N-methyl-D-aspartate Glutamate Receptor Antagonists and the Promise of Rapid-Acting Antidepressants

THE EXCITING FINDings reported by Diazgranados and her collagues[1] regarding the antidepressant efficacy of the uncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine in depressed patients with bipolar disorder add to the emerging interest in rapid-acting antidepressants (RAAs).

Their article describes robust, clinically relevant, and rapid alleviation of depression symptoms in patients with bipolar disorder that persists far beyond the presence of the drug in the body. Ketamine has a terminal half-life of approximately 3 hours. Yet after 2 days, or 16 half-lives, of ketamine, the effect size of its antidepressant effects was large (0.8). Impressively, at 2 weeks

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there were still traces of the antidepressant effects of single ketamine dose, associated with an effect size of 0.22. Further, 6 of 17 patients had a clinical response to ketamine within 40 minutes of infusion and 9 of 16 patients experienced a remission of their depression during the study. The magnitude of these ketamine effects was particularly impressive because the changes were observed in patients who had treatment-resistant symptoms and who were already receiving mood-stabilizing medications. These data suggest that the benefits of ketamine in patients with bipolar disorder mirror those reported earlier for patients with unipolar depression.[2-4]

Given the limited antidepressant efficacy and the possibility of their accelerating mood cycling in patients with bipolar disorder,[5,6] the new findings could help to address an unmet need among patients. Further, consistent with earlier articles,[7,8] mood stabilizers may provide a measure of protection against transient psychotogenic ketamine effects. The high rates of comorbid alcohol abuse and dependence in this sample (44%) also may have influenced the reported findings. Individuals with a personal[9,10] or family[10] history of alcohol dependence show reduced dysphoric and psychotogenic responses to ketamine and superior antidepressant responses.[11]

In the small number of patients diagnosed with bipolar disorder and treated with lithium and valproate in this study, ketamine appeared to be relatively safe and well-tolerated. There was no evidence that ketamine increased mood cycling, worsened mood, or produced sustained psychosis but one must be cautious about drawing inferences about the safety of ketamine from this study. First, the patients were treated with lithium or valproate. Thus, the findings may not generalize to patients who are not treated with these mood-stabilizing medications or who are medication-free. Second, the sample size was too small to draw firm inferences about safety. Third, the follow-up period was too short to rule out the possibility of late-appearing effects on mood cycling. These safety concerns are important to bear in mind. Ketamine is a Food and Drug Administration–approved medication, and clinical practitioners may be tempted to apply the ketamine infusion approach with their patients before the full profile of risks and benefits are understood.

Perhaps the greatest challenge that emerges from these exciting data and from the prior ketamine studies is to conduct research that determines whether RAAs can play a role in routine treatment. These drugs hold the possibility of fundamentally changing the treatment of depression by creating the opportunity for rapid relief for patients in extreme need. If RAAs could be integrated into treatment safely and effectively, one might shorten or mitigate hospitalization, prevent lost work or school days, reduce suicide, reduce health care costs, and have other beneficial effects. Further, a growing array of RAA approaches, such as sleep deprivation and muscarinic receptor antagonism, may give those who provide treatment and patients with a number of options to achieve this end. Yet, none of these approaches has been studied sufficiently to incorporate into routine clinical practice. The questions that must be answered for ketamine apply to each of these other treatments are:

1. What is the optimal dose? It is possible that ketamine and other NMDA receptor antagonists will retain some antidepressant efficacy in doses that minimize their cognitive and perceptual effects. But it is also possible that the magnitude of antidepressant effect is dose-related and that optimal responses are seen at perceptual doses of ketamine. Inadequate dosing also may explain the lack of efficacy of memantine in a prior article.[12]

2. What is the optimal mode of ketamine administration? Ketamine may be administered via intravenous, intramuscular, oral, and intranasal routes, the less invasive administration approaches are more attractive for clinical practice.

3. Where should NMDA receptor antagonists be administered and

by whom? Intravenous ketamine administration may require additional training or the presence of medical support equipment to be conducted safely.

4. What is the best way to sustain the initial benefit? It appears that repeated doses of ketamine will sustain antidepressant responses but it is not clear whether or how to transition patients from NMDA receptor antagonists to other forms of treatment for long-term management of depression.

5. How do we identify patients who are most likely to benefit or most likely to have adverse reactions? This is a particularly important question because both ketamine and the muscarinic receptor antagonists are agents that have clear cognitive, behavioral, and physiologic effects.

6. What are the best ways to reduce NMDA receptor function? Several approaches have been proposed to retain ketamine's efficacy with a more favorable clinical profile including competitive NMDA receptor antagonists, subtype-specific NMDA receptor antagonists, drugs that target modulatory sites (glycine, polyamine, redox, etc) on NMDA receptors, and drugs that indirectly alter NMDA receptor function via signal transduction pathways.

7. Are there particular synergies or toxicities associated with combining NMDA receptor antagonists and other treatments? Combinatorial pharmacotherapy is the rule rather than the exception in clinical practice with chronically ill patients.

It seems that with ketamine and other RAA approaches, psychiatry has important new tools for probing the biology and treatment of depression. These findings raise our expectations for future treatments and highlight flaws in our current treatment approaches. Future research will be needed to determine if or how ketamine or other RAAs will be integrated into clinical practice.

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