Medical News & Perspectives

Ketamine Minus the Trip: New Hope for Treatment-Resistant Depression

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In 2006, psychiatrist Carlos A. Zarate Jr, MD, and colleagues at the National Institute of Mental Health (NIMH) published a seminal finding in *Archives of General Psychiatry* (now *JAMA Psychiatry*): A single intravenous dose of ketamine—an anesthetic agent with hallucinogenic properties—produced robust antidepressant effects in patients with treatment-resistant depression (TRD) compared with placebo. The effects of the glutamatergic modulator were observed within 2 hours, far sooner than selective serotonin reuptake inhibitors (SSRIs), and persisted for a week.

Author Audio Interview

The discovery not only demonstrated ketamine's powerful effect on intractable depression, but also spurred the development of more targeted drugs to mimic its benefits without its hallucinogenic and adverse effects. Ketamine—known by recreational users as "Special K," among other street names—is a schedule III controlled substance with a risk of dependence.

Today, intravenous ketamine is increasingly being used off-label to treat TRD and other mood disorders in academic medical centers and standalone clinics around the country. "For those patients who have tried existing treatment options, have gone through [many] antidepressants that were appropriately dosed and adequate in duration, have tried the talk therapies and even electroconvulsive therapy [ECT], I can see the need and the urgency of wanting to try other treatment options," Zarate said.

A recent consensus statement from an American Psychiatric Association task force found "compelling evidence" of the antidepressant effects of ketamine infusion but highlighted gaps in knowledge guiding its use. Chief among the task force's concerns: Ketamine's long-term safety and durability have not been studied in large-scale clinical trials.

"We have very few guidelines on what is the best way to administer ketamine," Zarate said. "Hopefully more longer-term studies will be conducted to help us sort that out."

As physicians await more data, scientists are developing other glutamatergic modulators targeting depression, with 5 of these agents currently in phase 2 or 3 clinical trials. Depending on the results of those studies, Zarate said intranasal esketamine could become available as soon as 2019 for TRD and major depressive disorder (MDD) with imminent risk of suicide. Intravenous rapastinel could follow for use in adjunctive treatment of treatment-resistant MDD.

These days, Zarate heads up research in experimental therapeutics for depression and bipolar disorder at the NIMH. He recently spoke with *JAMA* about ketamine, new investigational ketamine-like agents, and the future of depression treatment. The following is an edited version of the interview.

National Institutes of Health

Carlos A. Zarate Jr, MD, (left) Chief of Experimental Therapeutics and Pathophysiology Branch and Section on the Neurobiology and Treatment of Mood Disorders at the NIMH.

JAMA: Why do we need new medications for depression?

DR ZARATE: Although we have a number of medications, they work exclusively on the monoamine neurotransmitter system—that's serotonin, norepinephrine, and dopamine. Unfortunately, these medications do not benefit many. We see very low response and remission rates. It's estimated that only about one-third remit, [and remission] usually takes approximately 10 to 12 weeks.

JAMA: Tell us the story of ketamine and depression. How did scientists hit upon the idea of using a hallucinogen to treat a mood disorder in the first place?

DR ZARATE: The theory goes back several decades. Basic scientists back then wanted to figure out better ways of treating our patients, so in preclinical studies

they examined not only the effects of monoaminergic antidepressants, but what other systems were also implicated. These earlier investigators noted that there were subtle effects [in models of depression] on NMDA [*N*-methyl-D-aspartate] and AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid] receptors, which are glutamate receptors.

The glutamate system is very important in learning, in memory, in plasticity, and other important functions of the brain. It's believed that glutamate is dysregulated [in] the circuits and synapses that are implicated in depression.

When glutamate is released, it activates the NMDA receptor complex. Ketamine blocks this NMDA receptor. It is hypothesized that this blocking of the NMDA receptor on GABA [γ-aminobutyric acid] interneurons leads to an increased release of glutamate from pyramidal cells. That increased release of glutamate—what we refer to now as the glutamate burst—preferentially [activates] AMPA receptors, [which] leads to an increase in BDNF, or brain-derived neurotrophic factor, a protein in the brain that's been implicated in the response to many different antidepressants. BDNF restores or produces an increase in synaptogenesis and plasticity and other mechanisms that are an important part [in maintaining] homeostatic regulation [of key brain functions].

JAMA: What do we know about the effectiveness of ketamine for depression?

DR ZARATE: There have now been many published clinical trials, and most of them have found that it is effective in treatment-resistant depression. The response and remission rates within a very short period of time are pretty prominent. It is efficacious even in treatment-resistant depression, meaning patients that have failed multiple antidepressants, and in many cases electroconvulsive therapy, which is one of the most effective treatments. And ketamine is efficacious in treatment-resistant bipolar depression, for which, unfortunately, we have very few treatment options. Further clinical research suggests that ketamine does have—although this is preliminary—very rapid antisuicidal efficacy and seems to have effects on anhedonia.

JAMA: You're among the researchers who are studying other glutamatergic modulators for depression. Why pursue these likely more expensive therapies when we could just use ketamine?

DR ZARATE: Ketamine, unfortunately, has certain limitations. When ketamine is administered intravenously, we see dose-related side effects, such as psychotomimetic and dissociative side effects. For example, one might experience a distortion of time, one might see trails of light or hear muffled sounds. There are also effects that result in transient elevations in blood pressure and heart rate, temporary impairments of cognition. There is the risk, with continued indiscriminate use, of hepatotoxicity and also reports that it might lead to a cystitis. In terms of oral administration, it's poorly absorbed. So although it will likely have an important clinical use in people with treatment-resistant depression, it would be very important to come up with drugs that are better tolerated [that] one can even give in people who do not have treatment-resistant depression. Newer treatments would also not have the risk of abuse potential that occurs with ketamine.

JAMA: Are other agents that are in development based on the same mechanism of action as ketamine?

DR ZARATE: The original preclinical evidence linking the NMDA receptor blocking or antagonism has led to a decade of preclinical and clinical studies with NMDA receptor antagonists, with the hopes of achieving the rapid antidepressant effects of ketamine, but without the side effects or risk of abuse. [But] the efforts to develop better or alternate versions of ketamine have been fraught with many difficulties from the start. Several broad and subunit selective receptor antagonists either failed or did not demonstrate the efficacy in treatment-resistant depression, or showed minimal efficacy. This has led to questions about whether preclinical studies [that] demonstrated the promise of NMDA receptor antagonism will actually lead to better treatments. So with that in mind, additional targets have been looked at in terms of its mechanism of action and some postulate that enhanced AMPA receptor throughput might be implicated in rapid antidepressant-acting agents.

For instance, there is a drug called rapastinel, an NMDA receptor modulator, [that] seems to have rapid antidepressant effects with a better side effect profile [than ketamine] that is currently being developed in treatment-resistant depression. Preclinical studies suggest that it also activates AMPA receptors.

There is another [NMDA receptor modulator] called AV-101. It seems to block the glycine site that is outside of the NMDA receptor channel. AV-101 is currently in the clinic and is being tested for treatment-resistant depression. Animal studies suggest it would have acute, rapid antidepressant effects, and without the side effects of ketamine.

Building on this work, our group in collaboration with other laboratories began to explore the cellular and molecular effects of ketamine, and we have found that the effects appear to be largely NMDA-receptor independent. Blocking an NMDA receptor appears to be linked to the side effects of dissociation and to the increases of blood pressure, and potentially to the abuse potential.

JAMA: What about esketamine?

DR ZARATE: The current form of ketamine is what we call racemic ketamine. That means it's formed by 2 isomers; enantiomers R [arketamine] and S [esketamine]. We have known for many years now that esketamine is much more potent as an anesthetic analgesic agent than arketamine. [Esketamine] is now being developed for intranasal use. You could have fewer side effects. It's currently in phase 3 studies. The phase 2 studies have been encouraging, showing that intranasal esketamine produces rapid antidepressant [effects], and suggests antisuicidal ideation effects, as well.

JAMA: Do you think these agents will potentially change the landscape of depression and treatment?

DR ZARATE: The mere fact of having rapid-acting agents would minimize the cumulative time ill—that is time that our patients spend in depression—thus minimizing the consequences of unremitting depression. And, in theory, [they] would minimize the impact of depression on brain and body health because depression not only has effects on brain, but it does have significant effects on body that are deleterious either by altering immune or inflammatory functions. So a rapid-acting

agent that is robust will get our patients back to their lives with minimal disruption and hopefully restore hope.

JAMA: Could these agents even potentially replace SSRIs?

DR ZARATE: That's a very good question. Because of its side effect profile and its risk for abuse, it would be very hard to bring ketamine earlier into the decision tree—that is, when somebody's experiencing their first or second episode of depression. But imagine if you were to have a ketamine without the abuse potential or the side effects. Very early, within the first episode of depression, or even [the] second, one could probably intervene. Some people have dozens of major depressive episodes that wipe away years of optimal function and ability to work, to contribute to society, have a family. Then imagine you're intervening very early in depression. You will eliminate all that time ill.

JAMA: Are there any other hallucinogens that you're interested in?

DR ZARATE: We are carefully following the wonderful work by our colleagues around the world. Ayahuasca, for example, is being reported to have rapid antidepressant effects and to be useful for treatment-resistant depression. Psilocybin [is] out there as well. LSD [lysergic acid diethylamide] for either PTSD [posttraumatic stress disorder] or anxiety. MDMA or ecstasy is another one. In a controlled research setting, we may be able to study patients or individuals who are exposed to these [agents] using brain imaging or other techniques to see what precisely they do in the brain. So I'm in favor of trying to learn as much [as we can], but as long as it's ethically and safely done.

JAMA: Is there a way to sum up why hallucinogens may help for psychiatric conditions?

DR ZARATE: Some have suggested that [they] turn on or off certain circuits at the precise and important time. Some have used the lay term of *rebooting* the brain. And you can imagine that maybe certain circuits have been stuck and functioning in the wrong manner, but treatments such as hallucinogens, electroconvulsive therapy, scopolamine—which is another treatment [that] seems to have effects in depression—ketamine, might temporarily reboot certain aspects of the brain function at specific circuits. It seems that plasticity and connectivity might be very important aspects of how these drugs might work. Whether they do it in a similar way or dissimilar way, we don't know yet. ■

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