A Word to the Wise About Ketamine

Recent reports of an acute antidepressant effect for intravenous ketamine, a schedule III agent used in anesthesia and pain clinics, have generated considerable hope and enthusiasm among both researchers and clinicians (1–4). The response partly reflects hope that a new mechanism of antidepressant action has been discovered and highlights the scarcity of agents that clinicians can administer to produce immediate effects on mood. Positive initial research reports (including the recent article in the *Journal* by Murrough et al. [4]) have unintentionally engendered growing off-label clinical use of ketamine in emergency rooms, specialty pain clinics and, most recently, free-standing private psychiatry clinics. If ketamine were a new drug, then the Food and Drug Administration would have required hundreds more patients to be rigorously studied before an approval for general distribution. However, because ketamine was already approved as an anesthetic, any physician can legally prescribe it. Some practitioners have even commissioned pharmacists to compound intranasal and other formulations. This unbridled enthusiasm needs to be tempered by a more rational and guarded perspective.

We Need To Know More About Acute and Longer-Term Efficacy and Risks

The data on clinical response to ketamine as an antidepressant are still relatively limited. The study by Murrough et al. (4) was the largest to date but still included only 47 patients treated with the drug. Will the data hold up in other controlled trials? The antidepressant effects of ketamine are generally short lived, lasting less than 1 week, although longer than its half-life. Unfortunately, to date we have no idea what we should do for follow-up therapy. In a recent report (3), repeated ketamine administration every few days appeared to be effective over a 2-week period with no clear tachyphylaxis to either the antidepressant or depersonalization effect, but that does not address what to do beyond 2 weeks, including dealing with the risk for dependence since ketamine is a drug of abuse.

Ketamine produces feelings of depersonalization and even psychosis (1–4), and it was previously used to test hypotheses regarding dopamine and glutamate in schizophrenia. In their study, Murrough et al. (4) undertook stringent patient evaluations to decrease the risk of psychotic reactions, but such evaluations may not be occurring in other settings. Clinicians outside a research setting generally do not have the resources to screen patients similarly.

We Need To Know More About the Mechanism of Action of the Mood-Elevating Effects

The antidepressant effect has been thought to reflect ketamine's glutamatergic properties, specifically its blocking of *N*-methyl-D-aspartic acid (NMDA) receptors, which should be a clue for follow-up therapy. However, other currently available agents (covering a variety of glutamatergic actions) have proven unsuccessful in antidepressant trials either as monotherapy or in combination with ketamine (5–7). Investigational agents have been mixed in their effects, with glycine partial or full agonists that act essentially as NMDA agonists also being effective for depression (unpublished 2012 report by R.M. Burch; 8, 9). This suggests

that NMDA antagonism may not be the primary mechanism of action for ketamine in major depression. Recent reports have indicated that ketamine has effects on intracelluar mTor that could account for its antidepressant properties (10).

Stimulants and opiates have long been associated with short-term, although generally clinically ineffective, therapeutic effects and problems with abuse. Ketamine has both opiate and stimulant effects (11, 12). It is a strong promoter of catecholamine, particularly dopamine, turnover (12), and its monoaminergic properties are similar to cocaine or amphetamine. Ketamine also has mu opioid receptor properties, consistent with its use for anesthesia and treatment of pain. This mechanism may be similar to the antidepressant effects of buprenorphine (13), although a study in healthy individuals did indicate that the effects of ketamine on responses to alcohol were not blocked by the mu antagonist naltrexone (14). To our knowledge, such a study has not been conducted in depressed patients. It is interesting that Rodriguez et al. (15) recently reported that ketamine given intravenously was similarly effective in refractory obsessive-compulsive disorder (OCD). This was reminiscent of a double-blind, placebo-controlled study by Koran et al. (16) a few years ago that reported that oral morphine improved OCD symptoms 1 day after administration—an effect that lasted 5 days. Comparison studies against stimulants and opioids would be helpful for assessing ketamine's mechanism of action for acutely elevating mood and its potential for providing overall benefit in the treatment of depression.

Until we know more, clinicians should be wary about embarking on a slippery ketamine slope.

Should Clinicians Prescribe Ketamine for Patients With Refractory Depression?

Without more data on what ketamine can do clinically, except to produce brief euphoriant effects after acute administration, and knowing it can be a drug of abuse, it is difficult to argue that patients should receive an acute trial of ketamine for refractory depression. Some ketamine investigators have argued for not using it outside of a hospital setting (17), but without extensive experience and a follow-up strategy, is even that the most prudent strategy? I would argue that waiting until we understand more about its effects and risks makes most sense. Patients have not benefitted in the past from the overuse of short-term treatments such as stimulants and opiates. The results have been toxicity and dependence from the immediate treatment and a failure to recommend and follow through with more definitive longer-term treatments required for patients with depression. The recent ketamine studies are exciting, and they open up important avenues for investigation that should be supported; however, until we know more, clinicians should be wary about embarking on a slippery ketamine slope.

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