Management of treatment-resistant depression: A review of 3 studies

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An estimated 7.1% of the adults in United States had a major depressive episode in 2017, and this prevalence has been trending upward over the past few years.[1] The prevalence is even higher in adults between age 18 and 25 (13.1%).[1] Like other psychiatric diagnoses, major depressive disorder (MDD) has a significant impact on productivity as well as daily functioning. Only one-third of patients with MDD achieve remission on the first antidepressant medication.[2] This leaves an estimated 11.47 million people in the United States in need of an alternate regimen for management of their depressive episode.

The data on evidence-based biologic treatments for treatment-resistant depression are limited (other than for electroconvulsive therapy). Pharmacologic options include switching to a different medication, combining medications, and augmentation strategies or novel approaches such as ketamine and related agents. Here we summarize the findings from 3 recent studies that investigate alternate management options for MDD.

Ketamine: Randomized controlled trial

Traditional antidepressants may reduce suicidal ideation by improving depressive symptoms, but this effect may take weeks. Ketamine, an *N*-methyl-D-aspartate antagonist, has become a target of research for its antidepressant effects at subanesthetic doses.

1. Grunebaum MF, Galfalvy HC, Choo TH, et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized clinical trial. Am J Psychiatry. 2018;175(4):327-335.

Grunebaum et al[3] evaluated the acute effect of adjunctive subanesthetic IV ketamine on clinically significant suicidal ideation in patients with MDD, with a comparison arm that received an infusion of midazolam.

Study design

- 80 inpatients (age 18 to 65 years) with MDD who had a score ≥16 on the Hamilton Depression Rating Scale (HAM-D) and a score ≥4 on the Scale for Suicidal Ideation (SSI). Approximately one-half (54%) were taking an antidepressant
- Patients were randomly assigned to IV racemic ketamine hydrochloride, .5 mg/kg, or IV midazolam, .02 mg/kg, both administered in 100 mL normal saline over 40 minutes.

Outcomes

- Scale for Suicidal Ideation scores were assessed at screening, before infusion, 230 minutes after infusion, 24 hours after infusion, and after 1 to 6 weeks of follow-up. The average SSI score on Day 1 was 4.96 points lower in the ketamine group compared with the midazolam group. The proportion of responders (defined as patients who experienced a 50%

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Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

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Ketamine, augmentation with aripiprazole may be effective strategies for treatment-resistant MDD

reduction in SSI score) on Day 1 was 55% for patients in the ketamine group compared with 30% in the midazolam group.

Conclusion

- Compared with midazolam, ketamine produced a greater clinically meaningful reduction in suicidal ideation 24 hours after infusion.

Apart from the primary outcome of reduction in suicidal ideation, greater reductions were also found in overall mood disturbance, depression subscale, and fatigue subscale scores as assessed on the Profile of Mood States (POMS). Although the study noted improvement in depression scores, the proportion of responders on Day 1 in depression scales, including HAM-D and the self-rated Beck Depression Inventory, fell short of statistical significance. Overall, compared with the midazolam infusion, a single adjunctive subanesthetic ketamine infusion was associated with a greater clinically significant reduction in suicidal ideation on Day 1.

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Compared with midazolam, ketamine produced a greater clinically meaningful reduction in suicidal ideation

Ketamine: Review and meta-analysis

Wilkinson et al[4] conducted a systematic review and individual participant data meta-analysis of 11 similar comparison intervention studies examining the effects of ketamine in reducing suicidal thoughts.

2. Wilkinson ST, Ballard ED, Bloch MH, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am J Psychiatry. 2018;175(2):150-158.

Study design

- Review of 11 studies of a single dose of IV ketamine for treatment of any psychiatric disorder. Only comparison intervention trials using saline placebo or midazolam were included:
- Individual patient-level data of 298 patients were obtained from 10 of the 11 trials. Analysis was performed on 167 patients who had suicidal ideation at baseline.
- Results were assessed by clinician-administered rating scales.

Outcomes

- Ketamine reduced suicidal ideation more rapidly compared with control infusions as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) and HAM-D, with significant benefits appearing on Day 1 and extending up to Day 7. The mean MADRS score in the ketamine group decreased to 19.5 from 33.8 within 1 day of infusion, compared with a reduction to 29.2 from 32.9 in the control groups.
- The number needed to treat to be free of suicidal ideation for ketamine (compared with control) was 3.1 to 4.0 for all time points in the first week after infusion.

Conclusion

- This meta-analysis provided evidence from the largest sample to date (N = 298) that ketamine reduces suicidal ideation partially independently of mood symptoms.

While the anti-suicidal effects of ketamine appear to be robust in the above studies, the possibility of rebound suicidal ideation remains in the weeks or months following exposure. Also, these studies only prove a reduction in suicidal ideation; reduction in suicidal behavior was not studied. Nevertheless, ketamine holds considerable promise as a potential rapid-acting agent in patients at risk of suicide.

Strategies for augmentation or switching

Only one-third of the patients with depression achieve remission on the first antidepressant medication. The American Psychiatric Association's current management guidelines[2] for patients who do not respond to the first-choice antidepressant include multiple options. Switching strategies recommended in these guidelines include changing to an antidepressant of the same class, or to one from a different class (eg, from a selective

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Table

Alternate management options for treatment-resistant MDD: 3 studies

Study	Design	Outcome
Grunebaum et al[3] (2018)	80 adult inpatients with MDD and suicide ideation, 54% of whom were taking an antidepressant, were randomized to a single infusion of ketamine or midazolam	Compared with midazolam, ketamine resulted in a greater clinically significant reduction of suicidal ideation at 24 hours after infusion
Wilkinson et al[4] (2018)	Systematic review and individual patient-data meta-analysis of 167 patients with suicidal ideation from 11 studies who received an infusion of ketamine or saline or midazolam as a control treatment	Compared with control treatment, ketamine reduced suicidal ideation more rapidly, with significant benefits appearing on Day 1 and lasting up to 1 week
Mohamed et al[5] (2017)	1,522 patients with MDD who did not respond to ≥1 adequate antidepressant trials were randomized to switching to bupropion, augmenting with bupropion, or augmenting with aripiprazole	Patients who received aripiprazole experienced a statistically significant but modest increased likelihood of remission compared with switching to bupropion, but no significant difference compared with augmenting with bupropion

MDD: major depressive disorder

Clinical Point

Ketamine holds considerable promise as a potential rapid-acting agent in patients at risk of suicide

serotonin reuptake inhibitor [SSRI] to a serotonin-norepinephrine reuptake inhibitor, or from an SSRI to a tricyclic antidepressant). Augmentation strategies include augmenting with a non-monoamine oxidase inhibitor antidepressant from a different class, lithium, thyroid hormone, or an atypical antipsychotic.

The VAST-D trial[5] evaluated the relative effectiveness and safety of 3 common treatments for treatment-resistant MDD:

- switching to bupropion
- augmenting the current treatment with bupropion
- augmenting the current treatment with the second-generation antipsychotic aripiprazole.

3. Mohamed S, Johnson GR, Chen P, et al. Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: the VAST-D randomized clinical trial. JAMA. 2017;318(2):132-145.

Study design

- A multi-site, randomized, single-blind, parallel-assignment trial of 1,522 patients at 35 US Veteran Health Administration medical centers with nonpsychotic MDD with a suboptimal response to at least one antidepressant (defined as a score of ≥16 on the Quick Inventory Depressive Symptomatology-Clinician Rated questionnaire [QIDS-C16]).
- Participants were randomly assigned to 1 of 3 groups: switching to bupropion (n = 511), augmenting with bupropion (n = 506), or augmenting with aripiprazole (n = 505).
- The primary outcome was remission (defined as a QIDS-C16 score ≤5 at 2 consecutively scheduled follow-up visits). Secondary outcome was a reduction in QIDS-C16 score by ≥50%, or a Clinical Global Impression (CGI) Improvement scale score of 1 (very much improved) or 2 (much improved).

Outcomes

- The aripiprazole group showed a modest, statistically significant remission rate (28.9%) compared with the bupropion switch group (22.3%), but did not show any statistically significant difference compared with the bupropion augmentation group.
- For the secondary outcome, there was a significantly higher response rate in the aripiprazole group (74.3%) compared with the bupropion switch group (62.4%)

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and bupropion augmentation group (65.6%). Response measured by the CGI–Improvement scale score also favored the aripiprazole group (79%) compared with the bupropion switch group (70%) and bupropion augmentation group (74%).

Conclusion

• Overall, the study found a statistically significant but modest increased likelihood of remission during 12 weeks of augmentation treatment with aripiprazole, compared with switching to bupropion monotherapy.

The studies discussed here, which are summarized in the ***Table***[3-5] (***page 39***), provide some potential avenues for research into interventions for patients who are acutely suicidal and those with treatment-resistant depression. Further research into long-term outcomes and adverse effects of ketamine use for suicidality in patients with depression is needed. The VAST-D trial suggests a need for further exploration into the efficacy of augmentation with second-generation antipsychotics for treatment-resistant depression.

Clinical Point

Augmentation with aripiprazole resulted in a statistically significant but modest increased likelihood of remission

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