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Current Status of Ketamine and Related Compounds for Depression

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Introduction

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 in the depressed state of bipolar disorder (BD)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 two enantiomers: S (+) ketamine and R (–) ketamine⁶. While case reports^{7, 8} have suggested improved tolerability (less psychotomimetic effects) with the S-enantiomer, most clinical trials have used the racemic mixture. Ketamine's bioavailability 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.

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Disclosure: Dr. Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr. Zarate has assigned his rights in the patent to the U.S. government but will share a percentage of any royalties that may be received by the government.

Efficacy of Ketamine

Most clinical trials have been conducted in adults with treatment-resistant MDD, though some trials have been conducted in patients with BD depression⁹⁻¹¹. Studies generally included patients with comorbid anxiety disorders and excluded those with recent polysubstance dependence histories. Administration routes have been overwhelmingly IV, and ketamine dosing has ranged from 0.25 to 0.5mg/kg for 40-60 minutes. A detailed review by Aan Het Rot and colleagues¹ tabulated response rates in *controlled trials* and found that at 24 hours, 25-71% of patients demonstrated a sustained ketamine response—defined as a >50% reduction in scores on at least one measure of depression; at 72 hours post-infusion, 14-50% of patients had maintained response. A recent study (NCT00768430) conducted to address concerns regarding effective blinding found that response rates to ketamine were superior to the active comparator midazolam (personal communication, James Murrough). Response rates to ketamine in that study were comparable to rates previously reported in placebo-controlled trials.

Preliminary research has been conducted regarding the use of ketamine for treatment-refractory obsessive compulsive disorder¹², and another study is investigating ketamine for post-traumatic 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 receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate (KA) 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 (PFC)^{13, 14}. Likewise, stimulation of mTOR signaling has been shown to depend on the activation of AMPA receptors to maintain ketamine's antidepressant effects^{13, 15}.

Eukaryotic translation elongation factor 2 (EEF2), and de-suppression of rapid dendritic protein translation, including brain-derived neurotrophic factor (BDNF), may also be involved in ketamine's antidepressant-like properties¹⁶. Likewise, another preclinical study demonstrated that the inhibition of glycogen synthase kinase-3 (GSK-3) was necessary for the antidepressant effect of ketamine in mice¹⁷. 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 (SWA) during non-rapid eye movement (NREM) sleep¹⁸.

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 likely contributes to the maturation of synaptic networks, dendritic protein synthesis, and homeostatic synaptic plasticity¹⁹. These dynamic changes underscore some of the persistent antidepressant effects observed in patients with treatment-resistant depression²⁰. For a detailed discussion of the signaling pathways underlying ketamine's antidepressant effects, see^{21, 22}.

Practical Considerations & 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 cases²³. In recent controlled studies^{24, 25}, no serious adverse events occurred. Adverse events included dissociation, feeling strange, dry mouth, tachycardia, and increased blood pressure; all ceased within 80 minutes post-infusion. 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 co-morbid disorders. These patients differ significantly from “real-world” patients, who are often on complex medication regimens and have multiple psychiatric co-morbidities.

The repeated use of ketamine is an issue of concern because of the potential of abuse and its long-term effects on cognition. Dependence on sub-anesthetic 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 abusers²⁶. Limited research is available on the repeated use of ketamine; however, one recent study administered up to six IV infusions of ketamine (0.5mg/kg) in an open-label fashion three 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 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 participants experienced elevated blood pressure and/or heart rate. Furthermore, these symptoms returned to baseline within four hours of each infusion and were overall mild and well-tolerated¹⁰. Another recent 12-month naturalistic observation of three patients receiving repeat IV ketamine infusions for treatment-resistant depression similarly highlights some of the risks, benefits, indications, and contraindications of long-term ketamine treatment²⁷.

Interestingly, ketamine has demonstrated the potential ability to rapidly reduce suicidal ideation in controlled²⁴ and open-label studies (including emergency room settings)²⁸⁻³⁰. 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 (NCT 01558063). 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 ketamine³¹.

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 of memantine, a noncompetitive, low-affinity NMDA antagonist found no significant antidepressant efficacy³²⁻³⁴. Two studies evaluated the glutamatergic modulator riluzole (100-200mg/day) as an add-on to ketamine. In both studies, riluzole failed to alter the course of antidepressant response after ketamine infusion^{35, 36}. However, MK-0657, an NR2B-selective NMDA oral antagonist, dosed daily (4-8mg/day) for 12 days, showed antidepressant properties in a small placebo-controlled trial, as assessed by two secondary depression rating scales³⁷. Another NR2B-selective NMDA IV antagonist (traxoprodil or CP-101,606) also displayed antidepressant efficacy in patients who had not responded to an SSRI³⁸. Finally, in a placebo-controlled, crossover study, the low-trapping nonselective NMDA antagonist AZD6765 (150 mg IV) had rapid

and short-lived antidepressant properties without psychotomimetic effects³⁹. Results from larger placebo-controlled, multicenter trials with AZD6765 are pending (NCT01482221).

Conclusions

Despite the dramatic increase in ketamine research, much work still remains before this agent can be recommended for routine clinical practice, especially outside a hospital research setting⁴⁰. 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 may ultimately have a more meaningful impact on the future development of novel therapeutics for mood disorders.

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