Plus

K for OCD

The pros and cons of ketamine

By Tracie White
Illustration by Kotryna Zukauskaite

Geuris "Jerry" Rivas, a native of New York, was diagnosed with severe obsessive-compulsive disorder when he was 15. Obsessions with organizing and reorganizing the belongings in his bedroom — posters, comic books, videos — took over most of his life.

Forced by germ obsessions to compulsively wash and rewash his hands, he started wearing gloves all day to both protect him from the germs and stop him from washing his hands raw. Now, at 36, OCD symptoms continue to cost him jobs and relationships. He's managed to turn his organizational skills into a profession — he's a home organizer and house cleaner — but still he struggles daily with his obsessions.

"It's caused me a great deal of suffering," Rivas says. "I've tried many, many medications. I've wasted so much of my life."

In 2012, running out of answers, Rivas took part in the first clinical trial to test ketamine as a treatment for OCD. While ketamine is approved by the U.S. Food and Drug Administration as an anesthetic, it is also an illicit party drug known as "Special K," with hallucinogenic effects and the potential for abuse. Over the past 10 years, dozens of small studies of ketamine's ability to treat a variety of mood and anxiety disorders have reported remarkable results — including the sudden alleviation of treatment-resistant depression, bipolar disorder and post-traumatic stress disorder. And these effects lasted days, sometimes weeks, after the hallucinogenic effects of the drug wore off.

With a single infusion of the drug, Rivas experienced for two weeks what it was like to live without the compulsions and obsessions that had for years controlled his life.

"I felt like, for the first time, I was able to function like a regular person," he says.

Pros and cons

Ketamine has brought hope to a psychiatric field desperate to find new treatments for severe OCD, a chronic condition marked by debilitating obsessions and repetitive behaviors. Current treatments, which include antidepressants such as Prozac, can take months to have any effect on the disease, if they work at all.

(/content/dam/sm/stanmed/images/20

Kotryna Zukauskaite

"Severe OCD takes such a toll on patients," says Carolyn Rodriguez (https://med.stanford.edu/profiles/carolyn-rodriguez), MD, PhD, who as a researcher at Columbia University ran the OCD trial. Now an assistant professor of psychiatry and behavioral sciences at Stanford, she has continued to explore the pros and cons of using ketamine to treat OCD. "The constant, intrusive thoughts that something is contaminated, the checking and rechecking, the repetitive behaviors. It interferes with your life, your jobs, your relationships."

Ketamine was developed in the 1960s and has been used for decades as an anesthetic during surgery. It remains a mystery just how the drug works in the brain, and there are safety concerns. There is evidence from people who take the drug routinely — in much higher doses — that chronic, high-frequency ketamine use may be associated with increased risk of bladder inflammation and cognitive impairment, Rodriguez says. And if taken regularly, it can lead to dependence.

But researchers like Rodriguez are intrigued about the drug's potential to help them identify a whole new line of medicines for fast-acting treatment of mental health disorders.

"What most excites me about ketamine is that it works in a different way than traditional antidepressants," Rodriguez says. "Using ketamine, we hope to understand the neurobiology that could lead to safe, fast-acting treatments. I feel that is part of my mission as a physician and researcher."

'Right out of a movie'

Rodriguez's interest in ketamine as a treatment for OCD was sparked about a decade ago when she was starting out as a research scientist at Columbia. A small, placebo-controlled study published in 2006 by a mentor of hers, Carlos Zarate (https://www.nimh.nih.gov/labs-at-nimh/principal-investigators/carlos-

zarate.shtml), MD, now chief of the section on neurobiology and treatment of mood disorders at the National Institute of Mental Health (https://www.nimh.nih.gov/index.shtml), had shown that ketamine induced dramatic improvement in treatment-resistant depression within two hours of infusion. It was a landmark study, drawing attention among the psychiatric community and launching a new field of research into the use of ketamine to treat various mood and anxiety disorders.

"What most excites me about ketamine is that it works in a different way than traditional antidepressants."

Rodriguez, intent on searching for better, faster treatments for her patients like Rivas with OCD, took note. There was an emerging theory that ketamine affects the levels of the neurotransmitter glutamate in the brain and increasing evidence that glutamate plays a role in OCD symptoms, she says. Perhaps ketamine could help regulate OCD symptoms as well as depression.

In 2013, Rodriguez and colleagues published their results from that first clinical trial of ketamine in OCD patients. The trial randomized 15 patients with OCD to ketamine or placebo.

In those patients who were given ketamine, the effect was immediate. Patients reported dramatic decreases in their obsessive-compulsive symptoms midway through the 40-minute infusion, according to the study. The diminished symptoms lasted throughout the following week in half of the patients. Most striking were comments by the patients quoted in the study: “I tried to have OCD thoughts, but I couldn’t,” said one. Another said, “I feel as if the weight of OCD has been lifted.” A third said, “I don’t have any intrusive thoughts. ... This is amazing, unbelievable. This is right out of a movie.” And while nearly all initially had dissociative effects like feelings of unreality, distortions of time or hallucinations, they were gone within two hours after the start of the infusion.

“Carolyn’s study was quite exciting,” Zarate says, adding that there were a number of similar, small but rigorous studies following his 2006 study that found fast-acting results using ketamine to treat bipolar disorder and post-traumatic stress disorder.

“We had no reason to believe that ketamine could wipe out any symptoms of these disorders within hours or days,” he says.

So how does it work?

Virtually all of the antidepressants used in the past 60 years work the same way: by raising levels of serotonin or one or two other neurotransmitters. Ketamine, however, doesn't affect serotonin levels. Exactly what it does remains unclear.

"There's a recognition that people like me and others are using the drug to treat patients now. There's an incredible need for something."

Since coming to Stanford in 2015, Rodriguez has been funded by the National Institute of Mental Health for a large clinical trial of ketamine's effects on OCD. This five-year trial aims to follow 90 OCD patients for as long as six months after they've been given a dose of ketamine or an alternative drug. Rodriguez and her research team want to observe how ketamine changes participants' brains, as well as test for side effects.

Ultimately, Rodriguez says, she hopes the study will lead to the discovery of other fast-acting drugs that work in the brain like ketamine but without its addictive potential.

Recent research in the field indicates that the glutamate hypothesis that triggered her pilot study might be further refined.

"Ketamine is a complicated drug that works on many different receptor sites," she says. "Researchers have fixated on the NMDA receptor, one of the glutamate-type receptors, but it might not be the only receptor bringing benefit."

In May 2016, researchers from NIMH and the University of Maryland — Zarate among them — published a study conducted in mice showing that a chemical byproduct, or metabolite, created as the body breaks down ketamine might hold the secret to its rapid antidepressant actions. This metabolite, hydroxynorketamine, reversed depressionlike symptoms in mice without triggering any of the anesthetic, dissociative or addictive side effects associated with ketamine, Zarate says.

"Ideally, we'd like to test hydroxynorketamine and possibly other drugs that act on glutamate pathways without ketamine-like side effects as possible alternatives to ketamine in OCD," Rodriguez says.

Beyond the clubs

Meanwhile, dozens of commercial ketamine clinics have popped up across the country, making treatments available to patients who are searching for help to stop their suffering now. Medical insurance companies usually cover ketamine's FDA-

approved use as an anesthetic but won't cover its use for other purposes, such as mental health disorders. So patients who have run out of treatment options are paying hundreds of dollars a dose for repeated ketamine infusions.

"The fact that these clinics exist is due to the desperation of patients," says Rodriguez.

She and other researchers are calling for guidelines to protect patients and more research to learn how to use the drug safely.

"I think it's a game changer, and it's here to stay," says David Feifel, MD, PhD, professor emeritus of psychiatry at UC-San Diego, who studies the effect of ketamine on clinical depression. Feifel began prescribing the drug for patients with treatment-resistant depression in 2010.

"I've found it to be very safe," Feifel says, adding that the American Psychiatric Association this year issued safety guidelines on how to use ketamine clinically for treatment of depression.

"There's a recognition that people like me and others are using the drug to treat patients now," he says. "There's an incredible need for something."

The drug hasn't worked for everyone he's treated, Feifel says, but for many it's been "life-changing."

Rodriguez says she understands what motivates the clinicians to prescribe the drug now to patients in dire straits — those who are suicidal or who have tried every possible medication and therapeutic option and continue to suffer each day.

"I see it as a way to treat people whose OCD is very, very severe," she says. "People who can't come out of the house, who are suicidal, who have no other options.

"I just don't like the idea of people being in pain," Rodriguez adds. "I want to see science translated into treatments now."

Meanwhile, researchers are learning more about the drug. Janssen Pharmaceutical is testing the efficacy of a version of ketamine, known as esketamine, as a therapy for treatment-resistant depression and for major depressive disorder with imminent risk for suicide. The FDA has fast-tracked both investigations. At Stanford, Alan Schatzberg, MD, a professor of psychiatry and behavioral sciences, along with other faculty including Rodriguez, is studying the mechanism of action for ketamine in treating depression.

Rodriguez is also interested in using ketamine to kick-start a type of cognitive behavioral therapy called exposure and response prevention, an evidence-based psychological treatment designed to help patients overcome OCD. The therapy involves teaching patients with OCD to face anxieties by refraining from ritualizing behaviors, then progressing to more challenging anxieties as they experience success.

Relaxation and other techniques also help patients tolerate their anxiety — for example, postponing the compulsion to wash their hands for at least 30 minutes, then extending that time period.

"My goal isn't to have people taking ketamine for long periods of time," Rodriguez says. But perhaps a short-term course of ketamine could provide its own kind of exposure and response prevention by allowing patients to experience that it is possible not to be controlled by their OCD, she says.

Rivas well remembers that infusion of ketamine he received during Rodriguez's first clinical trial to test the drug. The rush made him feel "like Superman."

"I felt like my body was bigger, that I was more muscular, that I could tackle anything," he says. But that feeling only lasted the duration of the 40-minute infusion. His OCD symptoms disappeared immediately and were still gone for two weeks after.

"I was amazed that something like that would work and work so fast," he says. His OCD symptoms today are still intrusive, but he manages to keep them under control by taking antidepressants and seeing a therapist. Still, each day when he comes home from work, he has to put gloves on before he enters his apartment building, and as soon as he enters his apartment, he must wash his hands.

"It's a ritual now," he says. "There has never been a time that I haven't done that, except those two weeks after the ketamine."

When he heard that certain private ketamine clinics are now offering the drug as treatment for OCD, he said he understands why patients take the risks and pay the high prices. As more research has become available, he's begun considering it himself.

"I've been suffering through my OCD for so long, I've gotten to the point where I'd try anything," he says.

USING KETAMINE TO TREAT SEVERE MENTAL ILLNESS

A conversation with Stanford psychiatrist Carolyn Rodriguez, MD, PhD, about how she got interested in the use of ketamine to treat obsessive-compulsive disorder and how she is determined to find out why, in studies, the drug has provided relief from symptoms.