

Treating depression—an expert discusses risks, benefits of ketamine

20 October 2017, by Jenny Chen

Up to a third of patients with depression don't respond to traditional forms of treatment. For those patients, the dark fog that hovers over their lives feels like it will never lift. But a new treatment called ketamine has recently made waves all over the internet. Hailed as a "miracle drug" and the first major antidepressant breakthrough in three decades, ketamine has improved the lives of many patients whose depression had dominated their lives for years. And yet, many of these articles also convey a note of skepticism. That's because ketamine is also a street drug, a popular hallucinogenic known as "special K."

Since the 1990s, doctors at Yale Medicine have led research into the use of [ketamine](#) as an antidepressant. We sat down to talk to one of them—Gerard Sanacora, MD, PhD—to learn exactly why ketamine is so helpful for people with severe depression, ask what patients and doctors should be cautious about, and hear about possible future applications for the drug.

People are calling ketamine one of the biggest breakthroughs in depression research. Can you tell us what the big deal is?

There are a couple of factors that make ketamine unique. Ketamine works really quickly—within a few hours—whereas other drugs might take a few weeks to take effect. This is important because we know that the longer someone stays in a depressive state, the higher chance they might do something to harm themselves. Ketamine also seems to work for patients who haven't benefitted from classic antidepressant medications. The most rewarding thing for me, as a doctor, is seeing severely depressed patients who have failed multiple treatments experience changes on the same day they start this new drug. We have several patients who were able to go back to work after several months of being on disability. That's very exciting.

The other treatment doctors prescribe for treatment-resistant depression is electroconvulsive therapy. How does ketamine compare?

Ketamine seems very promising because of all the studies that have shown results in patients with difficult to treat depression but it's a little too early to compare the two. One thing to note is that people who undergo electroconvulsive therapy might have to get ketamine as an anesthetic anyway, so if ketamine itself at higher doses can do the trick, it might be a more attractive alternative. We're actually doing a study right now to compare the two treatments head to head.

What's the biological reason why ketamine works?

We're not entirely sure yet, but we think that it helps regenerate synaptic connections between brain cells damaged by stress and depression. Currently, we're looking at how talk therapy might work in conjunction with ketamine, since it helps patients create new neural pathways for positive thought patterns, for long-term change.

OK, so why isn't ketamine a widely-prescribed treatment yet? What are the potential drawbacks?

First of all, ketamine is not an FDA-approved [treatment](#) for depression. We still need more evaluation and research. Plus, even though studies show that it's effective on 40 to 60 percent of patients, we really don't know what the long-term effects of the drug are. In animal models, there's evidence that ketamine can have toxic effects on the brain if used early in life, and that repeated dosing at a high level can cause changes in the brain structure. Plus, there are potential cardiovascular and behavioral side effects.

Ketamine is also a drug of abuse. It's known as

"special K" on the streets and it's the No. 1 club drug in some Asian countries. I've never seen our patients receiving controlled ketamine administrations for the treatment of depression turn into a ketamine abuser, but we have to be careful about regulating the drug, so that it doesn't end up in the hands of people who don't need it.

What's a common misconception people have about ketamine as a treatment for depression?

A lot of people who read about ketamine think that it's a medication you take every day, like the kind you might take for your blood pressure. But it's not. It's a powerful drug that should only be administered by medical professionals. It can really have significant effects on physiological and psychological functioning and you can't drive for 24 hours. What's more, there's no published evidence that taking ketamine on regular basis is effective.

Is ketamine safe or effective for children with depression?

The research on ketamine for kids with depression is even more nascent than the research on its effects on adults, but we are looking into it. Earlier this year, researchers at the Yale Child Study Center published one of the first case studies on the effects of ketamine for depression in adolescents. The study followed a 16-year-old boy who had attempted suicide three times. After repeated ketamine infusions, his depressive symptoms reduced and he no longer had suicidal thoughts. The study was led by Michael Bloch, MD. But just like with adults, ketamine should only be used for certain pediatric patients who have severe mental health problems that have not responded to other medications. It's not a first line treatment option. Right now, we are conducting a randomized controlled trial of ketamine with 18 teens diagnosed with [major depressive disorder](#) who have failed at least one adequate trial of a traditional antidepressant.

When did Yale start researching ketamine?

In the late 1990s, John Krystal, MD, now the chair of psychiatry at Yale, and other investigators were using ketamine to study how the neurotransmitter

glutamate could contribute to symptoms of schizophrenia in healthy subjects. He started thinking about how glutamate might also play a role in depression. This was new, because previous research had only really looked at chemicals like serotonin and norepinephrine. It turns out that the system in the brain that uses glutamate and causes schizophrenic-like symptoms might contribute to the neurobiology of depression. In a seminal study, Dr. Krystal discovered that ketamine produced a rapid antidepressant effect in patients with major depressive disorder and published a now widely cited paper describing the findings.

How did you get involved?

At the time, I had been working on other studies that showed abnormal levels of the amino acid neurotransmitters GABA and glutamate in the brains of patients with [severe depression](#). My findings, combined with Dr. Krystal's discovery of ketamine's rapid antidepressant effects, convinced me that the glutamatergic system (what we call the system that involves both GABA and glutamate) could be an important focus for new antidepressant research. That's when our lab started investigating how ketamine and other drugs affect glutamate levels in the brains in people with depression.

Is Yale Medicine running clinical trials to investigate ketamine? If so, what are they?

Yes, we are. Currently, we're running clinical trials that look at the clinical effectiveness and longer-term safety of ketamine and the related drug, esketamine, in the treatment of depression. As we've already talked about, we have studies comparing the effectiveness of ketamine to electroconvulsive therapy for patients with major depressive disorder. We are also one of the medical institutions participating in a large study looking at the ability of esketamine to rapidly treat the symptoms of [depression](#) in patients with troubling suicidal thoughts. In addition to those clinical trials we also are collaborating on several studies looking at exactly how and why ketamine works for depressed patients.

What does the future look like for ketamine?

Depending on the results of the ongoing [clinical trials](#), it's quite possible that we will see more medical institutions offering ketamine as a treatment. We're also likely to see the FDA approve the use of esketamine in the near future. These are all very exciting prospects. In the meantime, we have been offering ketamine treatment to selected [patients](#) outside of research protocols when appropriate at the Interventional Psychiatry Service at Yale New Haven Psychiatric Hospital.

Provided by Yale University

APA citation: Treating depression—an expert discusses risks, benefits of ketamine (2017, October 20) retrieved 26 August 2022 from <https://medicalxpress.com/news/2017-10-depressionan-expert-discusses-benefits-ketamine.html>

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