

Ketamine for treatment-resistant depression: recent developments and clinical applications

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ABSTRACT

Approximately one-third of patients with major depressive disorder (MDD) do not respond to existing antidepressants, and those who do generally take weeks to months to achieve a significant effect. There is a clear unmet need for rapidly acting and more efficacious treatments. We will review recent developments in the study of ketamine, an old anaesthetic agent which has shown significant promise as a rapidly acting antidepressant in treatment-resistant patients with unipolar MDD, focusing on clinically important aspects such as dose, route of administration and duration of effect. Additional evidence suggests ketamine may be efficacious in patients with bipolar depression, post-traumatic stress disorder and acute suicidal ideation. We then discuss the safety of ketamine, in which most neuropsychiatric, neurocognitive and cardiovascular disturbances are short lasting; however, the long-term effects of ketamine are still unclear. We finally conclude with important information about ketamine for primary and secondary physicians as evidence continues to emerge for its potential use in clinical settings, underscoring the need for further investigation of its effects.

INTRODUCTION

Unipolar major depressive disorder (MDD) affects approximately 350 million people, making it the leading cause of disability worldwide, associated with harmful consequences onto the well-being of affected individuals and society.^{1,2} Currently prescribed antidepressant treatments targeting the monoamine system only alleviate depressive symptoms in about half of the patients.³ These rates become significantly lower in patients who had already failed to improve after two or more antidepressant treatments at adequate doses and duration (ie, treatment-resistant depression, TRD).⁴ This results in unnecessary exposure to lengthy trials of ineffective medications. Moreover, currently approved antidepressants targeting the monoamine system have a long onset in initiating response, typically 6–12 weeks. There is a clear unmet need for more efficacious and rapidly acting antidepressants.

Emerging evidence of the impaired relationship between the glutamate neurotransmitter system and neuronal plasticity in depression⁵ has guided the search for alternative antidepressant treatments. Ketamine is an ionotropic glutamatergic *N*-methyl-D-aspartate receptor antagonist, on the WHO Essential Medicine List for use as an anaesthetic and prescribed off-label to treat chronic pain.^{6,7} Research since 2006 on the use of ketamine for treating depression has shown that subanaesthetic doses (0.5 mg/kg) administered over a 40 min intravenous (IV) infusion period can have rapid-acting antidepressant effects on patients with TRD.^{8–10} The presumed mechanisms of the antidepressant effects of ketamine involve activating synaptic plasticity by increasing brain-derived neurotrophic factor (BDNF) translation and secretion, as well as via glycogen synthase kinase-3 (GSK-3) inhibition.^{11,12} BDNF is also associated with behavioural responses to classical antidepressants. Whereas it takes several weeks for BDNF-mediated synaptic plasticity triggered by standard antidepressants, such synaptic plasticity changes seem to occur in a matter of hours after administration of ketamine.¹³ Animal models suggest that inhibition of GSK-3 in the hippocampus and prefrontal cortex is necessary for a rapid antidepressant effect.^{11,12} Recent reviews of ketamine and depression have discussed the safety and efficacy of ketamine, different administration methods, efficacy on various symptoms of depression consistent with the National Institute of Mental Health (NIMH) Research Domain Criteria initiative, as well as the risks of misuse of ketamine outside medical settings.^{14,15} The current review will focus on recent developments in the use of ketamine, as well as clinical applications for primary and secondary care. We identified the pertinent literature by searching of the National Library of Medicine PubMed and the Google Scholar databases for

articles published between 1980 and February 2016. No language constraints were applied. The search included the key words 'depression', 'ketamine', 'treatment resistant', 'antidepressant', 'primary care'. We focused on clinical trials, including both open-label and randomised studies. The reference lists of reports identified were used to find additional publications.

How do patient characteristics predict response and response duration?

Multiple clinical trials suggest that a single low dose (0.5mg/kg) of IV ketamine results in a 50–70% response rate in patients with TRD.¹⁶ Additional research has shown that depressed patients can experience symptom relief as early as 2 h, and lasting up to 2 weeks after a single administration of IV ketamine.¹³ The wide estimates of the duration of ketamine's antidepressant effect are a result of the variability in study population across ketamine trials, including variability in age, gender, duration of depression and depressive episodes, as well as comorbidities (eg, generalised anxiety disorder, post-traumatic stress disorder (PTSD), bipolar disorder (BD)).¹⁷ In order to address this uncertainty, Romeo *et al*¹⁷ conducted a meta-analysis of six double-blind, randomised, placebo-controlled, cross-over trials (two in BD). Compared with placebo, ketamine significantly reduced depression severity starting at day 1 postinfusion through day 7 in MDD, but only days 1–4 in BD.^{10,17} Although the focus of this review is on unipolar major depression, it is important to note that ketamine was associated with a greater improvement at days 1, 2, 3, 4 and 7 in participants with unipolar major depression compared with bipolar depression.¹⁷ The apparent shorter duration of the effect of ketamine in bipolar depression is important for planning the frequency of treatments in clinical practice. In order to address the heterogeneity of samples across studies, meta-analyses evaluated the contribution of comorbid anxiety disorder, lifetime history of antidepressant treatment, as well as duration of depression and current episode to mean differences in depression improvement between ketamine and placebo. No significant relationship was found between any of these variables and mean differences between ketamine and placebo.¹⁷ This is clinically very important, as all these clinical variables have been associated with poor response to traditional antidepressants.¹⁸ Of note, IV ketamine was also reported as efficacious in the treatment of PTSD.¹⁹ Ketamine may therefore be beneficial in these populations, which are less likely to respond to standard antidepressants.

Additionally, in evaluating ketamine responders versus non-responders after a single infusion of IV ketamine, there was no difference in many demographic and clinical characteristics.¹⁶ On neuropsychology testing, slower processing speed at baseline uniquely predicted greater improvement in depression at 24 h following ketamine.²⁰ Of note, prior studies have found just the opposite pattern for standard antidepressants—slow processing speed predicts poor outcome.²¹ Moreover, other clinical predictors of efficacy may include increased body mass index (BMI), family history of alcohol use disorder and anxious depression.²² Ketamine treatment in potential clinical practice may most effectively target severely depressed patient with cognitive dysfunction or anxiety.

Does route of administration (IV vs intranasal) and adjunctive treatment affect efficacy?

The mode of administration may affect ketamine's efficacy for treating MDD. In several meta-analyses, depression symptoms significantly improved after IV administration of ketamine compared with placebo.^{9 14} While several meta-analyses have compared the duration of antidepressant effect with IV and intranasal (IN) ketamine^{10 17} and concluded there was no difference between IN and IV administration from day 1 through day 7, the comparison is based on a single study with IN ketamine²³ with N=20 participants. Further large studies exploring the IN route of administration sponsored by Janssen have recently completed (ClinicalTrials.gov ID: NCT01998958) or are currently underway (NCT02417064), using IN S-ketamine (the S-enantiomer of racemic ketamine); these will be able to better estimate the duration of effect and optimal dosing frequency for IN administration.

It is also important to explore the interaction of ketamine treatment with ongoing antidepressant and/or augmentation therapy (eg, anxiolytics, antipsychotics, mood stabilisers). The majority of clinical trials to date have required a washout of concomitant medication, while only a few have tested ketamine efficacy as an adjunct of ongoing antidepressant treatment or Electroconvulsive Therapy (ECT). Both study designs have shown that ketamine is effective in improving depression.^{8 9} Therefore, in clinical practice, it would not be necessary for physicians to washout patients of their current antidepressant treatment.⁹

Efficacy of single IV infusion versus repeated IV infusions

Single doses of IV and IN ketamine administration have consistently shown antidepressant efficacy for up to 7 days. Few studies have examined the effects of repeated administrations of ketamine. In a trial testing the effect of six IV ketamine infusions over 2 weeks, 70.8% of 24 patients with unipolar depression and free of concomitant medications responded with an average duration of response lasting 18 days.²⁴ Response after six IV ketamine infusions was strongly predicted by response at 4 h after the first infusion. In contrast, in a study, 28 unipolar and bipolar depressed participants with ongoing antidepressant treatment were offered either three or six IV ketamine infusions over 3 weeks; 29% of patients responded to ketamine treatment.²⁵ In this study, 11% of patients responded within 6 h after a single infusion, and all responders at endpoint had a response prior to the third infusion. The duration of the response following the final infusion lasted between 25 and 168 days.²⁵ Despite their differences, both studies^{24 25} concluded that response to a series of repeated ketamine administrations could be predicted after the first one or two infusions. This is very important as in clinical practice a longer series of ketamine administrations would only be justified in patients experiencing early response (to the first two treatments).

Several studies are continuing to investigate the safety and efficacy of repeated ketamine infusions. A multisite study comparing IV ketamine given at twice a week or three times a week over a period of 1 month (NCT01627782) has recently completed; the publication of results is pending. An additional recently completed study has explored repeated

self-administration of IN S-ketamine over a 2-week period (NCT01998958). Additional clinical trials are currently underway (NCT02417064) to study the long-term effects of repeated administration in addition to ongoing antidepressant treatment. The effects of self-administration and repeated-administration will also require further study since this promising intervention has the potential for greater accessibility but is also increasing the risk of diversion (as ketamine is a drug of abuse).

Ketamine's effect on suicidal ideation, anhedonia, cognition

Suicidal ideation (SI) is among the most clinically concerning of depression, and remains a leading cause of death.^{26 27} A majority of studies investigating the efficacy of ketamine for depression have excluded individuals at imminent risk for suicide; however, patients with moderate degree of SI were still included. Studies consistently show a significant decrease in SI after ketamine administration.^{9 27} In a review assessing ketamine's effect on suicidality in patients with TRD, single doses of ketamine decreased both depression and SI, with maintained improvement for up to 2 weeks following repeated infusions.^{28 27} In a study of N=14 patients with MDD experiencing SI admitted to the Emergency Room (ER), a single dose of ketamine (0.20 mg/kg) administered over 1–2 min (as opposed to the more common dose of 0.50 mg/kg administered over 40 min) reduced SI significantly when assessed 40 min postinfusion.^{29 27} A larger (N=24) study of suicidal patients with a variety of mood and anxiety disorders admitted to an inpatient psychiatric unit reported rapid (within 24 h) improvement of SI after IV ketamine compared with midazolam.³⁰ Rapid improvement in SI supports the potential for ketamine to be used in clinical settings that necessitate urgent care for SI or behaviours. It is still difficult to determine the antisuicidal properties of ketamine given that research studies typically do not include those at highest risk for suicide; however, research is continuing to study the possible neuroinflammatory pathways that identify both suicidality and ketamine's pharmacological properties.²⁷

A review investigating the antisuicidal properties of ketamine shows a significant reduction in negative cognitions and anhedonia postketamine, providing evidence of some of the specific protective factors associated with ketamine.²⁷ A review of open label clinical trials reveals that high SI pretreatment may be associated with a *higher* response 24 h postketamine treatment.³¹ Recent research additionally suggests that specific antisuicidal effects of ketamine may be related to improvements in cognitive emotional and executive functioning (eg, memory, cognitive flexibility, planning, behavioural inhibition); the neural networks involving the prefrontal cortex support both improvements in depression and cognition.³¹ Lally *et al*³² also reported that after a single dose of IV ketamine, 87% of patients showed improvement in anhedonia at 4 h postinfusion. Improvement in anhedonia was correlated with improvement in depression overall,³² so it is unclear whether improvement in anhedonia is pseudo-specific (eg, caused by the antidepressant effect). Given that impairments in the reward system of the brain are associated with depression, suicidality and anhedonia, it is likely that ketamine targets this neural circuit, which includes areas of the dorsal anterior cingulate cortex, orbitofrontal cortex, hippocampus and basal ganglia.^{15 31 33} It is important for physicians to be aware that clinical presentations including severe depression, anhedonia, SI and/or cognitive deficits have been associated with positive outcomes after IV ketamine.

Safety and potential for abuse

Ketamine has been shown to be safe and effective as an anaesthetic in children and adults at doses ranging from 1 to 3 mg/kg.¹⁶ When used for treating pain and depression, ketamine has been administered at doses ranging from 0.1 to 1 mg/kg. These subanaesthetic doses can be associated with short-lasting neuropsychiatric effects including neurocognitive disturbances, sensory-motor disturbances and dissociation, as well as time-limited increases in heart rate and blood pressure.¹⁶

Up to 4 h following ketamine administration, common adverse events may include dizziness, blurred vision, headache, nausea or vomiting, dry mouth, restlessness, and impairments in coordination and concentration.⁸ Global and meta-analytic reviews of ketamine for depression studies also report mild side effects, such as dry mouth, tachycardia, as well as increase in blood pressure and dissociation, during the 40 min of ketamine administration and briefly afterwards.^{8 9 14} However, patients with a history of cardiovascular illness would require careful monitoring, as brief blood pressure elevations might be problematic.⁹ Historically, ketamine has been used as a recreational substance,¹⁵ therefore making the potential for abuse a clinical concern and a necessary research focus. As this is still an experimental drug, it is important to be mindful of the unstudied long-term effects in relation to dosing and frequency of administration. With long-term use of ketamine, potential side effects, such as mild cognitive disturbances and urinary cystitis would need to be monitored regularly.²² In recognising the uncertainty of long-term effects of ketamine used at subanaesthetic doses, it important to understand the evidence of cognitive impairments among abusers of ketamine (while recognising that those participants frequently mix multiple substances of abuse). Chronic ketamine abusers show signs of memory impairment over 1 year³¹; however, participants with TRD receiving IV ketamine less frequently and at lower doses show improvement in cognitive performance.³¹

THE ROLE OF PRIMARY CARE PHYSICIANS AND SPECIALISTS

Primary care physicians (PCPs) should understand the high prevalence of MDD and TRD, and the high levels of associated dysfunction. PCPs tend to be the initial contact for patients with MDD.³⁴ Since current antidepressants are not effective in approximately one-third of patients with MDD,⁸ it is important for PCPs to recognise them and to be aware of emerging alternative treatments, such as ketamine. Referral to specialty care or consultation with psychiatrists may be required for these difficult-to-treat patients.³⁴ This link between primary and specialty care is crucial for effectively treating a ubiquitous illness, such as depression. Since ketamine is Food and Drug Administration (FDA) approved as an anaesthetic, but not as an antidepressant, some specialists (psychiatrists or anaesthesiologists) are administering ketamine off-label for clinical care. The route of administration and dosing are based on promising results from clinical trials, recognising that minimal information exists to guide

ongoing treatment with ketamine after the first 6–12 infusions. Institutions conducting clinical research trials on optimising the efficacy of ketamine are ongoing, meaning there is no standardised administration outside of the research setting. To date, all randomised controlled trials in TRD have used a dose of 0.5 mg/kg with converging evidence of its promising efficacy; however, an ongoing study sponsored by the US NIMH (NCT01920555) aims to establish the optimal IV ketamine dose for TRD in the range 0.1–1.0 mg/kg.

CONCLUSION

A growing body of research supports the acute efficacy of ketamine as a rapidly acting treatment for treatment-resistant unipolar depression, bipolar depression and PTSD. The potential for more prevalent and accessible use of ketamine for clinical treatment requires that physicians be mindful of the necessary controlled conditions for which ketamine have been studied, including the characteristics of responders in research trials. In order for a specialist to appropriately recommend this treatment, it is necessary to be familiar with predictive factors of clinical response, including increased BMI, family history of alcohol use disorder (in a first degree relative), dimensional anxious depression²² and cognitive slowing (low processing speed).³⁵ However, the wide range of the duration of response, as well as the diverse presentation of MDD make it challenging to predict the efficacy of ketamine.²² Research is underway examining biological predictors of response to ketamine, including genetic, central neurobiological and peripheral measures,²² but it is premature to recommend their adoption in clinical practice. The antidepressant effect of ketamine strongly depends on biochemical processes that interact with and target the glutamate receptor, which still needs to be further understood in humans in order to potentially develop screening procedures for appropriately prescribing of ketamine.²² In conclusion, a critical number of studies support the efficacy of ketamine as a rapidly acting treatment for patients with TRD, while some studies also suggest efficacy in bipolar depression, PTSD and in those with acute SI. At this point, clinicians and patients should be aware of the limited information available regarding optimal dosing and long-term effects of ketamine treatment. We remain, however, cautiously optimistic and believe that ketamine has the potential to become a very important tool in the clinical treatment of severe mood and anxiety disorders (table 1).

Table 1 Summary of clinical perspectives on ketamine administrations for treatment-resistant mood disorders

Clinical efficacy	Ketamine administrations have been associated with rapid clinical improvement (within 24 h) in patients with treatment-resistant unipolar depression, bipolar depression, PTSD and those with acute suicidal ideation. The effect of a single dose of ketamine appears to last up to 7 days in unipolar TRD and 3–4 days in bipolar depression.
Clinical factors associated with response	Common clinical factors associated with poor response to traditional antidepressants (comorbid anxiety disorders, history of non-response to multiple antidepressants, chronic duration of depression) do not predict lower response to ketamine. Severely depressed patients with cognitive dysfunction or anxiety may be a very good target for ketamine treatment in clinical practice.
Repeated administrations	Repeated doses of ketamine have been reported to be safe and to additionally prolong clinical response. Very limited data exists for more than 6–12 repeated ketamine administrations for mood disorders. Response to a series of repeated ketamine administrations could be predicted after the first one or two infusions, it is generally not useful to continue ketamine administrations after non-response to initial treatments.
Alternative route of administration and doses	Most studies have tested IV ketamine administrations. Intranasal ketamine has positive effects, comparable with IV ketamine, and is currently developed for patient self-administration. The most commonly used dose of IV ketamine was 0.5 mg/kg, ongoing studies are testing doses in the range 0.1–1.0 mg/kg.
Safety considerations	It is acceptable to administer ketamine in addition to ongoing antidepressant treatment. Time-limited side effects of ketamine (experienced during the 40 min of ketamine administration and briefly afterwards) include short-lasting neuropsychiatric effects including dizziness, blurred vision, headache, nausea or vomiting, dry mouth, restlessness, and impairments in coordination and concentration, dissociation (abnormal reality perception), as well as increases in heart rate and blood pressure. Additional monitoring should be warranted for patients with prior history of cardiovascular illnesses; previous history of psychosis may also be a relative contraindication for ketamine. Long-term use of ketamine has been associated mild cognitive disturbances and urinary cystitis; no data exist in patients with mood disorders but such effects should be nevertheless monitored.

IV, intravenous; PTSD, post-traumatic stress disorder; TRD, treatment-resistant depression.

Competing interests JS reported no biomedical financial interests or potential conflicts of interest. In the past 3 years, JWJM has served on advisory boards for Janssen Research and Development and Genentech, has provided consultation services for ProPhase, LLC and Impel Neuropharma and has received research support from Janssen and Avanir Pharmaceuticals; he is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the combination of ketamine and lithium for suicidal ideation. Over the past 5 years, DVI has been a consultant for Avanir, Axome, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, Servier, Sunovion and has received research support through the Icahn School of Medicine at Mount Sinai from Alkermes, Astra Zeneca, Brainsway, Euthymics, Neosync, Roche, Shire. The Icahn School of Medicine at Mount Sinai is named on a licensed patent on ketamine for the treatment of depression. Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approval for the treatment of depression.

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