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Comfortably numb

It started life as an anaesthetic, then became a psychedelic club drug. Now researchers think ketamine could hold the key to understanding and treating depression, says **Erika Check**.

B held my hand and we started our roller coaster out… I can't feel my body anymore except this overriding general fuzziness. The lines on the ceiling become a tunnel and I am flying down it faster than sound… Then the room does a somersault and I with it… I'm scared… this is a thrill ride and the car is the dimensions of existence.

Such are the wonders of the drug ketamine, according to U.S. 9, who described this experience with the drug on an online forum called the Erowid Experience Vaults[1]. Many others around the world use ketamine illegally, going "down the K-hole" to abandon reality and alter their consciousness. Now neuroscientists are getting in on the act. They are finding that although ketamine makes some lose their minds, it might help others to find their sanity.

Ketamine was invented in the 1960s by chemists at the drug company Parke-Davis in Detroit. The drug was a powerful anaesthetic, but also caused 'dissociative' effects, such as the feeling of leaving one's body and entering other planes of existence. Although popular with recreational drug users, ketamine is only used medically as an anaesthetic in animals and children, who are less prone to its psychedelic side effects.

But back in the 1960s, a handful of scientists used these side effects to explore human consciousness (see 'Exploring the dark', overleaf). Today, scientists are using ketamine as a tool to study mental illness, and perhaps even treat it. Clinical trials suggest that the drug might help patients with severe depression. And these experiments are changing the way scientists think about the nature of the disease and how it might be treated.

The World Health Organization estimates that depression is the world's leading cause of disability. But doctors and scientists are still mystified by what the disease actually is. The label 'depression' is a catch-all term for a condition with a huge array of possible symptoms and causes. Some depressed people feel sad, guilty or tired; others cycle into hyperexcited mania, or feel worried and anxious. Genes, stress and negative thought patterns have all been linked to depression. But it is not clear what chain of events causes a particular set of symptoms in an individual.

Scientists also aren't quite sure why modern antidepressant drugs succeed or fail to cure depression in different patients. The drugs act on neurotransmitters, the chemicals that brain cells use to communicate. Most of today's drugs target a particular class of neurotransmitter called the biogenic amines. These include serotonin, which is targeted by selective serotonin reuptake inhibitors, or SSRIs. Fluoxetine and sertraline, sold in the United States as Prozac and Zoloft, are members of this enormously popular category of drugs.

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— Nuri Farber

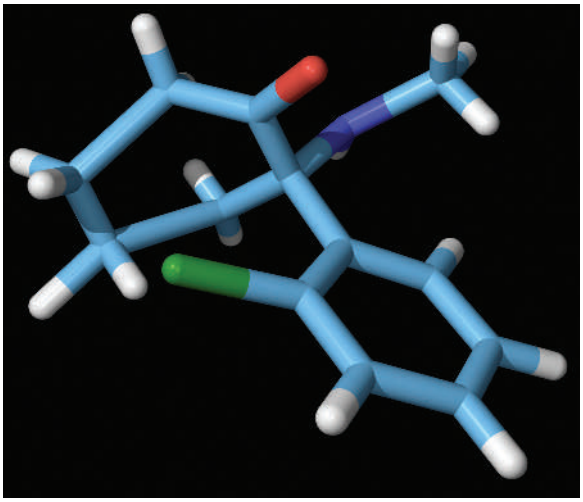
But the drugs that act on biogenic amines take weeks to work, and fail to help at least 40% of depressed patients[2]. So neuroscientists suspect that these drugs don't hit depression at its source and are searching for other approaches.

The search took a dramatic turn in August this year, when a team led by Husseini Manji, at the National Institute of Mental Health in Bethesda, Maryland, published a study[3] looking at the effects of ketamine on 18 severely depressed patients, all of whom had failed to respond to standard treatments.

In the double-blind trial, doctors gave the patients intravenous ketamine or placebo saline drips, and then scored the responses. After taking ketamine, 12 of the patients improved by at least 50% on a depression rating scale. Patients felt better as little as two hours after treatment.

And one-third of the patients still felt better a week later.

Although unexpected, Manji's results are not the first to hint that ketamine has unexpected benefits. In 2000, John Krystal at Yale University and his colleagues published the results of a similar trial on eight severely depressed patients who didn't respond to standard medications[4]. This too suggested that ketamine might work as an antidepressant. Four of the patients felt much better after the ketamine treatments — their depression scores dropped by more than half, by one rating scale. And it worked fast. The patients felt better just three days after their treatment .



T. EVANS/SPL

In the frame: ketamine may ease the effects of stress on brain cells.

Special forces

At the time, these results astonished other psychiatrists. "Ten years ago, I would have said there's no way in hell this drug would work as an antidepressant," says Nuri Farber, a psychiatrist at Washington University in St Louis. Many remained sceptical, and were wary about the whole idea of treating mentally unstable people with a psychoactive drug. Psychiatrists have on occasion used ketamine to deliberately destabilize normal subjects: by giving it to stable people, psychiatrists can induce a schizophrenia-like state and study the brain chemistry that may underlie the disease[5]. So psychiatrists didn't exactly rush to try ketamine in their own clinics. "It was such a small study, and nobody else was following this path. It was sort of a novelty," Krystal says. "People didn't take it as seriously as they might have."

The findings languished in the literature until one of Krystal's colleagues, Dennis Charney, left Connecticut to work at the National Institute of Mental Health. There, he began working with Manji, who had been studying chemical relatives of ketamine in mice. Manji, Charney and a psychiatrist named Carlos Zarate decided to find out whether the ketamine study was more than a fluke.

When they took ketamine, Zarate's patients did experience trippy side effects such as dizziness and euphoria. But most of these effects wore off after 80 minutes[3] — before the drug's antidepressant effects kicked in. That is surprising: usually, drugs that trigger highs, such as cocaine or ecstasy, are followed by a depressive low. "It's not what I would have expected," says Farber. "If anything, I would have expected these patients to crash and burn."

One possible explanation for this is that ketamine uses different pathways to trigger its psychedelic and antidepressant effects. Another possibility is that patients have to go out of their minds before they can get back to normal. "What ketamine does is briefly make people crazy," says Eric Nestler, a neuroscientist and psychiatrist at the University of Texas Southwestern in Dallas. "The question becomes: is that disruption in cognitive function what's creating this improvement in mood?"

"What ketamine does is briefly make people crazy. Is that what's creating this improvement in mood?"
— Eric Nestler

Right now, it is impossible to answer that question. But Zarate, Krystal and other researchers who have studied ketamine's link to depression have one idea about what's going on. Their hypothesis has to do with the way ketamine works in the brain.

Ketamine hinders the activity of a complex molecular machine called the *N*-methyl-D-aspartate receptor, the NMDA receptor for short. It is one of the receptors for a neurotransmitter called glutamate. That activity could relate to one theory of depression: that the disease occurs when brain cells are just too stressed to thrive. This link is based on two facts and one highly controversial idea.

First, scientists know that the NMDA receptor can control brain-cell growth and survival. Second, they know that excessive levels of glutamate kill brain cells in some conditions, such as stroke and Alzheimer's disease[6]. Here's the controversial part: there is some evidence supporting the idea that depression is caused by brain-cell death.

So, by jamming the NMDA receptor, could ketamine be correcting a toxic glut of glutamate that is harming brain cells and causing depression? It is already known that stress floods the brain with glutamate, says Zarate. "It might be that these neurons are struggling to regulate glutamate, and if you stress them over and over, they become injured."

This hypothesis is still very new[7]. There is some evidence linking glutamate, and the NMDA receptor, to depression. Twenty-five years ago, for instance, scientists at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, showed that chemicals that target the NMDA receptor have antidepressant effects in animals[8]. Scientists have since found that deceased depressed human patients, such as suicide victims, have abnormal numbers of NMDA receptors. And brain-imaging studies have found that depressed people have much higher levels of glutamate in one region of their brains than healthy people[9].

But Nestler and other psychiatrists caution that it is impossible to know yet whether ketamine affects brain-cell survival. Glutamate is the most common neurotransmitter in the brain, used by perhaps half of all brain cells. And the NMDA receptor is involved in a huge array of different processes, such as learning and memory, as well as cell growth and survival. So it is difficult to pin down the precise reason why tweaking glutamate through the NMDA receptor would influence human

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John Krystal published one of the first studies to use ketamine as an antidepressant.

happiness. And although it is true that the NMDA receptor is involved in cell survival, this takes a long time, whereas ketamine's antidepressant effects seem to kick in within hours.

Until the mechanism can be clarified, psychiatrists say, Zarate's and Krystal's studies are important for one major reason: they provide evidence that biogenic amines such as serotonin don't tell the whole story about depression. "We've had a preoccupation over so many years with biogenic amines," says John Olney, a psychiatrist at Washington University who has been studying neurotransmitters for 35 years. "The idea that glutamate might be involved in depression has evolved very slowly. We're still trying to understand it."

What's the use?

Nestler agrees. "All our available drugs act on the serotonin and noradrenaline systems, and this drug clearly does not," he says. "It's very important as a proof of principle that a drug acting on a different neurotransmitter system can have a mood-elevating effect."

Even if ketamine works, it's not an ideal drug. Clinical trials have studied the drug in only 26 patients, and no one has investigated how long its beneficial effects might last; there are also those psychedelic side effects. So neuroscientists are continuing to look into whether other drugs that hit the glutamate system could help mentally ill patients. A trial of one NMDA blocker — memantine, used to treat Alzheimer's patients — found the drug didn't cure depression[10]. But the study's authors think that is because memantine does not bind as tightly to the NMDA receptor as ketamine does.

Another candidate, riluzole — already used in patients with Lou Gehrig's disease — seems more promising. It works by preventing brain cells from making excess glutamate and dumping it into surrounding brain tissue. Patients taking the drug have reported some improvement, but riluzole has yet to undergo large clinical trials for depression. Other drugs are entering tests.

Whether or not these trials prove successful, at least the fresh take on depression is finally helping neuroscientists climb out of the serotonin rut. And maybe an ageing drug with a tarnished reputation will help them find their way. ■

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Exploring the dark

"You're supposed to be reputable scientists! Not two dorm kids freaking on Mexican mushrooms!"

The 1980 movie *Altered States* tells the story of a scientist called Eddie Jessup who uses psychedelic drugs to explore the depths of human consciousness. A fellow scientist objects to the experiments, chastizing Jessup when he witnesses the outlandish behaviour his drug-taking produces.

The Jessup character was partly inspired by reality: a number of scientists in the 1950s and '60s experimented on themselves, using drugs, including ketamine, to explore the nature of consciousness.

Among them was John Lilly, who worked at the National Institute of Mental Health in the 1950s. While at the institute, Lilly began working with a sensory-deprivation tank (pictured). After leaving the institute in 1958, Lilly embarked on a full-time career in self-experimentation with his own sensory-deprivation tank and a cornucopia of psychedelic drugs, including LSD (lysergic acid diethylamide) and ketamine. Scenes from *Altered States* are actually based on Lilly's experiments with ketamine, which he described in his autobiography *The Scientist*[11].

Lilly began his scientific life with mainstream studies in electrophysiology, but his later career took him down some bizarre paths. He began working extensively with dolphins, even dosing them with LSD, believing that humans could communicate with them. And he began an extensive programme of experimentation with ketamine. He believed the drug connected him with aliens, and with a God-like entity he called the Earth Coincidence Control Office.

But some of his beliefs weren't quite so distant from the scientific mainstream. In a 1991 interview with the editors of a book called *Mavericks of the Mind*, Lilly said that he agreed with the idea that "the brain is a huge, diverse chemical factory". Lilly told his interlocutors: "We cannot make generalizations about any one of these chemicals yet but, for instance, if you give an overdose of this one people get depressed, if you give an overdose of that one they get euphoria, and so on." **E.C.**