Mind-bending therapies

Roughly one-third of people with depression don't respond to conventional antidepressants. A new wave of mind-altering drugs could provide relief — but some researchers worry that the hype outweighs the hope. **By Cassandra Willyard**

Tom Hendricks lay back on his bed and pulled a mask down over his eyes. Then he took a ketamine mint and placed it between his cheek and gums. He let the electronic music coming through his headphones wash over him. About 20 minutes later, he felt the drug take effect. He saw colours and shapes that changed in time with the music. "It almost was a synaesthesia effect where the sounds and music would paint pictures," he says. Embedded within those pictures, Hendricks saw his consciousness and the dark cloud hanging over it.

Hendricks (a pseudonym), a 51-year-old retired marine living in Texas, had tried dozens of combinations of medications to alleviate the depression he had struggled with for decades. They all failed. Ketamine was different — Hendricks's depression began to lift. "It was like I was doing therapy with myself," he says. It wasn't a panacea, of course. He still struggled with suicidal thoughts until electroconvulsive therapy was added. But the ketamine provided desperately needed relief. "It was absolutely life-changing," he says.

The antidepressant landscape hasn't changed much since the approval in the 1980s of fluoxetine (marketed most famously as Prozac). Most new drugs hit the same targets as the old ones, albeit with fewer side effects. For about two-thirds of people with depression, these conventional medications work. But for the remaining third — people such as Hendricks — they don't seem to have much of an impact. Even when they do work, people often need to take them for weeks before they see any improvement. "You have a scenario where someone's depressed and seeks treatment. They try one medication and it takes them a couple of months to know if it's working. And then you switch to another medication and that's another couple of months, and before you know it, you're half a year down the road," says Todd Gould, a neuroscientist at the University of Maryland in Baltimore. Those who respond to ketamine feel relief quickly, "sometimes within hours", he says.

Ketamine, long used as an anaesthetic, is part of a wave of mind-altering drugs that are gaining traction for treating depression. In the United States, hundreds of clinics now offer the drug as an 'off-label' depression treatment (meaning that doctors prescribe it although ketamine isn't approved for that purpose). And in 2019, the US Food and Drug Administration (FDA) approved a related compound — a nasal spray called esketamine — for treatment-resistant depression. Other psychedelic compounds are in clinical trials. Psilocybin, the 'magic' ingredient in magic mushrooms, is farthest down the path to FDA approval. But although ketamine and now esketamine are available in clinics, many of these substances remain illegal. Psychedelics advocates hope to change that.

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Dried mushrooms containing psilocybin.

Studies suggest that these drugs have enormous promise for depression, and the media has bolstered excitement with stories about people who seem to have been cured of this often debilitating condition. But some researchers see more hype than hope, arguing that the studies have been marred by bias and flawed methodologies. They worry that risks are being overlooked and that people are, once again, being offered the false promise of a quick fix. "We're playing on people's vulnerability," says Joanna Moncrieff, a psychiatrist and researcher at University College London, and a critic of psychiatric drugs. "If you're unhappy and things are going wrong in your life, you want to think there's a magic pill," she says. "We all do."

Astonishing anaesthetic

When scientists discovered ketamine's efficacy in depression in the early 2000s, the results[1] came as a shock. Earlier studies had hinted that the compound might have some antidepressant effects, but no one expected it to have such a profound impact so quickly. Nor did they expect the results to last. "The idea that ketamine was making those changes rapidly really was a paradigm shift," says Gould. So dramatic were the results, in fact,

that many researchers didn't believe them.

Today, however, few sceptics remain. When researchers examined data[2] from more than 500 people with depression who received a series of 4–8 ketamine infusions between 2016 and 2020, they found that slightly more than half responded to the therapy, meaning their score on a common patient questionnaire for depression fell by 50% or more. Of the 356 participants who had previously had suicidal thoughts, 73% experienced a reduction in them. Crucially, that effect seemed to last. The researchers found that people who responded to the ketamine infusions had, on average, about an 80% chance of still experiencing relief four weeks later and an approximately 60% chance at 8 weeks, without maintenance infusions.

Despite its efficacy, ketamine is still approved for use only as an anaesthetic. Because the drug is no longer protected by a patent, companies don't have a financial incentive to take it through expensive clinical trials. People with depression can get ketamine therapy, but only "through a weird back door", says Albert Garcia-Romeu, a psychologist at Johns Hopkins University in Baltimore. Each clinic that offers the drug off-label has its own protocol. "Some people will give it with talk therapy, others will not. Some people will give it to you intravenously," he says. Other doctors, such as the one Hendricks saw, offer it orally. "It's really kind of a weird grey area," Garcia-Romeu adds.

Ketamine is composed of a pair of compounds, esketamine and arketamine, that are mirror images of each other – like a pair of gloves. These two component compounds are patentable, which is why the pharmaceutical company Janssen, headquartered in Beerse, Belgium, was able to turn esketamine into a marketable drug. Esketamine marks the first time a new class of drug has been approved to treat depression since Prozac was approved in 1988.

The esketamine nasal spray (marketed as Spravato) is one that patients self-administer under a doctor's supervision. It must be used in combination with a conventional antidepressant. But at hundreds of dollars a dose, the therapy is more expensive than intravenous ketamine – and not necessarily easier to access. People have to take the drug in a clinic and stay put until the initial effects have worn off. And, like ketamine, esketamine can produce dissociative effects and elicit out-of-body experiences. "You don't want someone taking esketamine and soon after getting in a car or a bike," Gould says. "That could be really, really dangerous." What's more, both drugs carry the potential for abuse.

And some researchers question just how well esketamine works. The medication was approved on the basis of just a handful of studies, only one of which demonstrated that it alleviates depression better than a placebo. The effect was modest: participants who received esketamine had just a four-point improvement in depression symptoms compared with the placebo group[3]. A separate double-blind trial with 300 participants showed that esketamine plus a conventional antidepressant reduced the risk of relapse by 51% over an antidepressant plus a placebo spray[4]. If you put all the trials together, Moncrieff says, "you can show that esketamine has a slightly larger effect".

The upside for esketamine, at least in the United States, is that the cost is covered by insurance. In the United Kingdom, the National Institute for Health and Care Excellence has declined to recommend the medicine three times, noting that the evidence of efficacy is uncertain and the long-term effects are unknown. That means the medicine is not available on the UK National Health Service.

"There's much more potential to generate new patterns of behaviour."

As for arketamine, Perception Neuroscience, a drug-development company based in New York City, has begun phase II clinical trials in about 90 people with treatment-resistant depression. Participants will receive either a placebo, or a 30- or 60-milligram dose. Because arketamine doesn't produce the dissociative and out-of-body effects that are common with ketamine and esketamine, the company is hoping to offer the drug as an at-home therapy.

Why ketamine works is something of a mystery. What is known is that it inhibits the NMDA glutamate receptor. That action is probably responsible for the drug's painkilling and anaesthetic effects, as well as the out-of-body feelings it can induce. For decades, researchers assumed that ketamine's antidepressant effects were also the result of NMDA receptor binding. But researchers have tested other drugs that inhibit the receptor in much the same way as ketamine does, and "those studies have failed to show ketamine-like effects", Gould says.

Ketamine does produce a variety of metabolites in the body, one or more of which could be responsible for its mood-lifting capabilities. Gould's team has identified one such molecule, called (2*R*,6*R*)-hydroxynorketamine. In animal studies[5], the metabolite can produce ketamine-like antidepressant effects all on its own, but without inducing the dizzying high that causes some people to misuse ketamine. Gould and his colleagues have launched a phase I trial of the metabolite in healthy volunteers, and hope to begin phase II studies in treatment-resistant depression in the coming year. If the trials succeed, that might open the door to a therapy that has the efficacy of ketamine without the dissociative side effects.

The second psychedelic revolution

Ketamine is often lumped with a group of drugs called psychedelics. The term once referred only to substances such as LSD and psilocybin, which produce hallucinations. But, in recent years, the definition has expanded to include other mind-altering drugs such as ketamine and MDMA. Although ketamine has a long history of use in Western medicine, some of the other therapies in the pipeline to treat depression do not. Psilocybin, LSD and other psychedelics come with the baggage of being banned substances in the United States and much of Europe. That makes research, and the path to approval, trickier.

New studies suggest psilocybin does hold promise. Both the London-based company Compass Pathways and the non-profit Usona Institute in Madison, Wisconsin, have been granted FDA breakthrough-therapy status for their psilocybin treatments and have launched phase II trials.

Compass Pathways' trial – the largest randomized controlled study of psilocybin so far – wrapped up in 2021. Researchers recruited 233 people and randomized them to receive a 25-mg dose of psilocybin, a 10-mg dose or a 1-mg dose designed to act as a placebo. The company reported that participants who received the 25-mg dose showed a significant decrease in depressive symptoms after 3 weeks compared with those who received the lowest dose. After three months, 20.3% of people in the highest-dose group were in remission, compared with 10.1% of those in the 1-mg group (see go.nature.com/3ptv9xf).

In these trials, psilocybin is administered during a treatment session lasting 6–8 hours. Participants don eye shades and headphones, and make themselves comfortable while listening to relaxing music. Their therapist is present to provide reassurance and ensure safety. During the psilocybin session, "we let the drug pretty much do the work", says Paul Hutson, a pharmacologist and head of the University of Wisconsin–Madison's Transdisciplinary Center for Research in Psychoactive Substances. (Hutson and other researchers from the centre are testing psilocybin on behalf of the Usona Institute.) In subsequent 'integration' sessions, however, therapists encourage participants to discuss

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The psychedelic-therapy experience at the Field Trip Clinic in Toronto, Canada.

their experiences and reflect on them.

Psilocybin "seems to offer a certain percentage of patients with really difficult to treat conditions a relief and a resolution of symptoms that nothing else seems to offer," says Guy Goodwin, chief medical officer at Compass Pathways. "That's pretty exciting. But, of course, it's not for everybody."

Caution ahead

Many researchers, however, aren't yet convinced that psychedelics live up to their marketing. "I just think it's been completely overblown," Moncrieff says. Some individuals might benefit from experiencing a psychedelic trip, but she thinks there are "other ways of having life-changing experiences" that might provide more lasting effects.

Part of the problem is that it's nearly impossible to conduct a blind study because psychedelics' unique effects mean that participants and investigators typically know who has, or has not, received the active compound. And that knowledge can influence expectations. Those who get the drug might anticipate that their depression will be mitigated, and this could lead to a variation on the placebo effect, with participants experiencing benefits because they know they have received the medication[6]. Those who don't get the drug, conversely, will expect to be disappointed.

In the Compass trial, all the participants knew that they would receive psilocybin. But most had no previous experience with psychedelics, so "they didn't really know what to expect", says Goodwin. That probably helped to keep at least some of the participants unaware of their dose. And if unblinding were wholly responsible for the results, Goodwin would have expected the 10-mg dose to have been effective, too.

Eiko Fried, a psychologist and researcher at Leiden University in the Netherlands, points out that the studies so far have been small and conducted by companies that want to move these therapies forwards. He would like to see major non-commercial funders, such as the US National Institutes of Health (NIH) in Bethesda, Maryland, sponsoring large trials.

The NIH does fund some research on psychedelics. Its National Institute of Mental Health (NIMH), for example, spends about US$15 million annually on preclinical and clinical research, says Steven Zalcman, chief of the NIMH adult pathophysiology and biological interventions development branch. The vast majority of that is focused on ketamine or ketamine-like compounds. But the NIMH is not currently supporting any trials of psychedelics to treat depression. One of the challenges is that any trials it funds must focus on the mechanism underlying the therapy. But how psychedelics might relieve depression isn't yet clear — making it difficult to formulate a hypothesis on which to base a trial.

Psychedelic drugs might work by reopening a window of brain development — one in which the brain is much more plastic. "In that place of greater plasticity, there's much more potential to generate new patterns of behaviour and experience," says psychiatrist Kelley O'Donnell, who studies psychedelics at New York University's Grossman School of Medicine.

Last year, researchers at Imperial College London published the results of a 59-person trial[7] comparing psilocybin with a conventional antidepressant called escitalopram. The researchers found that, six weeks on, psilocybin performed about as well as escitalopram. But the two compounds seem to work in different ways. Brain imaging revealed that psilocybin seemed to increase connectedness in some of the brain's networks, perhaps leading to more-flexible thought patterns. Escitalopram did not have the same effect[8].

"You can almost think of it like a record that might be skipping," says Garcia-Romeu. "You get stuck in these rigid patterns that are inflexible and unhealthy. You're constantly negatively thinking about the world and yourself." Psychedelics help smooth the ruts so that new patterns can form.

If researchers could uncover the mechanisms behind these drugs' activity, they might be able to develop compounds that relieve depression without causing hallucinations or out-of-body experiences. In 2019, the US Defense Advanced Research Projects Agency announced a programme called Focused Pharma that aims to do exactly that. The programme hinges on the hypothesis that the profound experiences people have when taking psychedelics are unrelated to the drugs' antidepressant effects.

O'Donnell, however, sees real value in the experiences people have when they use psychedelics. These trips might allow them to access emotions that are otherwise too painful to process. The drugs, she says, can offer "moments of profound insight and wonder and awe, as well as other moments of terror, and some of joy, and some of connection and others of profound loneliness and isolation" — all of which can be unpacked afterwards during therapy. "I really believe that these medicines are catalysts."

What is clear is that new therapies are urgently needed. The coronavirus pandemic has left more people in mental distress than ever before. Psychedelics offer the possibility of relief for people who have no other options.

That includes Hendricks. Before trying ketamine, he "basically had become a recluse", he says. He credits the drug with reviving his interest in many of the things that gave his life meaning: writing, music and sports. "It opened up the world to me again."

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