See article by Vaccarino et al



# Ketamine and Cognitive Function in Depression:
## Detrimental, Neutral, or Advantageous?

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Cognitive function remains one of the lesser-appreciated outcomes in clinical intervention trials for mood disorders—despite the fact that impaired attention, executive function, and processing speed are commonly associated with depression.[1,2] Monoaminergic antidepressants have collectively shown modestly positive, though inconsistent, effects on cognitive function during treatment for major depression; effect sizes tend to be small, and domains other than psychomotor speed and delayed recall may not show appreciable impact.[3] The field has long sought to identify antidepressant interventions that can improve domains of cognitive function associated with depression, or at the very least spare any worsening of cognitive performance as often occurs with anticholinergic or antihistaminergic compounds.

In this issue of the *Journal*, the review of cognitive effects associated with ketamine treatment for major depression by Vaccarino et al[4] is especially timely and pertinent on several levels. First, interest in the use of ketamine as a novel intervention for treatment-resistant depression has grown enormously in the past few years: a MEDLINE search of the linked terms *major depression* and *ketamine* finds a tripling of annual citations from 2013 to the present, and currently there are over 200 worldwide studies related to *ketamine* and *depression* registered on ClinicalTrials.gov. Although the mechanisms of action of ketamine are diverse,[5] ketamine's effects on glutamate modulation via blockade of the *N*-methyl-D-aspartate (NMDA) receptor are still thought to contribute to its antidepressant efficacy; however, randomized trials with a number of other NMDA receptor antagonists in major depression (such as memantine, riluzole, or rapastinel) have yielded mixed results.[6] In principle, ketamine is believed to exert neuroprotective effects by stimulating synaptogenesis through neurotrophic pathways such as mammalian target of rapamycin (mTOR) in the prefrontal cortex.[7]

Second, despite enthusiasm about the aforementioned putative mechanistic actions, there has been little consistent information about whether ketamine is associated with predictably beneficial, detrimental, or neutral effects on cognitive function. Vaccarino et al[4] note from their review that, at present, the available data do not reveal a procognitive effect when ketamine is efficacious in the treatment of depression—although the absence of evidence does not prove the evidence of absence. No prospective trials with ketamine have, as yet, been conducted with cognitive function as a primary or coprimary outcome measure in major depression, limiting the ability to test the hypothesis that ketamine could improve cognition or assess whether an interaction may exist between improvement in depression and cognitive function. Herein lies a major methodological conundrum based on the existing literature: the available data preclude knowing when cognitive improvement (as has been noted in several open as well as randomized trials) might be a pseudospecific artifact of improvement from depression or when it might be a standalone consequence of ketamine, or whether there may be instances in which depression symptoms could improve but adverse cognitive effects nevertheless emerge iatrogenically (as often occurs after electroconvulsive therapy [ECT]). Dedicated studies are needed to parse these important distinctions, as was done in trials of vortioxetine in major depression (in which path analyses showed an independent procognitive drug effect while controlling for changes in depression symptoms over time).[8]

Third, and perhaps most compelling, are data separate from the present undertaking which show that patients who chronically abuse ketamine demonstrate deficits in executive function and visual/verbal memory as compared to healthy controls, who appear to recover after 12 weeks of abstinence from ketamine.[9] Neuroimaging studies among adolescent- and young adult–onset chronic ketamine abusers reveal decreased gray matter volume in a number of cortical and subcortical regions,[10] raising the question of whether, under certain conditions, high-frequency dosing of ketamine poses possible neurotoxic, rather than neuroprotective, effects. Note also that existing trials of intravenous (IV) ketamine in major depression generally focus on a dose of 0.5 mg/kg, with less known about the safety and efficacy of higher doses; it is hard to draw inferences about cognitive effects (either good or bad) from higher parenteral doses, or from variable oral doses taken by substance use disorder populations. Further complicating matters is the reality that most observational studies of patients who chronically abuse ketamine often include individuals who also use other illicit psychoactive substances.

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Pragmatic questions linger about the cognitive safety of long-term prescribed ketamine or esketamine for depression. Maintenance treatment with intranasal esketamine is standardly prescribed initially twice weekly and ultimately no more often than once or twice a month. In the US Food and Drug Administration registration trials for esketamine in major depression, secondary outcomes involving serial cognitive assessments were performed but have not yet been reported. While Vaccarino et al[4] found no evidence of adverse cognitive effects from a single ketamine infusion, multiple infusions (studied only up to 6 infusions over 2 weeks) in major depression patients, or use during ECT, little information exists about long-term frequent infusions—leaving unanswered the question of whether high frequency of administration could be a mediating factor that influences cognitive neutrality versus detriment. For parenteral racemic ketamine, no guideline exists for the use or duration of repeated long-term dosing, even though some practitioners advocate multiple infusions weekly over the course of several weeks.[11] The absence of long-term randomized data with IV ketamine limits the ability to anticipate the risk for long-term adverse cognitive effects. An additional pragmatic concern is that some clinicians, again on a purely anecdotal or theoretical basis and with no empirical trials database, sometimes advise the use of compounded oral ketamine lozenges between infusions as a possible strategy to buttress a sustained antidepressant effect. Apart from the low bioavailability of oral ketamine (about 10%–20%),[5] existing data to support meaningful antidepressant efficacy are mainly limited to retrospective reports, with none addressing cognitive safety.[12]

There is presently no guideline on the best management strategy for relapse prevention after an initial response to IV ketamine. No other NMDA antagonist or other pharmacology has shown a clear maintenance effect to sustain euthymia, understandably prompting many clinicians to analogize from the literature on maintenance ECT and advocate repeated maintenance ketamine infusions, following the general dictum of "what gets you well keeps you well." While long-term repeated ketamine infusions are increasingly becoming the norm to prevent relapse after a response in major depression, a formal database is urgently needed to evaluate the safety, efficacy, and optimal dosing frequency of repeated ketamine infusions in order for such well-intended practices to become evidence-based.

In sum, the review by Vaccarino et al[4] points out existing gaps in knowledge about the cognitive impact of ketamine in major depression, juxtaposed with potential adverse effects seen in substance abuse or healthy control populations. Their findings remind us of the many unknowns that remain regarding the safety of frequent repeated long-term infusions, the possible mediating effect of changes in depression on changes in cognition, concerns about subpopulations that may be at greater risk for adverse cognitive effects, and the need for properly designed long-term randomized trials focusing on cognition as a primary or coprimary outcome.

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