characterized.
- Additional agents capable of rapid-onset antidepressant activity need to be identified.

TABLE 1.

Key pharmacodynamic targets of ketamine and esketamine

Target	Pharmacodynamic Effect	Potential Clinical Effect[a]
Glutamate system		
N-methyl-D-aspartate (NMDA) receptor	Strong antagonist	Antidepressant and procognitive effects; acute dissociative effects
α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor	Indirect agonist (through increase glutamate release)	Antidepressant effects
D-Serine site	Antagonist	Antidepressant effects
Glutamate	Increased release	Antidepressant effects
Opioid system		
μ Opioid receptor	Weak agonist	Antidepressant and analgesic effect and potentially acute euphoric effect
μ Opioid 2 receptor	Antagonist	
κ Opioid receptor	Agonist	
δOpioid receptor	**Agonist**	
Monoamine system		
Serotonin transporter	Weak inhibitor	Antidepressant effect
Norepinephrine transporter	Weak inhibitor	Antidepressant effect
Dopamine transporter	Weak inhibitor	Antidepressant effect
Dopamine 2 receptor	Agonist	Acute psychotomimetic effects
Serotonin (5-HT_3) receptor	Weak antagonist	Antidepressant effect
Cholinergic system		
Cholinesterase	Inhibitor	Procognitive effects
α7 Nicotinic receptor	Antagonist	Antidepressant effects
α4 β2 Nicotinic receptor	Antagonist	
Muscarinic receptors (M1–3)	Antagonist	Increased blood pressure and heart rate
Other		
σ_1 Receptor	Agonist	Antidepressant and cardiac effects

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Target	Pharmacodynamic Effect	Potential Clinical Effect[a]
σ_2 Receptor	Agonist	Antidepressant and cardiac effects
Mammalian target of rapamycin (mTOR)	Downstream activation via glutamate system	Antidepressant effects
Brain-derived neurotrophic factor (BDNF)	Downstream from mTOR increasing BDNF levels	Antidepressant and procognitive effects
$GABA_A$ receptor	Agonist	Acute anxiolytic effects
mTORC1	Activation	Neuroplastic effects

[a]The clinical significance of specific targets remains unclear, and results have been mixed. Potential proposed clinical effects are synthesized and summarized here.

TABLE 2.

Comparison of routes of administration of ketamine and esketamine

Route	Bioavailability	Dose Range (Acute)
Intravenous	100%	0.5–1.0 mg/kg infused over 40–60 minutes twice weekly for 2 weeks
Intramuscular	90%–95%	Not established, likely similar to intravenous
Subcutaneous	90%–95%	Not established, likely similar to intravenous
Intranasal	30%–50% (significant differences between devices and solution)	Esketamine: 56–84 mg intranasally twice weekly for 4 weeks Racemic ketamine: 50–150 mg intranasally twice weekly
Oral	10%–20% (potential variability between capsules and liquid forms)	Highly variable (0.5–7.0 mg/kg daily to once weekly), with 100–250 mg 2–3 times per week most accepted
Sublingual	20%–30%	Not established, likely similar to oral
Transdermal	10%–50% (highly variable by vehicle used)	Not established