Current Status of Ketamine and Related Compounds for Depression

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Several clinical trials have demonstrated the rapid antidepressant effects of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine for the treatment of both major depressive disorder (MDD) and the depressed state of bipolar disorder.[1] While these results from academic settings are promising, generalizability to "real-world" clinical populations is a looming question. This brief review will address pragmatic clinical issues and highlight recent developments regarding ketamine and related compounds for depression.

Background and Basic Pharmacology

In the late 1970s, studies confirmed that NMDA receptors were genuine synaptic receptors. Research later demonstrated that NMDA antagonists produced antidepressant-like effects in animal models of depression.[2,3] These preclinical findings were complemented by subsequent noteworthy clinical observations[4,5] with intravenous (IV) ketamine, which was found to produce rapid antidepressant effects.

Ketamine hydrochloride was synthesized by Parke-Davis in 1963 and approved by the FDA in 1970, primarily as an anesthetic agent. Ketamine is a noncompetitive, high-affinity NMDA antagonist. Most preparations contain equal (1:1) concentrations of its 2 enantiomers: *S*(+) ketamine and *R*(–) ketamine.[6] While case reports[7,8] have suggested improved tolerability (fewer psychotomimetic effects) with the *S*-enantiomer, most clinical trials have used the racemic mixture. The bioavailability of ketamine is highest via intravenous and intramuscular (IM) routes (~90%) and decreases significantly with oral bioavailability (~16%). Ketamine's elimination half-life is 2–2.5 hours, and it is *N*-demethylated by cytochrome P450 enzymes in the liver.

Efficacy of Ketamine

Most clinical trials of ketamine have been conducted in adults with treatment-resistant MDD, though some trials have been conducted in patients with bipolar depression.[9–11] Studies generally included patients with comorbid anxiety disorders and excluded those with recent polysubstance dependence histories. Route of administration has been overwhelmingly IV, and ketamine dosing has ranged from 0.25 to 0.5 mg/kg for 40–60 minutes. A detailed review by Aan Het Rot and colleagues[1] tabulated response rates in *controlled trials* and found that at 24 hours postinfusion, 25%–71% of patients demonstrated a sustained ketamine response—defined as a >50% reduction in scores on at least 1 measure of depression; at 72 hours, 14%–50% of patients had maintained response. A recent study (ClinicalTrials.gov identifier: NCT00768430) was conducted to address concerns regarding effective blinding and found that remission rates to ketamine were superior to those for the active comparator midazolam. The study demonstrated that 35% of patients given ketamine showed signs of remission after both 1 and 7 days, compared to 8% and 18% for midazolam at the same time measurements.[12]

Preliminary research has been conducted regarding the use of ketamine for treatment-refractory obsessive-compulsive disorder,[13] and another study is investigating ketamine for posttraumatic stress disorder (NCT00749203).

Putative Mechanism of Action

Glutamate receptors mediate excitatory responses in the central nervous system, and their synaptic connections rely on the dynamic interplay of NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate ionotropic-type glutamate receptors along with G-protein–coupled metabotropic receptors. Elegant preclinical studies have demonstrated that ketamine rapidly activates the mammalian target of rapamycin (mTOR) pathway, with concordant increases in synaptic signaling proteins and increased density and function of new spine synapses in the medial prefrontal cortex.[14,15] Likewise, stimulation of mTOR signaling has been shown to depend on the activation of AMPA receptors to maintain ketamine's antidepressant effects.[14,16]

Eukaryotic translation elongation factor 2 and desuppression of rapid dendritic protein translation, including brain-derived neurotrophic factor (BDNF), may also be involved in ketamine's antidepressant-like properties.[17] Likewise, another preclinical study[18] demonstrated that the inhibition of glycogen synthase kinase-3 was necessary for the antidepressant effect of ketamine in mice. Interestingly, BDNF may serve as an indicator for ketamine's antidepressant response when linked to surrogate markers of central synaptic plasticity, such as slow-wave activity during non–rapid eye movement sleep.[19]

While it is beyond the scope of this review to fully address these issues, it should be noted that ketamine's ability to enhance glutamatergic signaling pathways and other secondary pharmacodynamic effects most likely contributes to the maturation of synaptic networks, dendritic protein synthesis, and homeostatic synaptic plasticity.[20] These dynamic changes underscore some of the persistent antidepressant effects observed in patients with treatment-resistant depression.[21] For a detailed discussion of the signaling pathways underlying ketamine's antidepressant effects, see Duman et al.[22,23]

Practical Considerations and Future Directions

Safety concerns. Clinically, ketamine has been routinely used as an anesthetic agent for more than 40 years, with rare reports of significant cardiorespiratory adverse events; dysphoric emergence phenomena have been observed in approximately 10%–20% of cases.[24] In recent controlled studies,[25,26] no serious adverse events occurred. Adverse events included dissociation, feeling strange, dry mouth, tachycardia, and increased blood pressure; all ceased within 80 minutes postinfusion. No significant changes were observed with regard to electrocardiograms, respiration, or laboratory values.

Nevertheless, it is important to emphasize that these studies included hospitalized patients with close medical monitoring and collaboration with anesthesiologists. In addition, patients with unstable medical illnesses or recent substance dependence histories were excluded. Most controlled studies included patients who were medication free and had fewer comorbid disorders. These patients differ significantly from "real-world" patients, who are often on complex medication regimens and have multiple psychiatric comorbidities.

The repeated use of ketamine is an issue of concern because of the potential for abuse and its long-term effects on cognition. Dependence on subanesthetic doses has not been observed in clinical trials; however, this concern merits consideration in more naturalistic studies. Urinary tract dysfunction has also been observed in ketamine abusers.[27] Limited research is available on the repeated use of ketamine; however, one recent study[10] administered up to 6 IV infusions of ketamine (0.5 mg/kg) in an open-label fashion 3 times weekly over a 12-day period to treatment-resistant patients with depression (N = 24). The overall response rate at the end of the study was 70.8%, with a median time to relapse of 18 days after the last ketamine infusion. No increasing trend in psychotomimetic

effects was observed over the course of the trial, and only one-third of the participants experienced elevated blood pressure and/or heart rate. Furthermore, these symptoms returned to baseline within 4 hours of each infusion and were overall mild and well tolerated. Another recent 12-month naturalistic observation of 3 patients receiving repeat IV ketamine infusions for treatment-resistant depression similarly highlights some of the risks, benefits, indications, and contraindications of long-term ketamine treatment.[28]

Interestingly, ketamine has demonstrated the potential ability to rapidly reduce suicidal ideation in controlled[25] and open-label studies (including emergency room settings).[29–31] Adequate tracking and monitoring of patients from emergency room settings would be warranted if such future use were implemented.

Optimizing ketamine and other related compounds. Dose-finding studies are currently being conducted to identify the optimal dose of ketamine (NCT01558063). IM routes may be beneficial for patients with poor venous access, and intranasal routes are also being explored (NCT01304147). New studies are also focusing on predictors/biomarkers of antidepressant response to ketamine.[32]

Other glutamatergic drugs or next-generation NMDA antagonists may provide a means of optimizing ketamine by harnessing its similar efficacy profile while minimizing its adverse effects. Three placebo-controlled trials[33–35] of memantine, a noncompetitive, low-affinity NMDA antagonist, found no significant antidepressant efficacy. Two studies[36,37] evaluated the glutamatergic modulator riluzole (100–200 mg/d) as an add-on to ketamine. In both studies, riluzole failed to alter the course of antidepressant response after ketamine infusion. However, MK-0657, an NR2B-selective NMDA oral antagonist, dosed daily (4–8 mg/d) for 12 days, showed antidepressant properties in a small placebo-controlled trial,[38] as assessed by 2 secondary depression rating scales. Another NR2B-selective NMDA IV antagonist, traxoprodil (CP-101,606) also displayed antidepressant efficacy in patients who had not responded to an SSRI.[39] Finally, in a placebo-controlled, crossover study,[40] the low-trapping nonselective NMDA antagonist AZD6765 (150 mg IV) had rapid and short-lived antidepressant properties without psychotomimetic effects. Results from larger placebo-controlled, multicenter trials with AZD6765 are pending (NCT01482221).

Conclusions

Despite the dramatic increase in ketamine research, much work remains before this agent can be recommended for routine clinical practice, especially outside a hospital research setting.[41] Refinements to its delivery or work with similar compounds may also produce viable and effective therapeutics for depression. Finally, while much of the attention has focused on ketamine's rapid antidepressant effects and usefulness in patients with treatment-resistant depression, it may very well be that elucidating ketamine's underlying mechanisms of action could ultimately have a more meaningful impact on the future development of novel therapeutics for mood disorders.

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