Ketamine for Treatment-Resistant Unipolar Depression: Current Evidence

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The discovery that a single IV infusion of low-dose (subanesthetic) ketamine exerts rapid antidepressant effects constitutes an expansion in our understanding of the neurobiology of depression and provides new avenues for drug development.

The World Health Organization projects that by 2020, MDD will be the second leading cause of disability worldwide, trailing only cardiovascular diseases. Although decades of research, the response to conventional antidepressant treatments is suboptimal. Based on Sequenced Treatment Alternatives to Relieve Depression (STAR*D) data, one-third of patients achieved remission after 12 weeks of treatment with a first-line antidepressant; one-third never achieved remission, even after 4 consecutive levels of treatments.

There is growing evidence for the role of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist used for many years as an anesthetic, in rapidly alleviating depressive symptoms in patients who have treatment-resistant depression (TRD). The mechanism of action through which ketamine exerts its antidepressant effects is not fully understood. However, the direct modulation of glutamatergic pathways is unique compared with currently approved antidepressant medications that mostly target mono-amnergic systems. As such, the discovery that a single intravenous infusion of low-dose (subanesthetic) ketamine exerts rapid antidepressant effects constitutes an expansion in the understanding of the neurobiology of depression and provides new avenues for drug development.

**Hypothesized mechanisms of ketamine**

Ketamine has a very complex pharmacological profile with a variable affinity for numerous receptors. Besides being an open-channel nonselective NMDA receptor antagonist, ketamine interacts with several receptors, including the intracellular σ receptors, the opioid μ receptors, serotonin-3 receptors, and muscarinic receptors, as well as the serotonin, norepinephrine, and dopamine transporters. Research on the molecular signaling pathways associated with the antidepressant effects of ketamine has only recently begun in preclinical models. In rodent models of depression, a single dose of ketamine was found to increase the number and function of new spine synapses in the prefrontal cortex and reverse the loss of spine density in animals exposed to chronic unpredictable stress. The antidepressant effects of ketamine were replicated using a selective antagonist of the NMDA receptor (NR2B subunit). These effects were blocked by adding a mammalian target of rapamycin (mTOR) inhibitor and were not observed in brain-derived neurotrophic factor (BDNF)-mutant mice. The findings suggest a role for specific neurotrophic signaling cascades in the therapeutic mechanism of ketamine.

Our study team published a preliminary finding that BDNF levels were significantly increased at 240 minutes postinfusion in patients who responded to ketamine, and BDNF levels were highly correlated with Montgomery-Åsberg Depression Rating Scale (MADRS) scores at 240 min. Similar results were seen by Kavalali and Monteggia and Browne and Lucki. These results form the basis of our understanding of ketamine’s possible antidepressant mechanism of action.

Several studies suggest that by blocking the excitatory NMDA receptors on γ-aminobutyric acid inhibitory interneurons, ketamine leads to activation of downstream glutamatergic neurons. This results in an increase in extracellular glutamate levels and activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptors regulate synaptic function through the activation of voltage-dependent calcium channels and the release of BDNF, which stimulates mTOR and spine formation. These studies have identified new targets for understanding the neural basis of the antidepressant properties of ketamine that extend beyond the NMDA receptor channel and glutamate. But most
important, these data are consistent with hypotheses that link the antidepressant effects of NMDA receptor antagonists to enhancement of neurotrophic and neuroplasticity-related factors and fit more broadly within neurotrophic theories of depression.\textsuperscript{17,18} The Figure provides a detailed illustration of the link in the induction of mTOR signaling and BDNF release through ketamine and novel glutamatergic modulators.\textsuperscript{19}

**Clinical studies**

There is rapidly growing literature on the quick antidepressant effect of ketamine since the first published report by Berman and colleagues\textsuperscript{20} in 2000. In this early study, 4 of 8 patients demonstrated a 50% or greater reduction in Hamilton Depression Rating Scale (HDRS) scores at 72 hours postinfusion. A subsequent larger study by Zarate and colleagues\textsuperscript{21} using a cross-over design found that of the 17 participants who received ketamine, 12 (71%), 8 (47%), 6 (35%), and 2 (12%) met response criteria at 24 hours, 72 hours, 1 week, and 2 weeks postinfusion, respectively. Despite the encouraging results of these two studies, they included a fairly small number of patients and used a cross-over design with an inert placebo-control condition.

Our group recently published a parallel-arm, randomized controlled trial (RCT) of ketamine in 72 patients with TRD in whom 3 or more trials of an antidepressant have failed. Patients were randomized to ketamine (0.5 mg/kg over 40 minutes) or midazolam under triple-masked conditions (patient, rater, anesthesiologist).\textsuperscript{22} Patients in the ketamine group had significantly greater improvement in the MADRS score at 24 hours compared with the midazolam group (t\([68] = 3.34; P < .001\)). After adjusting for baseline scores and site, the MADRS score was 7.95 points lower in the ketamine group than in the midazolam group (95% confidence interval [CI], 3.20 to 12.71), corresponding to a large effect size (Cohen’s \(d = 0.81\)). Ketamine also increased the likelihood of response at 24 hours compared with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14; \(P < .006\)). Our results provided further evidence that supports the use of ketamine as a novel option for patients with TRD.

A main advantage of ketamine over currently FDA-approved antidepressants is the robustness and rapidity of its effect. Based on the STAR*D study, fewer than half of depressed patients will respond to first-line treatment, about two-thirds of whom achieve response criteria after 6 weeks of treatment. A meta-analysis of ketamine double-blind RCTs showed a statistically significant difference on HDRS as early as 80 minutes after the start of treatment.\textsuperscript{23} Of note, the clinical effects of ketamine were not mediated by nonspecific mood-elevating effects, but rather by targeting core depressive symptoms, such as sad mood, helplessness, and worthlessness, as well as suicidality.

**Effects on suicidal ideation**

Ketamine’s effects on suicidal ideation seems independent of its antidepressant effect.\textsuperscript{22} A post hoc analysis of 2 trials in TRD found that open-label intravenous ketamine was associated with rapid reductions in explicit and implicit suicidal cognition within the first 24 hours. This effect persisted for patients who received up to 5 additional infusions over 2 weeks.\textsuperscript{24} The rapid antisuicidal effects of a single administration of ketamine were recently replicated in an RCT.\textsuperscript{25} DiazGranados and colleagues\textsuperscript{26} saw decreases in the Scale for Suicidal Ideation scores within 40 minutes of ketamine infusion (0.5 mg/kg over 40 minutes). These results further support the possibility of ketamine’s rapid antisuicidal effects.

Larkin and Beautrais\textsuperscript{27} reported complete resolution of suicidal ideation in 14 actively suicidal patients following an intravenous bolus of ketamine (0.2 mg/kg) over 1 to 2 minutes in the emergency department (ED). MADRS item 10 (suicidality) score decreased significantly, from 3.9 at baseline to 0.6 within 40 minutes of treatment; this improvement was maintained for 10 days postinfusion.

**Feasibility of using ketamine in clinical practice**

There has been some skepticism regarding the practicality of administering intravenous ketamine infusions in clinical practice.\textsuperscript{28} However, one of the most important features of the Larkin and Beautrais study is that it took place in the ED, which suggests the feasibility of using ketamine in a busy ED setting. Ketamine is available in oral, subcutaneous, intranasal, intramuscular, and intravenous formulations. This is a significant advantage over current antidepressants. Intramuscular formulation could be considered for acutely suicidal patients when access to intravenous lines are limited.\textsuperscript{29–31} An intranasal formulation with a controlled delivery system may address concerns of ketamine abuse if prescribed in outpatient settings. Indeed, a recent report found that a single administration of intranasal ketamine was effective for patients with depression.\textsuperscript{32} Studies of intranasal esketamine (the S-isomer of racemic ketamine) for acute suicidal depression have been initiated (ClinicalTrials.gov Identifier NCT02133001).

Another advantage of ketamine is the potential use of BDNF, a peripheral biomarker, to predict
antidepressant response to ketamine.\textsuperscript{12,33} Thus, within 24 hours of the first ketamine dose, clinicians are able to make informed decisions on whether to continue ketamine or use a different therapeutic modality.

**Safety and tolerability**

Ketamine is classified as a schedule class III agent by the FDA, with potential for abuse liability. However, ketamine’s safety and utility in specific clinical populations is well characterized based on years of use in anesthesiology and emergency medicine. Perry and colleagues\textsuperscript{34} reviewed the safety of ketamine in a psychiatric research setting and concluded that ketamine was safe in healthy volunteers. The emerging evidence of patients with TRD who receive subanesthetic doses of ketamine further cements its safety and tolerability.

Because of its sympathomimetic effects, ketamine may produce increases in blood pressure, heart rate, and cardiac output, and it can provoke ischemia in patients with underlying coronary artery disease.\textsuperscript{35} Although frequently mild and self-limited, ketamine-induced perceptual disturbances have been reported in up to 30\% of study samples.\textsuperscript{36} Psychotomimetic disturbances may manifest as vivid dreams, visualization of psychedelic color, suspension in space, kaleidoscopic floating, and out-of-body experiences. Some patients describe these psychic experiences as bizarre or frightening, while other patients find them pleasurable, joyful, and fascinating.\textsuperscript{37} Finally, repetitive high anesthetic doses of ketamine have been linked to apoptosis and increased brain cell death in rodents and nonhuman primates.\textsuperscript{38-40} The available data support a favorable risk to benefit profile of subanesthetic low-dose ketamine; however, the long-term effects in humans have not been explored.

**Future directions**

The clinical use of ketamine in the treatment of TRD is still unsettled. The optimal dose of ketamine has not been established, which is the focus of a new NIMH-sponsored trial (ClinicalTrials.gov Identifier NCT01920555). Most of the studies thus far have used a slow infusion over 40 minutes of 0.5 mg/kg, but the study by Larkin and Beaultrais\textsuperscript{27} showed antisuicidal effectiveness at a lower dose given as a bolus. Moreover, higher anesthetic doses of ketamine (2 to 3 mg/kg) seem to lack effect on mTOR signaling.\textsuperscript{9}

While the ketamine antidepressant effect is fast, it is short-lived. Most patients relapse within 2 weeks of a single infusion.\textsuperscript{22,41} Repeated ketamine infusions have not led to substantial prolongation of the antidepressant effects. Two studies piloted a 2-week course of ketamine (0.5 mg/kg) administered 3 times weekly on a Monday-Wednesday-Friday schedule in patients with TRD.\textsuperscript{42,43} The response rate after the sixth infusion was 71\% in the report by Murray and colleagues.\textsuperscript{43} However, the median to relapse was 18 days. The augmentation of a single ketamine infusion with the glutamate modulator riluzole showed no difference from placebo in preventing relapse post-ketamine.\textsuperscript{44,45} Using ketamine in combination with electroconvulsive therapy (ECT) did not improve outcomes whether at anesthetic or subanesthetic dose. While earlier response was noted in the groups receiving ketamine, no difference was noted between the study groups at the end of the ECT course.spe

**Conclusions**

It is important to recognize that RCTs for ketamine as treatment for MDD are still in their early stages, and the evidence is limited. Several treatment modalities have been recommended for patients who have inadequate responses to repeated antidepressant trials, including augmentation with lithium, triiodothyronine, or second-generation anti-psychotics, and neuromodulatory techniques, such as repetitive transcranial magnetic stimulation. Although, its use is curtailed by cognitive adverse effects and the public’s opinion about “shock therapy,” ECT remains the most effective therapy for patients with TRD.

While there is understandable enthusiasm regarding ketamine’s potential, there are insufficient data to support its integration in clinical care at this time. The broader effectiveness of ketamine in varied clinical settings has not been systematically examined. More studies are needed on critical issues, such as dose optimization, alternative drug delivery routes, methods to prevent relapse following resolution of depressive symptoms, and understanding neurobiological mechanisms underlying the putative antidepressant actions of ketamine.

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Figure. Potential glutamatergic targets for novel antidepressants

Disclosures:
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