Maintaining Rapid Antidepressant Effects Following Ketamine Infusion:
A Major Unmet Need

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ABSTRACT

Objective: Several controlled trials have demonstrated the rapid effects of intravenous ketamine. As a result, the use of this off-label treatment has grown exponentially in recent years. This use is expected to continue to grow after the approval by the US Food and Drug Administration of intranasal esketamine for treatment-resistant depression—a decision that firmly establishes *N*-methyl-D-aspartate (NMDA)–receptor antagonism as a valid antidepressant mechanism of action in the public view. The limitation, however, of intravenous ketamine administration is that much less is known about how to maintain initial treatment gains. Thus, although intravenous ketamine has proved to be a rapid-acting antidepressant, maintaining its early therapeutic gains in an efficient manner has emerged as a major unmet need in the field.

Data Sources: PubMed/MEDLINE was searched from inception to March 1, 2019, using the following terms: *ketamine*, *randomized*, *depression*, and *placebo*. There were no language or date restrictions.

Study Selection: The search was limited to randomized, placebo-controlled trials to maintain initial treatment gains of intravenous ketamine for major depressive disorder. A total of 115 manuscripts were identified, and 110 were excluded because they did not describe randomized, double-blind clinical trials.

Data Extraction: The remaining 5 articles were reviewed.

Results: Three negative studies involving 2 oral agents (lithium and riluzole), a small negative study involving repeated ketamine infusions, and a positive yet insufficiently controlled larger study supporting infusions 2 or 3 times weekly were published.

Conclusions: This evidence base is insufficient to inform clinical practice. Fortunately, a wide variety of molecular targets exist for this indication. Psychotherapy and exercise may also play a beneficial role. More studies are urgently needed to establish how best to maintain rapid symptom improvement seen with ketamine infusions.

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Major depressive disorder (MDD) is one of the most common medical illnesses, with a lifetime prevalence of 16.2% for adults in the United States.[1] It is also a chronic and debilitating illness, leading to poor quality of life as well as significant morbidity and mortality.[2]

Developing Novel Therapies for MDD

Drug development for MDD has historically been dominated by the monoamine hypothesis.[3] However, over the past two decades, there have been sustained and considerable efforts to uncover novel circuitry-based treatments.[4–7] Here, glutamatergic-based mechanisms have garnered the most attention, with ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and glutamatergic modulators accumulating substantial data in support of their role as a rapid-acting antidepressant therapy in MDD. To date, several randomized controlled trials[8–13] have demonstrated intravenous ketamine's robust effects, evident within 24–72 hours of treatment. For logistical and practical reasons, the field has sought to develop agents that could replicate these rapid antidepressant effects with less burdensome and costly routes of administration. Ketamine's poor oral bioavailability secondary to extensive first-pass metabolism has led to the consideration of convenient non-oral routes, such as the intranasal formulation.[14]

Esketamine and Ketamine: Strengths and Weaknesses

Esketamine, the *S*-enantiomer of ketamine, was recently approved by the US Food and Drug Administration (FDA) for use in patients with treatment-resistant depression (TRD) based on data from 3 phase 3 trials in TRD,[15–17] in which intranasal esketamine plus a newly initiated antidepressant was compared to a newly initiated antidepressant plus intranasal placebo. While the agency found sufficient evidence for efficacy at study endpoint (28 days) for approval, it was also noted that a key secondary endpoint of achieving clinical response at 24 hours that is thereafter maintained was not reported as being statistically different between the treatment groups in 2[15,16] of the 3 phase 3 trials that included an assessment at 24 hours post-randomization.

Whether due to differences in study design (intranasal ketamine studies involved the initiation of a new antidepressant at randomization for all patients whereas intravenous ketamine studies do not, though little effect can be expected 24 hours after the first dose of an oral monoaminergic antidepressant), population (TRD versus non-TRD), or route of administration (intravenous versus intranasal), the weight of the evidence continues to be in favor of intravenous racemic ketamine as a rapid-acting antidepressant. For instance, a meta-analysis by Kishimoto et al[18] estimated an effect size of 1.0 (Hedges *g*) in favor of intravenous ketamine versus placebo 24 hours post-infusion. Clearly, unless double-blind studies are conducted comparing rapid-acting

Clinical Points

- It is unclear how to keep depressed patients well who experience a quick improvement in mood immediately after a single ketamine infusion.
- This article uncovers a handful of failed attempts at finding such a strategy but provides many suggestions for future investigation.

effects of intranasal esketamine versus intravenous ketamine in MDD, many patients will continue to seek treatment with the latter formulation in private or academically affiliated ketamine clinics. In fact, the number of clinicians who have provided this off-label service has grown exponentially over time.[19] This number is expected to continue to grow after the approval by the FDA of intranasal esketamine for TRD.

The limitation, however, of intravenous ketamine administration versus intranasal esketamine is that very little is known about how to maintain initial treatment gains. While the results of a randomized, double-blind, placebo-controlled trial[19] of intranasal esketamine clearly demonstrated the efficacy of repeated inhalations in maintaining treatment effects long-term, the effect size for a single infusion of ketamine drops to 0.38 (Hedges *g*) by day 5 and is no longer statistically significant after day 9.[18] Thus, while intravenous ketamine has proven to be a rapid-acting antidepressant, maintaining its early therapeutic gains in an efficient manner has emerged as a major unmet need in the field. Since the publication of the first, uncontrolled report[20] on the effect of repeated ketamine infusions on mood in depressed patients (recently replicated in an open-label trial[13] of 4 successive weekly ketamine infusions in responders), a number of controlled studies have been conducted examining maintenance effects following acute response to ketamine. The current work will review efforts toward this goal from double-blind randomized clinical trials (RCTs) as well as propose future opportunities for treatment development in this area.

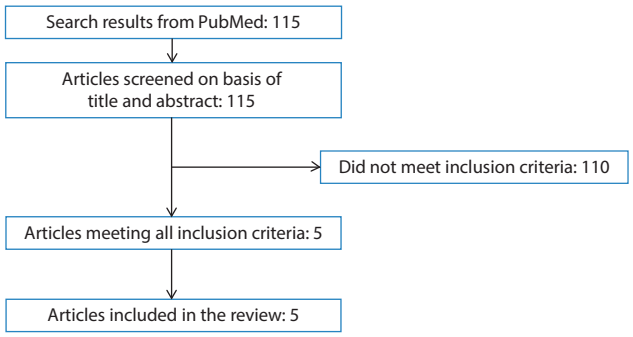
METHODS

Studies were identified using searches of PubMed/MEDLINE from inception to March 1, 2019. Specifically, a search was conducted by cross-referencing the terms *ketamine*, *randomized*, *depression*, and *placebo*. No year or language limits were set. The search was limited to randomized, double-blind, placebo-controlled studies evaluating the efficacy of treatment strategies to help maintain acute therapeutic gains seen with intravenous ketamine. All eligible manuscripts were obtained and reviewed. See Figure 1 for more details.

RESULTS

A total of 115 abstracts were identified. Of these, 110 did not describe randomized, double-blind clinical trials and were excluded. The remaining 5 articles[11,21–24] were included and are reviewed as follows.

Figure 1. PRISMA Diagram of Study Inclusion



The first controlled trial to examine how to maintain rapid antidepressant effects with intravenous ketamine was published by Mathew et al[21] about 10 years ago. In that study, 26 patients with MDD who had not experienced sufficient response to 2 or more antidepressant treatments during the current episode received open-label intravenous ketamine (0.5 mg/kg). Fourteen patients who were responders (50% or greater reduction in Montgomery-Asberg Depression Rating Scale [MADRS][25] score) 72 hours following ketamine infusion were randomized in a double-blind fashion to riluzole (100–200 mg/d) versus placebo for a total of 32 days. Time to relapse was the main outcome measure, defined as (1) a MADRS score of ≥ 20 for 2 consecutive visits, (2) a minimum absolute increase of ≥ 10 points in MADRS score for 2 consecutive visits, and (3) meeting criteria for a major depressive episode. No significant difference in time to relapse was found between the 2 treatment groups (80% of patients taking riluzole relapsed versus 50% on placebo).

A subsequent trial examining the use of oral riluzole after intravenous ketamine was conducted by Ibrahim et al[22] at the intramural program of the National Institute of Mental Health (NIMH). In that study, 42 patients with MDD who had not experienced sufficient response to 2 or more antidepressant treatments during the current episode were randomized to riluzole (100–200 mg) or placebo initiated 4–6 hours after a single infusion of ketamine (0.5 mg/kg) and maintained for 4 weeks. The main outcome measure of the study was the change in 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) scores during treatment. As in the earlier trial,[21] no difference in efficacy between the 2 groups was reported.

Singh et al[11] randomized 68 patients with MDD who had not experienced sufficient response to 2 or more antidepressant treatments during the current episode to receive either intravenous ketamine (0.5 mg/kg) or placebo (sodium chloride) either 2 or 3 times weekly for up to 4 weeks. In the twice-weekly dosing group, the mean change in Montgomery-Asberg Depression Rating Scale (MADRS) score at day 15 from baseline was −18.4 versus −5.7 for ketamine and placebo, respectively. This corresponds to an

approximate effect size of 1.14 (Cohen *d*) during 4 weeks, which is comparable to the effect size of a single dose of intravenous ketamine at 24 hours.[18] In the group that received 3 infusions per week, the mean change in MADRS score at day 15 was −17.7 versus −3.1 for ketamine and placebo, respectively, which corresponds to an effect size of 2.24 (Cohen *d*)—a much larger effect than that seen 24 hours after a single ketamine infusion. These results suggest that weekly ketamine infusions can maintain (if twice weekly) or even amplify (if 3 times weekly) rapid gains seen with ketamine infusion in MDD.

A subsequent smaller study of patients with TRD and chronic suicidal ideation, however, did not replicate these findings. Ionescu et al[23] randomized 26 patients with MDD who had not experienced sufficient response to 3 or more antidepressant treatments during the current episode to receive 2 weekly infusions of either intravenous ketamine (0.5 mg/kg) or placebo (sodium chloride) for up to 3 weeks. There was no significant difference in $HDRS_{17}$ scores at study endpoint between the two groups.

More recently, Costi et al[24] randomized 34 outpatients with MDD who had not experienced sufficient response to 2 or more antidepressant treatments during the current episode and who showed at least partial improvement (at least 25% reduction in MADRS scores) 24 hours following a single infusion with ketamine (0.5 mg/kg) to receive either lithium or placebo for 4 weeks. Lithium was dosed from 600 to 1,200 mg with the goal of achieving a target blood level of 0.6–0.9 mEq/L. Patients also received 3 additional infusions of ketamine (0.5 mg/kg) during the first 2 weeks. There was no statistically significance difference in efficacy between the two groups at endpoint (per MADRS scores).

DISCUSSION AND FUTURE DIRECTIONS

A handful of randomized, double-blind, placebo-controlled trials have been published to date examining various pharmacologic strategies aimed at preserving rapid antidepressant effects seen after ketamine infusion. Of these strategies, repeat (2 or 3 times weekly) infusion has emerged as most promising,[11] with 4 caveats. First, it employs saline as its control rather than midazolam, widely considered in the field as a more suitable comparator.[10,12,13] Given the likelihood of unblinding during ketamine infusions, a confirmatory study using intravenous midazolam (or even a closer-matching comparator since midazolam is not associated with dissociation) is needed. Second, if repeat infusion is confirmed, it would still not address the need of developing efficient maintenance strategies, since 2 or 3 infusions per week would require a significant time commitment and clinical resources and incur considerable cost. Third, the strategy does not explore whether higher doses of ketamine given less frequently—a somewhat more efficient approach—could also achieve the same goal. Fourth, subjects were blinded to drug-placebo but not to frequency of administration. Blinding the frequency of administration in future trials would confirm that the 3-times-per-week schedule can extend immediate treatment gains as seen in the study by Singh et al[11] (ie, yield a greater effect size at week 4 than at 24 hours after the first dose).

Unfortunately, however, the remaining studies, which all focused on the use of oral agents, failed to show any benefit. To advance the field, we must look either for existing treatments with a proven safe and effective track record in maintaining antidepressant effects or for novel mechanisms. Lithium, 1 of 2 pharmacotherapies with positive data from longer treatment phases (continuation) of adjunctive therapy in MDD,[26] was found not to be effective in this capacity.[24] Intranasal esketamine, the other combination therapy with positive, placebo-controlled longer-term (maintenance) data,[27] is a logical candidate and could be investigated in this role, as could oral racemic ketamine[28] and other NMDA-receptor antagonists.[29] In addition, the role of cognitive-behavioral therapy, a popular maintenance therapy for MDD that is also not associated with the typical side effect burden involved with long-term pharmacotherapy, should also be examined especially in light of open-label data.[30] The same argument can be made for transcranial magnetic stimulation.[31]

Several preclinical models also suggest a role for novel drug development in this area. There is ample evidence involving the role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) via acute glutamate-mediated sodium and calcium neuronal influx as well as long-term increases in AMPAR-mediated synaptic transmission and dendritic spine density as a central mechanism of action for ketamine.[32] Candidates for investigation here would involve AMPA potentiators, including some of *R*-ketamine's first-pass metabolites such as (2*R*,6*R*)-hydroxynorketamine.[33–36] Additional preclinical models point to the role of brain-derived neurotrophic factor (BDNF)/tyrosine kinase B (TrkB)–mediated hippocampal neurogenesis and maturation as key steps in sustaining the acute effects of ketamine.[37] To identify such candidates, data from assays specifically designed to quickly and efficiently select for hippocampal neurogenesis in vitro should be sought.[38–41] Fortunately, plausible molecular targets are plentiful. More specifically, potassium voltage-gated channel subfamily KQT–type potassium channels have been shown to influence neuronal differentiation in mouse hippocampus[41,42] and could serve as a target for treatment development. A similar argument could be made for sigma-1 receptor agonists,[43] metabotropic glutamate receptor 2 antagonists,[44] metabotropic glutamate receptor 5 agonists,[45] orexin A receptor agonists,[46] delta- and mu-opioid receptor antagonists,[47] and α_7-nicotinic receptor agonists.[48] Agents that are more selective for the hippocampus are preferable, since a broad and indiscriminate induction of neurogenesis via direct activation of the mammalian target of rapamycin protein or complex with the use of lipophilic drugs may increase the risk of malignancies such as breast cancer or the risk of epilepsy.[49,50]

This review has two main limitations that should be noted. First, as with any work, other experts in the field may

interpret the data extracted from this search and presented in this review differently. Readers interested in furthering their knowledge of this topic are therefore encouraged to seek additional resources in the literature, learn about the different viewpoints, and drive conclusions accordingly. Second, although a thorough and systematized search of the literature was performed, it should be noted that important works might have been inadvertently omitted from inclusion in the present review, particularly new or unpublished works.

In conclusion, there is a rising trend involving the use of off-label ketamine infusions for the rapid relief of depressive symptoms, a practice substantiated by a significant body of literature. Yet, maintaining these acute antidepressant effects has emerged as a major unmet need in the field. Despite the approval of an intranasal form of esketamine for TRD, many patients will most likely continue to seek off-label treatment with intravenous ketamine. Fortunately, a wide variety of molecular targets exist for this indication. More studies are urgently needed to establish how best to maintain rapid symptom improvement seen with ketamine infusion.

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