A Trip Out of **Depression**

KETAMINE, AN ANESTHETIC AND ILLICIT PARTY DRUG, IS EMERGING AS A FAST-ACTING ANTIDEPRESSANT

BY SIMONE GRIMM AND MILAN SCHEIDEGGER

ILLUSTRATION BY PETER HORVATH

For 20 years Joan* quietly suffered from an unrelenting desire to commit suicide. She held down a job as a special-education teacher and helped care for her family in the northeastern U.S. Yet day after day she struggled through a crushing depression and felt neither joy nor pleasure. Except for the stream of psychiatrists recommending different antidepression treatments—all of which failed to provide relief—Joan kept her condition private. She says it was the fear of hurting her students or abandoning her father that kept her alive. "I really don't know how I survived," she says.

**A pseudonym to protect the patient's privacy.*

The sense of dissociation that a large dose of ketamine can generate has made it a popular recreational drug.

GETTY IMAGES

A few years ago Joan got a break. She came across a clinical trial for a drug called ketamine that had succeeded in treating patients with intractable major depressive disorder. She enlisted. Following one dose, she experienced her first reprieve from suicidal thoughts in two decades. She realized the drug was working while she was sitting outside on a pleasant day and noticed that the leaves on a tree looked bright green and that a spider was building a web. "It sounds crazy, but normally everything was clouded and gray," she says. "Nothing stirred me."

Depression ranks among the most prevalent psychiatric conditions in the U.S. Research from 2008 suggests that approximately 14.3 million, or 6.4 percent, of American adults experience a major depressive episode in a given year. Only about half the people who try antidepressant drugs respond to them, however. When they do, several weeks or even months may elapse before a patient experiences relief, a critical failing for people at immediate risk for suicide. Ketamine, in contrast, appears to ease the most severe symptoms of depression within minutes or hours, even in patients who have a dismal track record with other treatments. The effects of a single dose can last at least a week in some patients.

Ketamine's promise has ignited excitement, as well as controversy, among clinicians and neuroscientists for the past several years. A Schedule III drug under the Controlled Substances Act, ketamine—commercially sold as Ketalar—is primarily used as

FAST FACTS

Defeating Depression

1» Ketamine is an analgesic, an anesthetic and a hallucinogen—yet the drug also seems to alleviate depression.

2» More commonly known as a party drug, ketamine changes the neurotransmitter balance in the brain, thereby affecting consciousness.

3» Deciphering ketamine's mechanism of action could pave the way for a new generation of antidepressants.

The **speedy relief** of ketamine sets it apart from typical antidepressants, as does **the way it interacts** with the brain.

an anesthetic in veterinarian medicine, particularly for horses, and as a short-term anesthetic and analgesic in hospitals during surgery or other painful procedures. The U.S. Food and Drug Administration has not approved it for treating depression, because its side effects can be harmful. The speedy relief it offers, however, sets it apart from typical antidepressants, as does the way it interacts with the brain. These factors combined have made ketamine a rising star in the world of depression research.

Rave Reviews

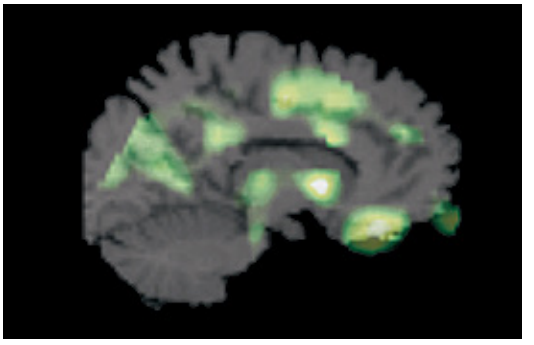
Ketamine was originally synthesized in the 1960s as an alternative to phencyclidine, more commonly known as PCP or "angel dust." Anecdotal reports of ketamine's mood-enhancing action have circulated in the medical community for more than 20 years. At the same time, it developed a growing reputation as a "rave" drug, with effects similar to the psychoactive drug ecstasy. Depending on the dose, a person taking ketamine may experience altered physical, spatial and temporal states; larger quantities may induce hallucinations and dissolution of the self.

The first controlled study of ketamine for treating depression was conducted in 2006 by psychiatrist Carlos A. Zarate, Jr., and his colleagues at the National Institute of Mental Health. They intravenously administered either ketamine or a saline solution to 17 severely depressed patients. On average, the participants had already tried six different antidepression regimens without success.

The outcomes exceeded all expectations. For half the patients, symptoms of depression dropped by 50 percent within two hours. By the end of the first day, 71 percent of the patients had responded to the drug—a third of them were virtually free of symptoms. Some of the study participants continued to feel relief from that single dose of ketamine for at least a week. "To our knowledge, there has never been a report of any other drug or somatic treatment that results in such a dramatic, rapid and prolonged response with a single administration," says lead investigator Zarate.

The researchers had similar success with patients suffering from bipolar disorder who were given ketamine during a depressive phase of their illness. Last year Zarate and his team published a study showing that thoughts of suicide decreased rapidly in these patients a mere 40 minutes after receiving a short intravenous infusion of the drug. The positive effect lasted for up to three days and was experienced by 79 percent of the treated test patients.

Yet the work is still new, and the drug needs to be tested in many more patients to verify the findings so far. The results of different ketamine studies have varied widely, ranging from a positive response rate as low as 25 percent to as high as 85 percent one day after a ketamine infusion. Part of the ambiguity may arise from the difficulty of designing a convincing control group for an experiment. During a ketamine infusion, patients immediately feel dissociated and drugged, so the challenge is to keep them unaware of whether they are receiving ketamine or a placebo. Psychiatrist James Murrough of Mount Sinai Hospital says studies are in the works in which some patients will receive a placebo that causes a temporary reaction that simulates the effects of ketamine.



Moderate doses of ketamine increased neuronal activity in numerous areas of the brain (*shown in green*). These regions include the prefrontal cortex and the thalamus.

Yet other scientists posit that the psychoactive effect of ketamine may in fact ease depression. Along with psilocybin—the psychoactive substance in certain mushrooms—and mescaline, which is derived from a Central American species of cactus, psychiatrist Franz X. Vollenweider of the University Hospital of Psychiatry Zurich considers ket-

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FROM "THE NEUROBIOLOGY OF PSYCHEDELIC DRUGS: IMPLICATIONS FOR THE TREATMENT OF MOOD DISORDERS," BY FRANZ X. VOLLENWEIDER AND MICHAEL KOMETER, IN *NATURE REVIEWS NEUROSCIENCE*, VOL. 11; SEPTEMBER 2010

Depression changes the way we view the world, often depriving it of beauty. Ketamine has helped some patients improve their outlook for several days at a time.

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amine a promising candidate for a psycholytic approach to therapy, in which psychoactive substances are used to alter a patient's mind.

Alternative Thinking

Clinicians treating patients are not the only ones keenly studying ketamine's potential. Neuroscientists have hailed the drug as the first breakthrough in depression medication research in 50 years because ketamine works on a different pathway in the brain than most antidepressants. Conventional drugs aim to elevate concentrations of serotonin, dopamine or noradrenaline, neurotransmitters that ferry important information between neurons.

Ketamine, on the other hand, briefly floods the space between two connected neurons with glutamate, a different neurotransmitter, which is abundant in the brain and crucial for learning and memory processes. Researchers are still attempting to understand exactly how ketamine's effect on the glutamate system mitigates depression, but studies show that various areas of the brain associated with depression respond after administration of the drug.

One hypothesis suggests that ketamine quickly and dramatically increases the function and density of synapses, the junctions between neurons, in areas of the brain where cells have atrophied because of stress or depression. The prefrontal cortex—a region essential to complex decision making, learning and memory—is one such area. In depressed people, it appears to have reduced volume and less activation than in healthy individuals, as well as fewer synapses on neurons in one subregion. A rodent study conducted by a team led by Ronald S. Duman of Yale University found that ketamine caused a burst of glutamate in the prefrontal cortex and a sudden increase in the formation of new synapses. Duman hailed ketamine as being "like a magic drug."

The ability of synapses to adjust their strength is essential to the function of a healthy brain, and their increased plasticity could be the neurobiological reason for the apparent change in perspective of patients who take ketamine. We hypothesize that depression is associated with an imbalance in the way glutamate

regulates the brain and that when the neurotransmitter floods the synapses it temporarily returns the system to a healthy, balanced state. Many chronically depressed patients have a glutamate deficiency, and the initial findings by our team in Zurich, along with Martin Walter of Otto von Guericke University in Magdeburg, Germany, support the idea that correcting the shortage normalizes brain activity associated with depression. Namely, we have observed that an increase in glutamate levels causes the prefrontal cortex to activate more intensely to emotional stimuli. The amygdala, which is often hyperactive in depressed individuals, becomes less responsive. [For more on glutamate and synaptic plasticity, see "A Lifeline for Addicts," by Michele Solis; Scientific American Mind, March/April 2013.]

Depressed patients also are low on glutamate in the anterior cingulate cortex, a region in the frontal lobes important in motivation and cognitive control. Psychiatrist James M. Stone of Imperial College London observed an uptick in glutamate concentrations in the anterior cingulate cortex of healthy human subjects within as little as 30 minutes of a ketamine infusion.

A short-term rise in glutamate does not alone explain its antidepressant action, of course. The buildup occurs because ketamine blocks the neurotransmitter from binding to a receptor known as NMDA. This blockage causes other types of glutamate receptors to become more strongly stimulated. That shift, too, can ultimately increase the density of nerve synapses. Numerous mechanisms most likely contribute to resetting the connections not only between individual neurons but also among the broader brain networks that regulate mood.

A Sense of Hope

In spite of progress on deciphering how it works, ketamine in its current form may never develop into an accepted treatment for depression. Research on ketamine addicts and those who take it in large doses as a party drug has uncovered unsavory side effects: users may experience learning and perception problems, as well as memory disorders, and in some cases can develop a severely inflamed bladder. Another concern is that ketamine's benefits may actually be relatively fleeting. A recent study by physicians at Mount Sinai found that out of 21 patients who received up to six infusions of ketamine over 12 days, 17 had lapsed back into depression a median of 18 days after the end of the treatment, whereas only four had not relapsed after 83 days when the study concluded. On the positive side, the participants experienced no notable adverse side effects.

Even if ketamine's efficacy becomes more strongly established, the road forward is unclear. Because ketamine has been available for decades, there is no patent for it and little financial incentive for pharmaceutical companies to research the drug and collect FDA approval for its use as an antidepressant. Given its drawbacks, some researchers hope instead to eventually develop new, less troublesome drugs based on ketamine's chemistry.

A few doctors in private practice have taken matters into their own hands. Glen Zehnder Brooks, an anesthesiologist in New York City, for example, recently opened a ketamine infusion clinic and treats depressed patients who are under the care of a psychiatrist. Brooks reports that "to see the transformation [in patients] is just amazing." He often works with Princeton, N.J., psychiatrist Steven P. Levine, who has gained a reputation for providing patients with ketamine. In fact, Joan discovered Levine through the Internet, after five years of participating in ketamine clinical trials. In each trial she responded positively and then relapsed, a pattern that left her filled with hope yet frustrated. "You know your brain will respond to the right stuff, so then why can't I get it? This is a terminal illness." Now she can schedule an infusion whenever her spirits sink dangerously low.

For the first time in decades, she says she is optimistic about the future. M

Ketamine **floods the space** between two neurons with glutamate, a chemical **crucial for learning** and memory.

(Further Reading)

- **Ketamine Use: A Review.** Celia J. A. Morgan and H. Valerie Curran in *Addiction,* Vol. 107, No. 1, pages 27–38; January 2012.
- **Ketamine for Depression: Where Do We Go from Here?** Marije aan het Rot, Carlos A. Zarate, Jr., Dennis S. Charney and Sanjay J. Mathew in *Biological Psychiatry,* Vol. 72, No. 7, pages 537–547; October 1, 2012.
- **Synaptic Dysfunction in Depression: Potential Therapeutic Targets.** Ronald S. Duman and George K. Aghajanian in *Science,* Vol. 338, pages 68–72; October 5, 2012.