Focus
The Journal of Lifelong Learning in Psychiatry

Focus (Am Psychiatr Publ). Winter 2019; 17(1): 8–12.
Published online 2019 Jan 7.
doi: 10.1176/appi.focus.20180030: 10.1176/appi.focus.20180030

PMCID: PMC6493154
PMID: 31975953

Ketamine for Treatment-Resistant Mood Disorders

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Abstract

Strong evidence supports the rapid, although temporary, antidepressant effects of a single intravenous ketamine infusion for treatment-resistant major depressive disorder (MDD) and bipolar depression. Although ketamine has diverse effects on brain neurotransmitters, current theories have implicated *N*-methyl-D-aspartate antagonist effects at the presynaptic interneuron in mediating its antidepressant effects. Intravenous ketamine administration for treatment-resistant depression (TRD) is generally safe and well tolerated when administered by trained professionals. Repeated intravenous ketamine infusions as an off-label treatment for TRD are increasingly available for clinical use, although their safety and effectiveness are not well characterized. Intranasal administration of esketamine—the (*S*)-enantiomer of racemic ketamine—recently completed phase 3 multicenter trials; a Food and Drug Administration application for its use in TRD is expected. Relatively little is known about the longer term side effects of ketamine for TRD. Concerns have been raised about its dissociative side effects, risk of abuse, and potential excitotoxic neuronal injury at higher doses and with repeated use. Treatment guidelines are needed to standardize ketamine use in psychiatric disorders. Ketamine research is transforming our understanding of the pathophysiology of mood disorders and leading the way toward developing new, rapid-acting interventions for TRD.

Keywords: Treatment guidelines, Depression

Ketamine was developed as a structurally related alternative to phencyclidine in 1962 (1). At that time, phencyclidine was being used as a dissociative anesthetic for humans and animals, but its use was discontinued because of concerns about emergence delirium and neurotoxicity; ketamine demonstrated similar anesthetic properties and was better tolerated. In 1970, ketamine was approved as an anesthetic agent by the U.S. Food and Drug Administration (FDA) and, to date, continues to be used for adult and pediatric anesthesia and analgesia. Its importance as a therapeutic option is underscored by the fact that the World Health Organization placed ketamine on its list of essential medicines.

Over the several decades of its use, ketamine anesthesia has demonstrated short-term side effects, such as behavioral agitation, psychoticlike symptoms (e.g., pseudohallucinations and dissociative symptoms), and cognitive dysfunction (memory deficits). These side effects are short term and dissipate within the time frame of ketamine and the norketamine metabolite's half-life, which is usually within a few hours postadministration. Because of these effects, ketamine is known as a "dissociative anesthetic."

The Mechanism of Action Underlying Ketamine's Antidepressant Effects

Ongoing investigations into the neurobiological correlates of ketamine's antidepressant effects are helping refine our understanding of depression in general and may lead to new therapeutic strategies. While ketamine affects multiple neurotransmitter systems—including opioid, monoaminergic, glutamatergic, muscarinic, substance P, and sigma receptors—the leading theories of its antidepressant properties implicate *N*-methyl-D-aspartate (NMDA) receptor antagonism, glutamate surge, and AMPA receptor activation. Skolnick and colleagues (1996) first postulated a role for the glutamate system in depression when they noted that NMDA receptor antagonists mimicked the effects of clinically effective antidepressants (2). These initial effects at the NMDA receptor may modulate cellular and molecular processes (e.g., mammalian target of rapamycin), eukaryotic elongation factor 2, glycogen synthase kinase 3, and brain-derived neurotrophic factor) that are known to be important mediators of neuroplasticity (3). More recent investigations have suggested that AMPA (4) and opioid (5) signaling may also play a significant role in this process. Still, the precise mechanisms implicated in the antidepressant response to ketamine remain largely unknown but it is likely that they are complex, are multiple, and interact in a synchronous manner to exert its unique therapeutic effects; see (6) for a review.

Single-Infusion Intravenous Ketamine

In the 1990s, researchers at Yale University exploring ketamine's cognitive effects serendipitously found that it had mood-enhancing properties. Berman and colleagues (2000) conducted the first reported controlled study of ketamine for the treatment of major depressive episodes (associated with both major depressive disorder [MDD] and bipolar depression) (7). Seven depressed subjects were randomized to receive a single intravenous ketamine infusion (0.5 mg/kg) followed by saline solution, separated by at least one week, or saline solution followed by ketamine solution. Compared with the findings with saline solution, depressive symptoms improved significantly within 72 hours postketamine infusion. In 2006, Zarate and colleagues conducted a randomized, placebo-controlled, crossover study of 18 subjects with treatment-resistant MDD (8). Subjects were tapered from psychotropic medications, went through a two-week medication-free period, and were randomized to receive infusions of intravenous ketamine (0.5 mg/kg) first, followed one week later by saline placebo, or vice versa. Ratings were collected before, during, and after each infusion. As measured by the 21-item Hamilton Depression Rating Scale, subjects with MDD who received ketamine experienced immediate symptom relief in as little as two hours, with sustained effects lasting up to one week.

Subsequently, ketamine (used in conjunction with lithium or valproate) was studied in subjects with treatment-resistant bipolar depression. A similar pattern of response was found, with rapid and significant antidepressant effects observed as early as one hour after the beginning of the ketamine infusion and peaking at 24 hours (9). In the past few years, these results have been widely replicated in the treatment of both MDD and bipolar depression. Although response rates to ketamine vary across studies, they have generally been around 50% in treatment-resistant populations. These studies have also found that a single ketamine infusion yields temporary antidepressant effects, with symptoms typically recurring within seven days. Subsequent trials comparing a single intravenous ketamine infusion to placebo or active control (e.g., midazolam) have confirmed these findings, which were conducted with saline as the comparator. For instance, a meta-analysis of nine randomized controlled trials (N=234) comparing a single ketamine

infusion to placebo or active control found that ketamine significantly reduced depressive symptoms starting at 40 minutes postinfusion; antidepressant effects peaked at 24 hours, and a loss of efficacy was observed at 10–12 days (10).

In addition to providing relief for typical depressive symptoms, ketamine has also been shown to have therapeutic effects for treating specific subtypes of depression or other psychiatric comorbidities. Clinical evidence supports its use for treating anxious depression (8, 9), anhedonia (11, 12), and the atypical symptoms of depression (13). Limited investigations have also explored ketamine use in treating other disorders, such as posttraumatic stress disorder (14).

Repeated-Dose Intravenous Ketamine

One strategy explored to extend ketamine's antidepressant effects has been to administer repeated intravenous doses over time. At present, evidence supporting the use of repeated ketamine infusions for treatment-resistant depression (TRD) is quite limited. An initial case series of 10 subjects with TRD who received six open-label ketamine infusions over 12 days found that, over the course of treatment, depressive symptoms were reduced by an average of 85% (15); these improvements lasted an average of 19 days after the last treatment. Repeated treatments were generally well tolerated, with minimal transient dissociative symptoms and other mild side effects (e.g., headache, sleep disturbance, and blurred vision). Two subsequent studies also examined repeated-dose intravenous ketamine. One study of 24 subjects with TRD found a response rate of 71% and a median time to relapse of 18 days (16). The other study demonstrated the feasibility of both twice-weekly and thrice-weekly ketamine infusions for four weeks, but found no significant difference in response rates between the two dosing regimens over a 15-day period (17). Adverse events included headache, anxiety, dissociation, nausea, and dizziness. Although these studies offer encouraging initial evidence for the feasibility and safety of repeated-dose intravenous ketamine, more research is needed to fully understand the long-term safety and effectiveness of repeated ketamine use.

Ketamine for Acute Suicidality

Ketamine has also demonstrated promising results in the treatment of acute suicidal ideation and behaviors. An initial open-label study found that a single intravenous ketamine infusion (0.5 mg/kg over 40 minutes) significantly reduced suicidal ideation (as measured by the Montgomery–Åsberg Depression Rating Scale, suicide item) at 24 hours in 26 subjects with TRD (18). Another open-label study of 33 subjects with TRD found that suicidal ideation was significantly improved at an earlier time point—within 40 minutes of starting a ketamine infusion—and that sustained effects were observed for up to four hours postinfusion (19). Ballard and colleagues subsequently confirmed these findings and further demonstrated that ketamine's antisuicidal effects occurred independently of its antidepressant or anxiolytic effects (20) and lasted approximately one week with a single administration (21).

In light of these important results, several trials are currently exploring the feasibility and effectiveness of intravenous and intranasal (see the following text) administration of ketamine for treating suicidality in different clinical venues, such as emergency room settings. The discovery of a rapid-acting intervention with acute antisuicidal effects could revolutionize the management of these clinically emergent situations.

Intranasal Route of Administration

One novel approach for ketamine use in treating TRD has been to investigate alternate routes of administration. Ketamine demonstrates good bioavailability via multiple routes of administration, including intravenous, intramuscular, subcutaneous, intranasal, and oral. Despite differences in pharmacodynamics, evidence suggests that repeated doses of intranasal ketamine may be effective for TRD. A randomized controlled trial of intranasal ketamine demonstrated significant benefits in subjects

with MDD compared with saline placebo at 24 hours after initiating treatment (22). Intranasal esketamine, the (*S*)-enantiomer of racemic ketamine, was similarly compared with placebo in a phase 2 trial and demonstrated initial safety and effectiveness as an adjunctive treatment to oral antidepressant therapy (23). Finally, another double-blind, randomized, placebo-controlled study found that intranasal esketamine was effective in treating depressive and suicidality symptoms in patients at imminent risk for suicide (24). As a result of these promising findings, intranasal esketamine is being commercially developed; a phase 3 multicenter trial has reportedly recently been completed. The FDA has given esketamine fast-track and breakthrough status, which will allow an expedited review for approval for use in TRD and suicidal ideation.

Safety of Ketamine Use

Common side effects associated with single ketamine infusions for TRD include: psychotomimetic symptoms (e.g., dissociative symptoms, hallucinations), sympathomimetic symptoms (e.g., hypertension, tachycardia), and vestibular effects (e.g., dizziness, nausea, and vomiting). These effects typically occur during the ketamine infusion and resolve within several hours. It should be noted that, because of these and other effects, ketamine is also used as a recreational drug and may be associated with abuse and dependence. Those abusing ketamine typically use multiple administrations of doses many times higher than those used to treat TRD and may develop tolerance and dependence (25). The psychotomimetic effects in some individuals may occasionally become overwhelming, with subjects experiencing significant dissociative symptoms, confusion, and loss of awareness of the external environment. This condition, sometimes referred to as the "K-hole," may be accompanied by the patient becoming noncommunicative and requires increased monitoring. Management is supportive, as the condition typically resolves without intervention. As used to treat TRD, with relatively lower doses and limited intravenous administrations, ketamine infusion has not demonstrated an increased risk of abuse or dependence.

Relatively little is known about the long-term risks associated with ketamine use for TRD, particularly repeated administrations. A systematic review of the existing literature identified 60 studies reporting ketamine's side effects, encompassing 902 individuals who had received ketamine and 356 who had received multiple doses (26). The most commonly reported side effects included psychotomimetic/dissociative symptoms (72%)—specifically, perceptual disturbances; odd or abnormal sensations; derealization; depersonalization; hallucinations; and feeling strange, weird, bizarre, or unreal. Other common psychiatric side effects included anxiety, agitation or irritability, euphoria or mood elevation, delusions, panic, and apathy. The most common medical side effects were headache, dizziness, blurred vision, and hypertension/tachycardia. In general, cardiovascular and neurological effects were time limited around the time of administration. The review concluded that the reporting of side effects in the literature was generally hindered by short-term, passive monitoring without the use of a structured assessment form.

It should be noted here that neurotoxicity from arylcycloalkylamines such as phencyclidine and ketamine is thought to result from the excitotoxic properties of glutamate modulators. Vacuolization of neuronal cytoplasm (Olney lesions) has been documented with phencyclidine and other NMDA antagonists in rats (27), and ketamine has been shown to cause neuronal lesions in nonhuman primates (28). However, it is not currently clear whether ketamine has similar neurotoxic properties in humans, particularly at the dose and frequency of administration used for anesthesia or treatment of TRD; anesthetic dosing (typically 1–3 mg/kg) is several times higher than that used to treat TRD (0.5 mg/kg). Nevertheless, over decades of use as an anesthetic agent, no definitive evidence has emerged that ketamine causes permanent neuronal injury. However, as noted earlier, human experience from anesthesia as well as recreational use has been associated with significant adverse events, such as delirium, hallucinations, other psychotic symptoms, confusion, and memory deficits. Other, less common significant risks include cystitis and hepatic injury.

Future Directions

As noted earlier, a growing body of scientific research supports the rapid antidepressant and antisuicidal effects of ketamine in TRD. Clinical use of ketamine for TRD is expanding, despite the lack of sufficient data and standardized guidelines to direct its use. It is important to recognize that most existing research has examined single-dose ketamine infusions. However, studies of repeated dose administration are now underway in response to the promising data generated from single-infusion studies.

The challenge of sustaining ketamine's initial antidepressant effects has been a primary focus of investigation. Although repeated intravenous and intranasal administration have been the most rigorously studied, other routes of administration—including oral, sublingual/transmucosal, subcutaneous, or intramuscular—may also have potential for prolonged (maintenance) use. In general, these alternate routes of administration for treating depression are not well studied (29).

The proliferation of ketamine clinics has nevertheless made intravenous ketamine an accessible treatment option for many individuals, and schedules for multiple dosing are being conducted in the absence of sufficient guidance data. Without a clear understanding of the long-term risks, ketamine should be reserved for those who have failed to respond to multiple existing treatment options based on current treatment guidelines, including electroconvulsive therapy. Overall, further evidence is needed to better understand the safety profile of ketamine for treating TRD in humans, particularly active monitoring of adverse events over longer periods of time.

Despite these challenges, ketamine research is fundamentally shifting our understanding of the pathophysiology of mood disorders. This paradigm shift has not only altered our expectation of the time frame in which antidepressant response is possible—within hours instead of weeks—but also expands our vision of depressive disorders as disorders of neuroplasticity processes rather than merely dysfunctions in monoamine neurotransmitter systems. This new perspective is transforming our understanding of the pathophysiology of mood disorders and will lead to the development of new, rapid-acting interventions for TRD.

Conclusions

Strong evidence supports the rapid, although temporary, antidepressant and antisuicidal effects of a single intravenous ketamine infusion for treatment-resistant MDD and bipolar depression. Continued investigation of ketamine via various routes of administration will continue to provide information about long-term safety and effectiveness for the treatment of depression. Given the growing use of intravenous ketamine and the potential approval of intranasal esketamine in the near future, evidence-based treatment recommendations for the use of ketamine in mood disorders need to be established.

Acknowledgments

The authors thank the 7SE research unit and staff for their support. Ioline Henter (National Institute of Mental Health) provided invaluable editorial assistance.

Footnotes

Funding for this work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIA MH002857), by a NARSAD Independent Investigator Award to Dr. Zarate, and by a Brain and Behavior Mood Disorders Research Award to Dr. Zarate.

Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydro- and hydroxylated metabolites of (*R,S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-

hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors report no financial relationships with commercial interests.

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