

Intravenous Ketamine for Treatment-Resistant Major Depressive Disorder

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ABSTRACT

Conventional pharmacologic treatments for major depressive disorder (MDD) generally take several weeks to several months to have a clinically meaningful effect. This time lag to response constitutes a major burden for patients and contributes to increased morbidity and mortality. Two published studies in patients with MDD have now provided evidence for rapid and robust antidepressant efficacy of a single intravenous (IV) infusion with a sub-anesthetic dose of ketamine hydrochloride compared with an infusion of saline. In the approximately 60% of patients who responded, ketamine's acute antidepressant effects were maintained for at least several days and up to 2 weeks. This article reviews the pathophysiologic rationale underlying this approach, the clinical evidence for the use of IV ketamine for treatment of MDD, ketamine's safety profile, and areas of uncertainty to be explored in future studies.

INTRODUCTION

The United States National Comorbidity Survey Replication recently estimated the lifetime prevalence of major depressive disorder (MDD) to be approximately 17%.¹ The occurrence of a major depressive episode (MDE) is often associated with significant impairment in multiple areas, including functioning in school or at work and interaction with family and friends. This may negatively impact patient outcomes long after the MDE has been resolved and may increase risk of

Needs Assessment: When patients present with a major depressive episode, one of the challenges inherent to current pharmacotherapy options is that medications often take several weeks to exert their antidepressant effects. A well-known anesthetic and analgesic medication, ketamine, has shown potential for providing a much more rapid relief of symptoms.

Learning Objectives:

- Summarize the evidence for a role of the glutamate system in major depressive disorder.
- List the most common acute adverse effects of intravenous ketamine infusion.
- Identify the main reasons why the antidepressant efficacy of ketamine is still considered preliminary.

Target Audience: Primary care physicians and psychiatrists.

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recurrence or relapse.² The clinical availability of therapeutic interventions with rapid onset of action may help reduce or even prevent the long-term effects of an MDE.

However, most existing pharmacologic treatments for MDD take several weeks to months to achieve their full clinical effects. This constitutes a major burden for patients, contributes to significant morbidity, and increases risk for suicide. The delay in onset of action that is typical of currently available antidepressants may exist because these medications exert their pharmacologic effects on systems upstream from the core pathophysiology of MDD.³ Thus, the interaction of these medications with their corresponding binding molecules (eg, receptors, transporters) activates intracellular signaling cascades that only in turn lead to changes in the expression and sensitivity of downstream neurotransmission molecules that are part of MDD pathophysiology. Most notable in this respect has been the recent accumulation of data indicating that antidepressants impact pathways that regulate cellular plasticity and survival in brain regions involved in mood regulation.⁴ In keeping with this are studies demonstrating atrophy and cell death in subgroups of patients with MDD.⁵⁻⁷

Plasticity and survival of brain cells involve multiple actions of the excitatory amino acid neurotransmitter glutamate.⁴ It is not surprising that there is an increasing interest in the use of glutamate system modulators for treatment of MDD.^{8,9} The potential efficacy of the high-affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, in particular, has received attention both in the scientific community and from the general public.¹⁰ This article reviews two published placebo-controlled studies in which ketamine was given intravenously to patients with MDD. A single dose of ketamine (0.5 mg/kg) infused over 40 minutes had robust antidepressant effects that appeared after only a few hours.^{11,12} In light of these two promising initial reports, ketamine may have potential as a novel antidepressant with rapid onset of action, which is essential for minimizing the long-term effects of an MDE.

DEPRESSION PATHOPHYSIOLOGY AND EFFECT OF TREATMENT

Rational drug development for treatment of MDD should be guided by a solid pathophysiologic model derived from both preclinical data and clinical observations. One such model focuses on the role of stressful experiences on glutamate function.¹³ The behavioral stress response involves multiple brain systems including not only activation of the hypothalamic-pituitary-adrenocortical axis but also initiation of complex cascades of reactions mediated by several neurotransmitters, including release of the excitatory amino acid

neurotransmitter glutamate.¹⁴ When a stressor is acute and mild, the stress response helps an organism adapt and cope. However, when the stressor is chronic and severe, and especially when it is considered uncontrollable and inescapable, it may have pathologic consequences, including MDD.^{15,16} Preclinical studies have found that chronic stress may lead to excessive extrasynaptic accumulation of glutamate.¹⁷ In addition, chronic stress induces changes at the level of the glutamatergic NMDA receptor.¹⁸ Over time, this persistent hyperactivity of the stress system may contribute to glutamate-mediated excitotoxicity leading ultimately to cell death in brain areas such as the hippocampus.^{19,20} In addition, accumulating evidence from post-mortem and brain imaging indicates that glutamate metabolism is altered in individuals who are depressed compared to those who are well.²¹⁻²⁴

Preclinical data on the involvement of the glutamate system in the mechanism of action of conventional antidepressants go back many years.⁸ For example, monoaminergic antidepressants have multiple effects on glutamate receptor function.²⁵⁻²⁷ In addition, there is abundant evidence of the positive effects of glutamatergic drugs in animal models of depression.⁸ These include antagonists at the NMDA receptor.²⁸⁻³¹ Most relevant for this review are animal studies of ketamine, which in glutamatergic pathways works as a high-affinity NMDA antagonist.³² In rats ketamine induces antidepressant-like effects in the forced swimming test and in the learned helplessness model of depression.³³⁻³⁵ These effects may be mediated by regulating the functional interplay between NMDA and non-NMDA ionotropic glutamate receptors, especially α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors.³⁶

CLINICAL EVIDENCE FOR KETAMINE

Though compelling, it was not the preclinical data that sparked interest in the potential use of ketamine as an antidepressant treatment. Instead, it was an experimental study in patients with MDD that originally aimed to characterize the psychotomimetic effects of a subanesthetic intravenous (IV) dose of ketamine in this population. In 2000, Berman and colleagues¹¹ at Yale University reported on the effects of ketamine 0.5 mg/kg and saline infusions on mood in nine drug-free symptomatic inpatients with recurrent MDD. Mood change following each of the two 40-minute infusions was measured using the 25-item Hamilton Rating Scale for Depression (HAM-D₂₅) and the Beck Depression Inventory, both acutely (40–230 minutes after the start of the infusion) and sub-acutely (1–3 days post-infusion). Treatment order was randomized across patients. The two infusions were separated by ≥ 1 week. HAM-D₂₅ scores were virtually unchanged

in the saline condition. In contrast, a significant ketamine-induced reduction in HAM-D₂₅ scores was first seen after 230 minutes and continued to develop over time. Three days post-ketamine, HAM-D₂₅ scores were reduced by an average of 48%. In four of the eight patients who received ketamine, the HAM-D₂₅ reduction was $\geq 50\%$ (one patient dropped out after having received saline during the first infusion). Within 1–2 weeks post-ketamine, all patients but one (who started antidepressants after responding to ketamine and never completed the saline condition) had relapsed.

Zarate and colleagues¹² replicated this study in a larger sample using an inpatient protocol at the National Institutes of Health which involved administration of IV ketamine (0.5 mg/kg) and IV saline in a randomized order 1 week apart. All 18 patients had a diagnosis of recurrent MDD and a HAM-D₂₁ score ≥ 18 at baseline. They had responded insufficiently to ≥ 2 adequate antidepressant trials in their lifetime and were therefore considered to be treatment resistant. Participants were rated 40–230 minutes after the start of the infusion and 1–7 days post-infusion. A significant ketamine-induced reduction in HAM-D₂₁ scores was first seen after 110 minutes. One day post-infusion, HAM-D₂₁ scores were significantly reduced in the ketamine condition (-56%) but not in the saline condition (-10%). At this point, 71% of patients reported $\geq 50\%$ decreases in HAM-D₂₁ scores following ketamine, versus 0% following saline. After 1 week, these percentages were 34% and 0%, respectively. Notably, whereas 17 patients received the ketamine infusion, only 14 patients received the saline infusion, because four patients who received ketamine first maintained the antidepressant response for >1 week.

These two studies^{11,12} suggest that IV ketamine can have a robust (large effect size) and rapid (within 2 hours) antidepressant effect in patients with MDD. A recent third study,³⁷ also conducted at Yale University and presented in abstract form at the 2007 Society for Biological Psychiatry Annual Meeting, again replicated the acute response to ketamine in an additional 10 patients (Table 1).^{11,12,37,38} Importantly, although neither study included patients who were actively suicidal, both Berman and colleagues¹¹ and Zarate and colleagues¹² observed meaningful reductions in suicidal ideation. Patients who responded acutely subsequently remained well for several days. The authors of this article and several other groups are currently conducting follow-up studies in order to develop adequate continuation treatment, with the goal of sustaining the acute ketamine response for longer time periods. For example, a recent report of two patients with treatment-resistant depression (TRD) who received one or more continuous ketamine infusions of approximately 0.3 mg/kg/h for 5 days found that the patients remained well for >1 year.³⁹ However, another case study in a patient with TRD and comorbid alcohol and benzodiazepine dependence found that the antidepressant effect of a second 0.5 mg/kg ketamine infusion was reduced compared to the first infusion.⁴⁰ Berman and colleagues¹¹ and Zarate and colleagues¹² excluded patients with recent alcohol and drug use disorders. It remains to be seen if including such patients will alter the antidepressant efficacy of IV ketamine in a placebo-controlled study.

TABLE 1
OVERVIEW OF PLACEBO-CONTROLLED IV KETAMINE STUDIES IN PATIENTS WITH MDD^{11,12,37,38}

	<i>Berman et al</i> ¹¹	<i>Zarate et al</i> ¹²	<i>Valentine et al</i> ³⁷
Patients enrolled in study/ patients who received the ketamine infusion (N)	9/8	18/17	10/10
DSM-IV diagnosis ³⁸	MDD, recurrent (n=8) Bipolar disorder (n=1)	MDD, recurrent, without psychotic features	MDD
Medication status	Medication-free for at least 2 weeks prior to infusion	Medication-free for at least 2 weeks prior to infusion Insufficient response to at least two adequate antidepressant trials in the past (treatment-resistant)	Medication-free prior to infusion
Study design	Within-group, cross-over, double-blind	Within-group, cross-over, double-blind	Within-group, cross-over, single-blind
Treatments (administered intravenously >40 minutes)	Ketamine (0.5 mg/kg) and saline, in randomized order	Ketamine (0.5 mg/kg) and saline, in randomized order	Ketamine (0.5 mg/kg) and saline, in non-counterbalanced order (saline first)

IV=intravenous; MDD=major depressive disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

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CLINICAL USE

While the interest in ketamine as an antidepressant developed fairly recently, its use in anesthesia and sedation in both adults and children goes back many years.^{41,42} Surgical anesthesia is typically produced by IV doses of approximately 1–3 mg/kg.^{43,44} The efficacy of ketamine as an analgesic agent is also well documented and may outlast that of anesthesia.^{41,42} Treatment at sub-anesthetic doses may in fact be sufficient for long-term therapeutic benefit in patients with chronic pain.^{45,46} Notably, a 2005 study in 40 patients with complex regional pain syndrome (CRPS) who had previously insufficiently responded to conventional treatments found that the effects of 10 open-label ketamine infusions (of up to 20 mg/hour infused over 4-hour periods, or 40–80 mg per infusion) included not only a decrease in subjective pain intensity scores and an increase in mobility, but also a reduced need for antidepressants.⁴⁷ These benefits lasted for periods lasting from 2 weeks to 15 months.

ADVERSE EFFECTS

Based on an extensive anesthesia literature, ketamine may be considered a very safe drug. Its sympathomimetic effects generally include mild-to-moderate increases in heart rate, blood pressure, and cardiac output.^{41-43,48} Ketamine produces no or only a mild respiratory depression.^{41,42} Unless patients present with cardiovascular disease and/or uncontrolled hypertension, acute risks associated with IV ketamine administration are therefore regarded as minimal.⁴⁸ Other adverse effects may include perceptual disturbances, which usually manifest as floating-in-space sensations and/or out-of-body experiences, but in rare events might also include visual or auditory hallucinations.⁴¹ While some patients describe these dissociative experiences as pleasurable, joyful, and fascinating (in 1999 ketamine was placed in Schedule 3 of the Controlled Substance Act), others find them bizarre or frightening.⁴⁸ The perceptual disturbances are usually mild and do not last long beyond ketamine administration.⁴² Several studies have addressed the question of prolonged psychological effects of ketamine in the general population, secondary to its anesthetic use, and concluded that ketamine does not place patients at a greater risk than do other anesthetics.^{49,50} Perceptual disturbances following ketamine may be more common and last longer in individuals with preexisting psychosis.^{48,49,51} However, an investigation of patients with schizophrenia who received a sub-anesthetic dose of IV ketamine in experimental studies found no evidence of enduring adverse effects and distress at follow-up 8 months later.⁵²

Consistent with ketamine's acute effects on perception, both Berman and colleagues¹¹ and Zarate and colleagues¹² found that, 40–45 minutes after the start of the ketamine infusion, patients reported more positive symptoms on the Brief Psychiatric Rating Scale (BPRS) than at baseline. Ketamine administration was also associated with a significant increase in subjective "high" and in scores on item 1 of the Young Mania Rating Scale (elevated mood).^{11,12} However, none of these effects were seen beyond 80 minutes. The authors of this article are currently investigating methods to attenuate the acute psychotomimetic and dissociative effects of ketamine. They are also carefully characterizing ketamine's acute side effect profile in patients with TRD using validated measures for adverse event reporting. A report on data from 295 healthy volunteers who were repeatedly administered ketamine (at the dose found to have antidepressant effects in patients with MDD) revealed no increase in positive symptoms, subjective "high," and perceptual alterations between the first and subsequent exposures.⁵³

Several experimental studies in healthy volunteers have found acute effects of ketamine on neuropsychological test performance. Ketamine impairs performance on tests of attention (eg, trail making, Stroop color-word test, continuous performance), memory (eg, immediate and delayed, verbal and non-verbal recall) and executive function (eg, word list generation fluency, Wisconsin card sorting).⁵⁴⁻⁵⁷ It has been argued that these acute impairments in cognition may have a long-term impact.¹⁰ However, studies investigating cognition in recreational ketamine users are confounded by several factors, including comorbid substance abuse.⁵⁸ Very few prospective controlled studies have addressed this critical issue, but a recent study in patients with treatment-resistant CRPS found no adverse neuropsychological effects of extended ketamine treatment at relatively high doses of 3–7 mg/(kg*h).⁵⁹

The absence of enduring adverse effects and behavioral sensitization following administration of a subanesthetic dose of IV ketamine also argues against the idea that its antidepressant effects may be offset by possible glutamate-mediated toxicity and cell death.¹⁰ This is corroborated by recent findings from preclinical studies³⁶ of increases in glutamatergic AMPA throughput in response to a subanesthetic dose of IV ketamine. It is likely that any toxicity precipitated by ketamine is dose dependent. Thus, the authors of this article hypothesize that, at the relatively low single dose required to achieve a therapeutic effect on mood, ketamine does not cause the cell death that may result from higher doses and more prolonged courses of treatment. Medications with similar pharmacologic properties, the glutamate receptor modulators riluzole and memantine, have been found to have neuroprotective effects in neurodegenerative disorders (amyotrophic lateral sclerosis and Alzheimer's disease, respectively).^{9,60-62}

AREAS OF UNCERTAINTY

Despite evidence from two published studies,^{11,12} ketamine's effectiveness in relief of MDD symptoms must still be considered a preliminary finding. Drawing conclusions on the effectiveness of ketamine is hindered by the fact that both studies used saline as the placebo control. The acute effects of ketamine and the acute effects (or lack thereof) of saline were likely to be readily distinguishable, which means it was impossible to maintain the integrity of the blind (in both patients and clinicians). The problem is illustrated by the fact that not all study participants received both IV ketamine and IV saline. In the study by Zarate and colleagues,¹² crossing participants over from one treatment to another after 1 week was problematic in patients who were administered ketamine on the first infusion day and showed an antidepressant response that lasted longer than 1 week. These patients never received the subsequent saline infusion. A longer inter-treatment interval might be one possible solution for future studies employing a within-group crossover design. Berman and colleagues¹¹ separated the two infusions by up to 2 weeks such that patients who had received ketamine on the first infusion day and showed an antidepressant response had relapsed, except for one patient who initiated continuation treatment following ketamine-induced mood improvement and never completed the saline infusion. A between-groups study may be preferable to ensure that patients complete the placebo condition.

The lack of a placebo control that maintains integrity of the blind in both patients and clinicians during the infusions may also explain why in one of the studies¹² the magnitude of psychotomimetic effects during ketamine infusion (ie, increase in BPRS positive symptoms) was correlated with the mood improvement at day 1 (ie, decrease in HAM-D scores). Neither study has reported if the elevated mood reported by patients 40–80 minutes after the start of the ketamine infusion was associated with the observed change in HAM-D scores at later time points.¹⁰ Such an association would call into question to what extent ketamine's antidepressant effects may have been based on patients' expectations derived from its acute effects. This issue of unmasking participants would remain even if ketamine was compared with saline in a between-groups study. To circumvent this, future studies should therefore consider the use of an active placebo control instead of, or in addition to, saline. The active control should have subjective effects similar to those of ketamine during the infusion but not have any known antidepressant effects after the infusion. A 2002 study⁶³ in medicated depressed patients undergoing surgery has found that those induced with propofol, fentanyl, and ketamine reported improved mood and reduced subjective pain 2–4 days post-surgery, whereas no

such changes were seen in patients induced with propofol and fentanyl alone. It is unlikely that patients were unblinded to the different treatments during the procedure, given that post-surgery confusion scores were similar across the two groups. This study provides some evidence that IV ketamine can have an antidepressant effect even when patients are masked to the treatment they are receiving.

The route of drug administration may have influenced the speed of ketamine's antidepressant response. IV administration bypasses first-pass metabolism and results in higher plasma concentrations than oral administration. Some studies have demonstrated a rapid response to IV administration of conventional antidepressants.^{64,65} Other studies reported no difference between IV and oral administration in the speed of onset of action of these drugs.^{66,67} From the point of view of patient convenience, oral administration of antidepressants is usually the preferred route. It remains to be seen if ketamine will have rapid antidepressant properties when administered orally or in other formulations (eg, intramuscularly, intranasally, transdermally). The current data on the efficacy of other glutamate-modulating medications available for oral administration in patients with MDD are mixed. Oral administration of riluzole may improve mood in patients with TRD.^{68,69} Oral administration of memantine had no significant antidepressant effects in a recent study in patients with MDD.⁷⁰ However, memantine has significantly lower affinity for the NMDA receptor than ketamine.⁷¹

Other areas of uncertainty include the relative effectiveness of the two optical enantiomers, S- and R-ketamine, and the role of neurotransmitters other than glutamate in ketamine's antidepressant effects. Ketamine is approved by the US Food and Drug Administration only as a racemic mixture of both enantiomers. The more active enantiomer, S-ketamine, has approximately 4–5 times greater affinity for the NMDA receptor than R-ketamine.⁷² In healthy volunteers, S-ketamine was found to produce emotional disturbances, cognitive impairments, and dissociative experiences, whereas R-ketamine induced a state of relaxation.⁷³ S-ketamine has been approved in some European countries based on evidence that it has more potent anesthetic and analgesic effects such that it can be used in smaller doses and therefore possibly decrease recovery time.⁷⁴ There is also some indication that the psychotomimetic or unpleasant effects of S-ketamine may be less pronounced than those of the racemic mixture.⁷⁵ S-ketamine-induced decreases in binding potential of the dopamine-2 receptor antagonist raclopride, measured using positron emission tomography in the striatum and surrounding brain areas, have been shown to correlate with subjective euphoria; this suggests that dopamine may play a role in its acute mood-elevating effects.⁷⁶ Most

experimental studies that administered single subanesthetic IV doses of racemic ketamine to humans have also found that ketamine has effects on dopamine receptors.⁷⁷⁻⁸⁰ These studies have also implicated a role for mu opioid receptors.⁸¹ In summary, ketamine has a complex pharmacologic profile, with its actions on the glutamate system and NMDA receptors being only one of multiple pathways that together are responsible for its diverse effects.

Other currently unresolved issues with ketamine include the following. First, the dose used thus far (0.5 mg/kg) may not be the optimal dose for induction and maintenance of the mood response. Second, it is unknown which medications are viable continuation treatment options in patients who show an initial favorable response (eg, repeated ketamine administration, use of another glutamatergic drug such as riluzole or memantine, or other more traditional approaches). Third, although there is no current evidence of addiction potential in controlled studies performed to date, the potential of ketamine abuse must continue to be considered. Finally, future studies should more closely measure the acute and longer-term side effects of ketamine at multiple time points following its administration.

COMPARISON WITH EXISTING RAPID ANTIDEPRESSANT TREATMENTS

Current treatments for MDD can be divided into “acute” interventions and continuation/maintenance strategies. However, besides ketamine only sleep deprivation produces antidepressant responses within 24 hours (Table 2). Sleep deprivation has a long-known rapid and robust efficacy in approximately 60% of patients with MDD.⁸² The magnitude of improvement is often equivalent to that observed after 6 weeks of antidepressant treatment. Hence, the acute therapeutic response to sleep deprivation must be mediated by mechanisms different from those mediating the gradual improvement obtained with antidepressants.⁸³ Functional brain imaging studies are highly suggestive of an association between clinical improvement and increased activity in the ventral anterior cingulate cortex.⁸⁴ Advantages of sleep deprivation include its noninvasive nature and safe use in pregnant and breastfeeding women. However, most patients relapse after one subsequent night of sleep regardless of medication status,⁸² which may explain why sleep deprivation is rarely

TABLE 2
COMPARISON OF KETAMINE WITH OTHER RAPID ANTIDEPRESSANT TREATMENTS

	<i>Ketamine</i>	<i>Sleep deprivation</i>	<i>Bright light therapy</i>	<i>Electroconvulsive therapy</i>
Procedure	Infusion of a single sub-anesthetic dose (0.5 mg/kg IV) administered over 40 minutes	Sustenance of wakefulness during the night	Exposure to broad-spectrum white light (10,000 lux for 30 minutes) in the early morning	Application of electrical stimulus above seizure threshold to scalp
Speed of onset of action	Within 2–4 hours	Within 24 hours	Within 1 week	After on average six sessions (2 weeks)
Response rate	Approximately 50% (72 hour post-infusion)	Approximately 60%	50% to 60%	Up to 90% (approximately 60% in TRD)
Post-treatment relapse	Within 2 weeks	During or after the following night of sleep	Between 2 days and 2 weeks	Within 6 months
Number of patients who received treatment	Small	Large	Large	Large
Advantages	Rapid reduction in suicidality?	Useful in those who may not tolerate medication trials Few side effects Relatively easy and inexpensive administration	Useful in those who may not tolerate medication trials Few side effects	Best evidence base (including for TRD)
Disadvantages	Risk of psychosis in vulnerable individuals	Risk of symptoms of (hypo)mania in vulnerable individuals Increased risk of seizures in patients with a history of convulsions Lack of access	Risk of symptoms of (hypo)mania and in vulnerable individuals Compliance is difficult for some patients Optimum dosing requires individual adjustment	Risk of symptoms of (hypo)mania in vulnerable individuals Requires general anesthesia Retrograde amnesia Lack of access

IV=intravenous; TRD=treatment-resistant depression.

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administered by clinicians in the US. Nevertheless, sleep deprivation has been successfully used to hasten the onset of action of antidepressants.⁸⁵

Bright light therapy (BLT) can also be administered safely in pregnant and breastfeeding women. Like sleep deprivation, it is non-invasive. However, compliance may be difficult for some, as patients are usually required to self-administer bright light in the early morning.⁸⁶ BLT reportedly has a response rate of approximately 60%. The effect size may be larger in patients with seasonal affective disorder (SAD) versus non-seasonal MDD.⁸⁷ Like sleep deprivation, BLT has been successfully used as an adjunct to conventional antidepressant treatment in order to speed up its antidepressant effect.⁸⁸ While BLT efficacy has mostly been studied over time periods in the range from weeks to months, at least two studies^{89,90} in patients with SAD are indicative that its onset of action may be faster than that of the commonly prescribed selective serotonin reuptake inhibitor, fluoxetine. Anecdotally, clinically meaningful mood changes have been found to occur even after time periods of 2–3 days.^{91,92} A 2004 Cochrane review of BLT studies in patients with non-seasonal MDD showed significant benefit in studies of up to a week, but no significant benefit in longer and better-controlled studies.⁹³ However, a 2005 controlled trial reported significant benefit of BLT in approximately 50% of patients with non-seasonal chronic MDD.⁹⁴

Electroconvulsive therapy (ECT) is usually administered to patients with TRD and generally involves three sessions per week, with most individuals requiring at least 6 treatments to achieve a response. ECT is considered the most effective antidepressant treatment, especially for patients with psychotic, melancholic, or bipolar depression.⁹⁵ It is considered another rapid antidepressant treatment, although onset of action is rarely achieved during the first treatment session (Table 2). Interestingly, a recent case report in a patient with severe, recurrent MDD showed that intramuscular administration of 100 mg of ketamine in combination with a single session of ECT resulted in marked clinical improvement within 8 hours of treatment which continued at least until the next ECT session 3 days later.⁹⁶ Disadvantages to ECT include its invasive nature, including the requirement of general anesthesia and the risk of significant retrograde amnesia, which in some patients may be irreversible.⁹⁷ Without continuation treatment, the majority of patients will relapse within 6 months.⁹⁸

RECOMMENDATIONS

The development of a rapid antidepressant strategy which is effective within 24 hours and can be sustained is an important therapeutic goal in psychiatry. Studies on the

antidepressant effects of ketamine are a work in progress. This article has presented the currently available data, with the intention to stimulate future research.

As of yet, there are no established guidelines for ketamine administration in patients with MDD. Berman and colleagues¹¹ and Zarate and colleagues¹² have administered ketamine on an inpatient basis. Ongoing studies by the authors of this article and elsewhere also use this approach. Patients are monitored by an anesthesiologist during infusion, are continuously observed by nursing staff, and remain in the inpatient setting for 24 hours post-infusion to ensure safety. Acutely, ketamine's potential side effects include respiratory or circulatory problems, especially in patients with lung disease and uncontrolled hypertension, respectively. Studies thus far have not encountered these problems; however, patient selection procedures actively excluded patients with known risk factors. At present, the use of ketamine for treatment of TRD in uncontrolled settings is discouraged by the authors of this article.

Nevertheless, in the future ketamine may offer the clinician a potentially efficacious and rapidly acting medication, especially for patients with TRD. As the therapeutic lag time inherent to currently available treatments for MDD is suboptimal, this and similar approaches are worthy of further investigation.

CONCLUSION

Ketamine is a well-known FDA-approved anesthetic and analgesic medication. In at least two placebo-controlled studies in patients with MDD,^{11,12} one of which included patients with TRD, ketamine has shown additional potential as a rapid and robust antidepressant. There was some evidence of a decrease in suicidality as part of the overall rapid clinical improvement. The acute antidepressant effects of a single ketamine infusion lasted up to 2 weeks. It remains to be seen if ketamine, in combination with existing or future continuation therapies, can be developed as a safe and effective treatment option for patients with an acute MDE. The development of a new pharmacologic intervention with acute and sustained antidepressant effects could have a significant impact on public health. **PP**

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