ONLINE EXCLUSIVE

Q/ Is ketamine effective and safe for treatment-resistant depression?

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EVIDENCE-BASED ANSWER

A/ **MAYBE,** but it's too soon to tell. There is limited evidence that ketamine by itself is effective in the very short term. Single-dose intravenous (IV) ketamine is more likely than placebo (odds ratio = 11-13) to produce improvement (> 50%) in standardized depression scores in 1 to 3 days, lasting up to a week. Twice- or thrice-weekly IV ketamine improves symptom scores by 20%-25% over 2 weeks (strength of recommendation [SOR]: **B**, meta-analysis of small, low-quality, randomized controlled trials [RCTs] and a single small RCT).

Augmentation of sertraline with daily oral ketamine moderately improves symptom scores for 6 weeks in patients with moderate depression (SOR: **B**, small, low-quality RCTs).

Augmentation of oral antidepressants (duloxetine, escitalopram, sertraline, venlafaxine) with intranasal esketamine spray improves response and remission rates at 4 weeks (16% for both outcomes) in patients with predominantly treatment-resistant major depression (SOR: **A**, meta-analysis of RCTs).

Ketamine therapy is associated with confusion, emotional blunting, headache, dizziness, and blurred vision (SOR: **A**, meta-analyses).

Nasal esketamine spray produces the adverse effects of dizziness, vertigo, and blurred vision severe enough to cause discontinuation in 4% of patients; it also can produce transient elevation of blood pressure (SOR: **A**, meta-analyses).

Evidence summary

Single-dose IV ketamine elicits a short-term response

A meta-analysis of RCTs evaluating a single dose of IV ketamine vs placebo for severe depression found that it increased the chance of a treatment response for up to 1 week afterward. Studies included patients with severe (N = 30), treatment-resistant (N = 40), and psychotic depression (N = 10), based on *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition* criteria.[1]

The primary outcome was treatment response: either an improvement of > 50% on a standardized depression scale or a Clinical Global Impression–Improvement scale score of 1 or 2 ("very much" and "much" improved, respectively, as assessed by a clinician). Ketamine increased the likelihood of short-term response or improvement at 24 hours (3 RCTs; N = 56; odds ratio [OR] = 11; 95% CI, 2-58); at 72 hours (3 RCTs; N = 56; OR = 13; 95% CI, 2-66); and at 7 days (4 RCTs; N = 88; OR = 2.6; 95% CI, 1.1-6.2).[1] Response rates equaled placebo at 2 weeks. The authors rated the RCTs as low quality.

Another systematic review of single-dose IV ketamine vs placebo for major depression and bipolar disorder included 3 additional small, low-quality RCTs, 2 of which showed short-term response to ketamine. The authors used Hedge's g statistic to standardize effect size (a score of magnitude 0.2 indicates a small effect; 0.6, moderate; 1.2, large; and 2, very large). One RCT (n = 26) found a very large 1-day response (effect size: –2; 95% CI,

A single dose of IV ketamine increased the chance of a treatment response for up to 1 week, compared to placebo.

–2.8 to –1.3), and 2 RCTs found conflicting responses at 12 days (RCT with N = 18: effect size: –0.2; 95% CI, –0.4 to 0.02 [no significant response] vs RCT with N = 8: effect size: –1.5; 95% CI, –2.5 to –0.5).[2]

More frequent dosing of IV ketamine improves symptoms

An RCT (N = 67) evaluating twice- or thrice-weekly IV ketamine vs placebo in patients with recurrent depression (with at least 1 treatment failure) found that ketamine significantly improved standardized depression scores and response rates at 15 days. Patients with clinically significant suicidality were excluded.[3]

Researchers randomized patients to IV ketamine (0.05 mg/kg) twice or thrice weekly or to saline control and used the 60-point Montgomery-Asberg Depression Rating Scale (MADRS). A response was defined as a reduction of the MADRS score by 50%.

Both ketamine arms produced greater symptom improvement at 15 days, compared to placebo (twice weekly: –18.4 vs –5.7; $P < 0.001$; thrice weekly: –17.7 vs –3.1; $P < 0.001$) in addition to higher response rates (twice weekly: 69% vs 15%; $P = .005$; number needed to treat [NNT] = 2; and thrice-weekly: 54% vs 6%; $P = .004$; NNT = 2).[3] There was no significant difference between twice- or thrice-weekly dosing. The study was flawed by dropouts (N = 57 at 15 days and N = 25 at 28 days), primarily attributed to ketamine adverse effects, that prevented assessment beyond 2 weeks.

Oral ketamine has a moderate effect on depression

A systematic review included 2 low-quality RCTs evaluating oral ketamine vs placebo as adjunctive treatment with sertraline, and oral ketamine vs diclofenac, and found improvement in patients with moderate depression.[4] In the first RCT (n = 45), researchers found that oral ketamine (25 mg bid) plus sertraline (25 mg titrated up to 150 mg/d) produced more treatment responses (> 50% reduction on a standardized depression rating scale) than placebo plus sertraline (2 weeks: 85.4% vs 42.5%; $P < .001$; 6 weeks: 85.4% vs 57.5%; $P = .005$).[4]

In the second RCT (n = 23), researchers randomized patients with mild-to-moderate depression and comorbid chronic headaches to take oral ketamine (50 mg tid) or oral diclofenac (50 mg tid) and measured effect size on standardized depression scores at 3 weeks (no difference) and 6 weeks (Cohen d effect size = 0.79 [rated as a moderate effect]; $P = .017$).[4]

Nasal esketamine + oral antidepressants boosts treatment response rates

A meta-analysis with 4 RCTs (N = 708) evaluating intranasal esketamine vs placebo as an adjunct to oral antidepressants for patients with predominantly treatment-resistant major depression found that it boosted response rates by about 40%. Researchers randomized patients to intranasal esketamine (mostly 28-84 mg twice weekly for 28 days) or placebo spray as an adjunct to oral antidepressants (duloxetine, escitalopram, sertraline, venlafaxine).

The primary outcomes were treatment response (≥ 50% reduction in depression scores) or remission (a MADRS score < 12). Adjunctive intranasal esketamine produced greater rates of treatment response compared to placebo at 24 hours (21% vs 7%; relative risk [RR] = 8.4; 95% CI, 1.4 to 21.2; $P < .02$; NNT = 7) and at 28 days (59% vs 43%; RR = 1.4; 95% CI, 1.2 to 1.60; $P < .0001$; NNT = 6).[5] Adjunctive intranasal esketamine also produced greater rates of remission at the end of the study (mostly at 28 days), compared with placebo (41% vs 25%; RR = 1.4; 95% CI, 1.2 to 1.7; $P = .0004$; NNT = 7).[5] The authors rated study quality as moderate to high.

Adverse effects are common, may cause Tx discontinuation

Ketamine-produced adverse effects (AEs) included confusion (2 trials; N = 76; OR = 3.7; 95% CI, 1.1-12) and emotional blunting (1 trial; N = 30; OR = 23; 95% CI, 1.1-489).[1]

A 2018 systematic review assessed the safety of ketamine in depression after single and repeated dose in 60 studies (N = 899; 20 RCTs, 17 open-label-trials, 20 case series, and 3 retrospective studies). The most common AEs reported were headache (35% of studies), dizziness (33%), dissociation (28%), elevated blood pressure (28%), and blurred vision (23%), with the majority reported to resolve shortly af-

ter administration. The most common psychiatric AE was anxiety (15%).[6] Included studies varied greatly in design and dosage form, and no meta-analysis could be performed.

Nasal esketamine produced more AEs causing discontinuation than did placebo (5.8% vs 1.5%; RR = 3.5; 95% CI, 1.34-8.9; number needed to harm [NNH] = 23), including blurred vision, dizziness, sedation, nausea, and dysphoria.[5]

A review (5 RCTs and 1 open-label trial; N = 1708) analyzing the cardiac safety profile of intranasal esketamine adjuvant therapy found that it produced transient and asymptomatic blood pressure elevations (OR = 3.2; 95% CI, 1.9-5.8; NNH = 13).[7]

Recommendations from others

A clinical practice guideline from the US Veterans Administration lists IV ketamine as 1 of the therapeutic options for patients with treatment-resistant depression and suicidal ideation.[8] However, a Department of Veterans Affairs Panel restricted its use to a preapproved case-by-case basis.[8]

Editor's takeaway

Physicians with patients facing the all-too-common problem of treatment-resistant major depression will be wondering if ketamine, either by itself or as an augmentation therapy, can help. Unfortunately, the outcomes we report here are too short term to answer that question, and we must await the results of further studies. Augmentation with intranasal esketamine, at a cost of $370/month, might offer some promise. JFP

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