



Ketamine for Depression, 1:

Clinical Summary of Issues Related to Efficacy, Adverse Effects, and Mechanism of Action

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Ketamine is an anesthetic drug that is also used for off-label indications such as the mediation of analgesia and sedation in various settings. It is additionally recognized as an agent with antidepressant potential. For depression, it is most commonly administered as a slow intravenous infusion in subanesthetic doses (usually 0.5 mg/kg). As an antidepressant, it is strikingly different from conventional antidepressant drugs in that it brings about rapid and marked attenuation of depressive symptoms even in patients with refractory depression. The benefits are observed within hours of administration, peak after about a day, and are lost 3–12 days later. Patients who do not benefit after the initial dose may benefit with serial dosing or at higher doses. Benefits can be maintained for weeks to months by the continuation of ketamine sessions at 2- to 4-day intervals. Adverse effects include dissociative and psychotomimetic changes that are almost always mild and transient, if present; transient elevation of heart rate and blood pressure often occur. These changes are usually well tolerated and are very seldom responsible for treatment discontinuation. Whereas ketamine is an *N*-methyl-D-aspartate receptor antagonist, and whereas much is known about its different biological effects, its actions that mediate the antidepressant response are presently not known for certain. Although big data on ketamine are presently unavailable, the drug holds promise in the treatment of depression, especially refractory depression.

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Introduction

Antidepressant drugs, starting with iproniazid and imipramine, entered psychiatry in the 1950s.¹ These and dozens of other antidepressant drugs were marketed (and many withdrawn) in the decades that followed. The drugs included tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, norepinephrine reuptake inhibitors, and others, with some antidepressant classes including a large number of drugs and others represented by a single drug.

Antidepressant drugs: different, yet the same. The presently available antidepressants vary across and within classes on many parameters: mechanism of action, efficacy against specific symptoms, adverse effect profile, metabolic pathways, and drug interactions, to name a few. There is, however, little difference in antidepressant efficacy between drugs, with the possible exception that drugs with dual serotonin and norepinephrine mechanisms may be marginally more effective than the selective serotonin reuptake inhibitors.²

Needed: a “clozapine for depression.” Clinical outcomes with antidepressant drugs are disappointing. In the National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression trial, the overall remission rates were 28%, 25%, 18%, and 10%, respectively, for the medication options at treatment steps 1, 2, 3, and 4.³ There are many treatment options for patients who are medication refractory,^{4–6} but an antidepressant drug with the impact that clozapine had on schizophrenia⁷ remains elusive.

Ketamine is far from becoming the “clozapine of depression.” However, there has been a great deal of study of the antidepressant properties of ketamine during the past 10 years, and some clarity is gradually emerging about the unusual potential of this drug. The present article will summarize the use of ketamine in depression with special focus on issues related to efficacy, adverse effects, and mechanism of action.

Uses of Ketamine in Clinical Practice

Ketamine was introduced as an anesthetic drug about half a century ago.⁸ Ketamine in subanesthetic doses has since demonstrated efficacy for other, but off-label, indications in adult and pediatric practice, including the management of pain in emergency settings,⁹ the management of postoperative pain,¹⁰ the treatment of medication-refractory headache,^{11,12} the reduction of agitation and violence in prehospital¹³ and emergency¹⁴ settings, and the mediation of pediatric sedation in various settings, ranging from dentistry to radiology.^{15,16} Ketamine in subanesthetic doses has also demonstrated rapid-onset efficacy in patients with severe and even treatment-refractory depression.

Ketamine for Depression: Efficacy Outcomes

Psychotomimetic and other effects of subanesthetic doses of intravenous (iv) ketamine (0.1 and 0.5 mg/kg infused across 40 min) were

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- Ketamine is an anesthetic drug. It is used in subanesthetic doses to treat pain, to effect sedation, or to ameliorate depression in various contexts.
- Ketamine as an antidepressant is most commonly administered as an intravenous infusion, across 40 minutes, in the dose of 0.5 mg/kg. It can also be administered by other routes.
- Antidepressant benefits with ketamine are usually dramatic; patients may achieve response and even remission of depression within a day, even when the depression was previously medication refractory. The benefits are usually lost in 3–12 days. Maintenance treatment with ketamine, scheduled once in 2–4 days, can maintain the treatment gains.
- Dissociative and psychotomimetic adverse effects are common but very seldom problematic.

demonstrated in healthy volunteers ($n = 19$) in 1994.¹⁷ Using a protocol of ketamine administration that was similar to that in the 1994 study,¹⁷ Berman et al¹⁸ conducted a small ($n = 7$) randomized, double-blind, placebo-controlled crossover trial of ketamine (0.5 mg/kg iv) in patients in a major depressive episode. They found a marked, early antidepressant effect that was identifiable at 4 hours post-ketamine and that persisted at a 72 hour assessment. Zarate et al¹⁹ confirmed these findings in a crossover-design randomized controlled trial (RCT) conducted in 18 patients with antidepressant-refractory major depressive disorder; the response and remission rates were 71% and 29% one day after the ketamine (0.5 mg/kg iv) infusion, and the antidepressant effect, though attenuated, remained statistically significant at 1 week.

The marked acute antidepressant efficacy of ketamine, even in medication-refractory patients, now seems beyond doubt. A meta-analysis²⁰ of 9 ketamine RCTs (pooled $N = 234$) found that ketamine attenuated depression significantly more than did control treatment. The antidepressant benefits were apparent at 40 minutes, peaked at day 1, and were lost by days 10–12. Response rates with ketamine were superior to those with control treatment between 40 minutes and day 7, and remission rates were superior between 80 minutes and days 3–5.²⁰ Although poorly studied, there seems to be a likelihood that, at least within the lower dose range of 0.1–0.5 mg/kg, the antidepressant efficacy of ketamine is dose-dependent.^{21–23} Higher doses may be indicated in those who do not respond at lower doses.²⁴

Most of the efficacy data were obtained in studies of patients with major depressive disorder, though some studies did include bipolar patients.

The Effect of Ketamine on Suicidality in Depression

Open studies and RCTs of single and repeated dosing with iv ketamine have shown that ketamine attenuates measures of suicidality in samples of patients with treatment-resistant depression^{25–28}; the benefit, however, may wear off within a week, as do the other antidepressant benefits of ketamine.²⁷

It is not clear whether ketamine has a specific antisuicidal effect over and above its antidepressant effect or whether suicidality attenuates in step with the attenuation of other depressive symptoms.

Use of Ketamine as an Augmentation Agent

Hu et al²⁹ examined the novel possibility that a single dose of iv ketamine could improve escitalopram (10 mg/d) outcomes in a 4-week RCT conducted in 30 patients with severe major depressive disorder. They found that response rates (92% vs 57%) and remission rates (77% vs 14%) were significantly greater in the ketamine group relative to the placebo group; additionally, ketamine was associated with earlier response and remission.

In contrast with these data on augmentation of escitalopram, a meta-analysis of 10 RCTs (pooled $N = 602$) of the use of ketamine anesthesia during a course of electroconvulsive therapy (ECT) found that ketamine did not improve antidepressant outcomes.³⁰

Adverse Effects of Ketamine in Antidepressant Trials

Subanesthetic doses of ketamine produce transient dissociative symptoms, cognitive impairment, and even psychotomimetic symptoms in healthy volunteers,¹⁷ and these findings have been obtained in the ketamine RCTs in depression, as well.^{31,32} As an example, Wan et al³³ pooled data from 205 ketamine sessions in 97 patients with major depressive disorder, obtained from 3 ketamine RCTs. They observed that 4 sessions had to be discontinued because of adverse effects (AEs). The commonest AEs during the initial 4 hours after a session included drowsiness, dizziness, poor coordination, blurred vision, and feelings of strangeness or unreality.

These AEs have so far not proven to be problematic. A meta-analysis of 9 ketamine trials (pooled $N = 234$) found no significant difference in all cause discontinuation between ketamine and control groups; whereas dissociative and psychotomimetic AEs were more common with ketamine, these were short-lasting and clinically not significant.²⁰

The hemodynamic changes associated with ketamine could be a cause for concern. For example, in the pooled analysis referred to earlier, Wan et al³³ found that transient mean peak increases were nearly 20 mm Hg for systolic blood pressure and about 13 mm Hg for diastolic blood pressure; nearly 30% of patients experienced transient blood pressure readings > 180 mm Hg systolic or > 110 mm Hg diastolic, or heart rates > 110 bpm.

Ketamine AEs are dose-dependent with regard to both likelihood of occurrence and severity.^{21,22} Ketamine AEs peak within 2 hours of an infusion and resolve within 4–24 hours. Other points to note are that when ketamine is gradually infused or otherwise dosed at 0.5 mg/kg, which is well below the anesthesia induction dose of 2–3 mg/kg, blood levels achieved are well below those associated with ketamine anesthesia, and even those associated with awakening from ketamine anesthesia.³⁴ Patients receiving subanesthetic doses of ketamine by different routes are almost always conscious

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through the procedure, and oxygen saturation remains within normal limits; there are no respiratory complications.^{33,34}

As far as could be ascertained, only 1 case of manic switch has been reported with (intramuscular) ketamine. The patient had chronic, treatment-resistant depression and was not previously known to be bipolar.³⁵ In general, the average patient rates iv ketamine as a very acceptable treatment.³³ An interesting opinion is that the AEs of ketamine diminish during maintenance treatment.³⁶

Finally, ketamine may be abused in the context of the management of depression,³⁷ and ketamine misuse or abuse may be associated with medical risks.³⁸ Cystitis, the pathogenesis of which involves many mechanisms, has been described in chronic abusers of high-dose ketamine³⁹; however, there have been no reports, so far, of ketamine cystitis or other medical concerns when the drug is used intermittently or for short spells in low, subanesthetic doses, as in the treatment of depression.

Strategies for Eliciting and Prolonging Efficacy

What if patients do not respond to the initial ketamine session(s)? There are 2 possible next steps that are supported by the results of small studies with successful outcomes: continue treatment sessions^{40–42} or increase the ketamine dose.²⁴ The threshold to identify nonresponders has not been defined, but it may be futile to continue treatment beyond 6 sessions.⁴³

Pharmacologic treatments in psychiatry tend to be effective only for as long as they are taken, and ketamine is no exception. As already stated, the antidepressant effects of ketamine wear off within 3–12 days. Maintenance treatment strategies are therefore necessary to maintain the treatment gains. In this regard, case reports with intranasal,⁴⁴ subcutaneous,⁴⁵ intramuscular,^{46–48} and iv^{49,50} ketamine and uncontrolled^{51,52} and controlled⁵³ clinical trials with iv ketamine have suggested that the antidepressant benefits of ketamine can be maintained by repeated dosing at 2- to 7-day intervals and that the benefits of ketamine can in this manner be extended for months^{45,47,49,50} to years.⁴⁴

Strategies for the Containment of Ketamine Adverse Effects

As already stated, the neuropsychiatric and cardiovascular AEs of ketamine are usually not clinically significant. When clinically significant, though, symptomatic intervention is sufficient. For example, an antihypertensive drug can be administered to attenuate blood pressure if it is considered that the elevated parameter crosses a predefined threshold³³; oral clonidine can be used as a prophylactic measure.⁵⁴

Strategies have been examined for the mitigation of the dissociative and psychotomimetic effects of ketamine in the treatment of depression.³² Whereas a lower dose or a longer duration of infusion could result in lower ketamine blood levels and hence fewer dose-dependent AEs, the antidepressant efficacy could also be compromised.³⁶ Whether the *S*-ketamine enantiomer is better tolerated is presently uncertain. Whether the coadministration of

psychotropic drugs for the prevention of ketamine-induced neuropsychiatric AEs improves AE outcomes without compromising efficacy is also uncertain. Intranasal dosing may be associated with greater tolerability than iv dosing.³²

The Mechanism of Antidepressant Action of Ketamine

As with electroconvulsive therapy, a great deal of information is available about the biological effects of ketamine^{55–58}; however, again, as with ECT, which of these effects is responsible for the antidepressant action is not known with any degree of certainty. This is hardly surprising, given that whereas a great deal of information is available about the neurobiology of depression, little is known for certain about what lies in the causal path. Yet, again, as with ECT, ketamine has many biological effects, and it is unlikely that the same effects are responsible for its anesthetic, analgesic, antidepressant, and other actions.

Ketamine is an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist but, at repeated subanesthetic doses, may result in glutamatergic facilitation. NMDA receptor antagonism by itself may be an insufficient or irrelevant mechanism because other NMDA receptor antagonists, such as memantine, do not have antidepressant properties. However, whereas some experimental NMDA antagonists have failed antidepressant development trials, at least 1 drug has shown promise and is presently under further study.³² AMPA receptor up-regulation and activation of downstream neuroplasticity signaling pathways may also be involved in the antidepressant mechanism of ketamine.^{55–58}

General Notes

Enthusiasm for the use of ketamine as an antidepressant has run ahead of the evidence. Although there is a great deal of research information available on the drug, presently none is of a standard that would justify a label for the drug in the treatment of depression. The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments has therefore issued a carefully drafted, conservative consensus statement on the subject that discusses important clinical and administrative matters such as patient selection, patient evaluation, and consenting; necessary clinician experience and training; treatment setting; drug dose and delivery; follow-up and assessments; repeated dosing and maintenance treatment; safety measures; and future directions.³⁴ There is much ongoing clinical research on many of these issues, including industry-driven research, as a visit to online clinical trial registries will reveal. One hopes that there will be greater clarity in the field, and perhaps a treatment approval, within the next few years.

The present article has summarized important clinical research in the field. The next article will examine certain specific issues related to ketamine and its position in the treatment of depression, including issues related to choice of enantiomer, drug dosing, routes of administration, drug interactions, clinical contexts that might merit consideration for ketamine use, and directions for research.

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