Psychoactive drugs are having a moment: The FDA will soon weigh in

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Lori Tipton is among the growing number of people who say that MDMA, also known as ecstasy, saved their lives.

Raised in New Orleans by a mother with untreated bipolar disorder who later killed herself and two others, Tipton said she endured layers of trauma that eventually forced her to seek treatment for crippling anxiety and hypervigilance. For 10 years nothing helped, and she began to wonder if she was "unfixable."

Then she answered an ad for a clinical trial for MDMA-assisted therapy to treat post-traumatic stress disorder. Tipton said the results were immediate, and she is convinced the drug could help a lot of people. But even as regulators weigh approval of the first MDMA-based treatment, she's worried that it won't reach those who need it most.

"The main thing that I'm always concerned about is just accessibility," the 43-year-old nonprofit project manager said. "I don't want to see this become just another expensive add-on therapy for people who can afford it when people are dying every day by their own hand because of PTSD."

MDMA is part of a new wave of psychoactive drugs that show great potential for treating conditions such as severe depression and PTSD. Investors are piling into the nascent field, and a host of medications based on MDMA, LSD, psychedelic mushrooms, ketamine, the South American plant mixture ayahuasca, and the African plant ibogaine are now under development, and in some cases vying for approval by the Food and Drug Administration.

Proponents hope the efforts could yield the first major new therapies for mental illness since the introduction of modern antidepressants in the 1980s. But not all researchers are convinced that their benefits have been validated, or properly weighed against the risks. And they can be difficult to assess using traditional clinical trials.

The first MDMA-assisted assisted therapy appeared to be on track for

FDA approval this August, but a recent report from an independent review committee challenged the integrity of the trial data from the drug's maker, Lykos Therapeutics, a startup founded by a psychedelic research and advocacy group. The FDA will convene a panel of independent investigators on June 4 to determine whether to recommend the drug's approval.

Proponents of the new therapies also worry that the FDA will impose treatment protocols, such as requiring multiple trained clinicians to monitor a patient for extended periods, that will render them far too expensive for most people.

Tipton's MDMA-assisted therapy included three eight-hour medication sessions overseen by two therapists, each followed by an overnight stay at the facility and an integration session the following day.

"It does seem that some of these molecules can be administered safely," said David Olson, director of the University of California-Davis Institute for Psychedelics and Neurotherapeutics. "I think the question is can they be administered safely at the scale needed to really make major improvements in mental health care."

Breakthrough therapies?

Psychedelics and other psychoactive substances, among the medicines with the oldest recorded use, have long been recognized for their potential therapeutic benefits. Modern research on them started in the mid-20th century, but clinical trial results didn't live up to the claims of advocates, and they eventually got a bad name both from their use as party drugs and from rogue CIA experiments that involved dosing unsuspecting individuals.

The 1970 Controlled Substances Act made most psychoactive drugs

illegal before any treatments were brought to market, and MDMA was classified as a Schedule 1 substance in 1985, which effectively ended any research. It wasn't until 2000 that scientists at Johns Hopkins University were granted regulatory approval to study psilocybin anew.

Ketamine was in a different category, having been approved as an anesthetic in 1970. In the early 2000s, researchers discovered its antidepressant effects, and a ketamine-based therapy, Spravato, received FDA approval in 2019.

Doctors can also prescribe generic ketamine off-label, and hundreds of clinics have sprung up across the nation. A clinical trial is underway to evaluate ketamine's effectiveness in treating suicidal depression when used with other psychiatric medications.

Ketamine's apparent effectiveness sparked renewed interest in the therapeutic potential of other psychoactive substances.

They fall into distinct categories: MDMA is an entactogen, also known as an empathogen, which induces a sense of connectedness and emotional communion, while LSD, psylocibin, and ibogaine are psychedelics, which create altered perceptual states. Ketamine is a dissociative anesthetic, though it can produce hallucinations at the right dose.

Despite the drugs' differences, Olson said they all create neuroplasticity and allow the brain to heal damaged neural circuits, which imaging shows can be shriveled up in patients with addiction, depression, and PTSD.

"All of these brain conditions are really disorders of neural circuits," Olson said. "We're basically looking for medicines that can regrow these neurons."

Psychedelics are particularly good at doing this, he said, and hold promise for treating diseases including Alzheimer's.

A number of psychoactive drugs have now received the FDA's "breakthrough therapy" designation, which expedites development and review of drugs with the potential to treat serious conditions.

But standard clinical trials, in which one group of patients is given the drug and a control group is given a placebo, have proven problematic, for the simple reason that people have no trouble determining whether they've gotten the real thing.

The final clinical trial for Lykos' MDMA treatment showed that 71% of participants no longer met the criteria for PTSD after 18 weeks of taking the drug versus 48% in the control group.

A March report by the Institute for Clinical and Economic Review, an independent research group, questioned the company's clinical trial results and challenged the objectivity of MDMA advocates who participated in the study as both patients and therapists. The institute also questioned the drug's cost-effectiveness, which insurers factor into coverage decisions.

Lykos, a public benefit company, was formed in 2014 as an offshoot of the Multidisciplinary Association for Psychedelic Studies, a nonprofit that has invested more than $150 million into psychedelic research and advocacy.

The company said its researchers developed their studies in partnership with the FDA and used independent raters to ensure the reliability and validity of the results.

"We stand behind the design and results of our clinical trials," a Lykos

spokesperson said in an email.

There are other hazards too. Psychoactive substances can put patients in vulnerable states, making them potential victims for financial exploitation or other types of abuse. In Lykos' second clinical trial, two therapists were found to have spooned, cuddled, blindfolded, and pinned down a female patient who was in distress.

The substances can also cause shallow breathing, heart issues, and hyperthermia.

To mitigate risks, the FDA can put restrictions on how drugs are administered.

"These are incredibly potent molecules and having them available in vending machines is probably a bad idea," said Hayim Raclaw of Negev Capital, a venture capital fund focused on psychedelic drug development.

But if the protocols are too stringent, access is likely to be limited.

Rachel del Dosso, a trauma therapist in the greater Los Angeles area who offers ketamine-assisted therapy, said she's been following the research on drugs like MDMA and psilocybin and is excited for their therapeutic potential but has reservations about the practicalities of treatment.

"As a therapist in clinical practice, I've been thinking through how could I make that accessible," she said. "Because it would cost a lot for [patients] to have me with them for the whole thing."

Del Dosso said a group therapy model, which is sometimes used in ketamine therapy, could help scale the adoption of other psychoactive treatments, too.

Artificial intelligence and analogs

Researchers expect plenty of new discoveries in the field. One of the companies Negev has invested in, Mindstate Design Labs, uses artificial intelligence to analyze "trip reports," or self-reported drug experiences, to identify potentially therapeutic molecules. Mindstate has asked the FDA to green-light a clinical trial of the first molecule identified through this method, 5-MeO-MiPT, also known as moxy.

AlphaFold, an AI program developed by Google's DeepMind, has identified thousands of potential psychedelic molecules.

There's also a lot of work going into so-called analog compounds, which have the therapeutic effects of hallucinogens but without the hallucinations. The maker of a psilocybin analog announced in March that the FDA had granted it breakthrough therapy status.

"If you can harness the neuroplasticity-promoting properties of LSD while also creating an antipsychotic version of it, then that can be pretty powerful," Olson said.