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HOPE AND HEALING

Dazzling scientific results aren't necessarily meaningful to patients. So, Monica Perez, PT, PhD, vowed to keep working.

A TRIP INTO THE FUTURE?

Once a key ingredient of the 1960s anti-establishment, psychedelics are now being studied as therapy for depression and addiction.

BY STACY KESS

Hallucinogenic drugs were once the darling of mid-20th century counterculture and on the fringe of questionable psychological research. But today, psychedelic compounds range from psilocybin—the key ingredient in "magic mushrooms"—and ibogaine—which is derived from the roots of a tree native to Central Africa—to lab-made compounds such as 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine). Psychedelics are now being tested for their therapeutic effects on everything from drug addiction to depression. Furthermore, a few U.S. states are beginning to legalize psilocybin for adults.

"We are witnessing a shift away from propaganda that was shared regarding psychedelics in the '60s and '70s," says Frederick Barrett, PhD, a cognitive neuroscientist and acting director of the Johns Hopkins Center for Psychedelic and Consciousness Research in Baltimore. "We are also exploring models for the therapeutic use of psychedelic drugs, and these may become available as a treatment for both mood and substance use disorders, if not for more indications."

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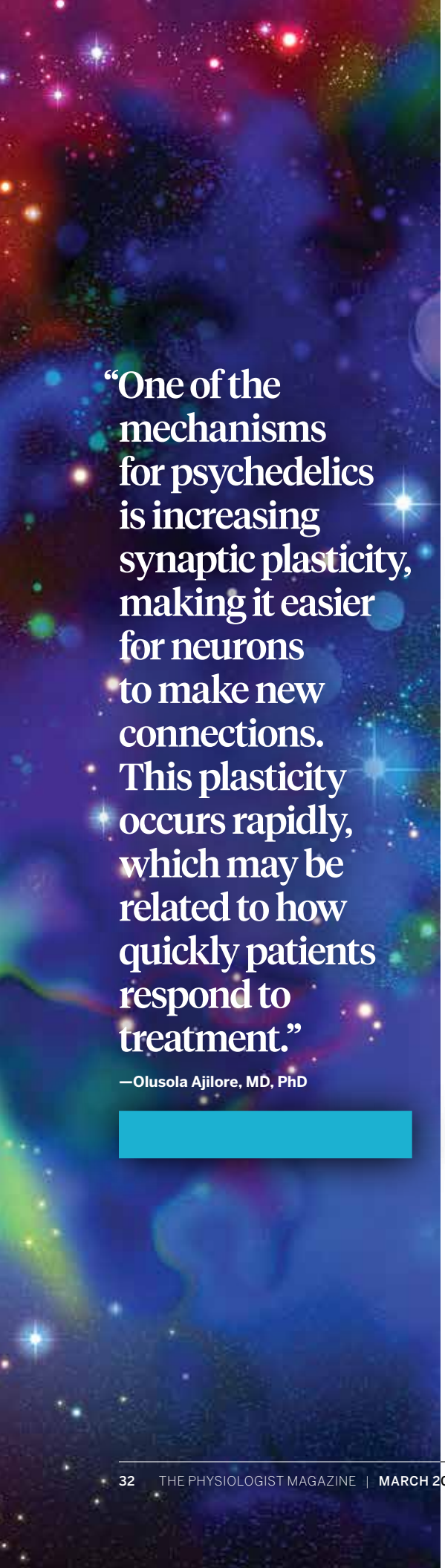

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In recent years, research around psychedelic compounds and their usefulness in neuropsychiatry has been ramping up at universities, hospitals and clinics across the U.S. and around the world. In the U.S., some of that research has been driven by patients, says Nolan Williams, MD, director of the Brain Stimulation Laboratory and of the Interventional Psychiatry Clinical Research Department of Psychiatry and Behavioral Science at Stanford University in Stanford, California.

Williams was approached anonymously by a program working with veterans four years ago to evaluate signals of efficacy and safety of ibogaine. "There have been a number of special forces veterans who have gone to Mexico, where this is legal, who took it and had dramatic improvements," he says. "These folks feel like there's a lot of benefit [for post-traumatic stress disorder, traumatic brain injury and suicidal ideation]. We have been performing rigorous evaluations of the effects of ibogaine prior to and after administration" via functional magnetic resonance imaging, electroencephalogram and psychological and neurocognitive evaluations.

Williams is not new to the world of mind-altering drugs. He previously worked on the human therapeutic mechanisms of ketamine and says he is agnostic to the nature of the therapy.

"We want to understand how all this works," he adds. "I'm trying to understand what's going on in the brain when [psychedelic effects happen]. If you understand what's going on in the brain, then you can emulate it or get to the end goals. Once you understand how something works, you can extend it out."

Although the results of his research are still in the early stages and will not be ready to share for a year or more, he said he remains pragmatic about the use of psychedelics: "I try not to bias myself."

For psychiatrists such as Olusola Ajilore, MD, PhD, who directs the Mood and Anxiety Disorders Program and is the director of Clinical Research Core/Center for Clinical and Translation Science at University of Illinois at Chicago, there is much promise in psychedelics. "There has been a lot of excitement and hype around the clinical benefits of psychedelics," he says.

That's why he's collaborating with researchers studying the actions of psychedelics at the cellular level and working with a resident on a project examining the knowledge, attitudes and beliefs about psychedelics for therapeutic uses in a diverse patient population.

"One of the mechanisms for psychedelics is increasing synaptic plasticity, making it easier for neurons to make new connections," he says. "This plasticity occurs rapidly, which may be related to how quickly patients respond to treatment. This is different from current antidepressants, which take four to six weeks to work."

Barrett, who is working with psilocybin in patients with comorbid depression and alcohol addiction disorders, said there are still "many questions, including how often people may need to repeat psychedelic interventions, how dosing and frequency of intervention may differ and be optimized for different indications, and whether there are some populations (such as those suffering from mania) for whom it is clearly contraindicated," he says. "Psychedelics are powerful drugs, and we still have a lot to learn about the safe administration of these compounds, but the science is progressing at pace, and we hope to soon have more traction in these areas."

HOW DO PSYCHEDELICS WORK?

Exactly what happens in the brain when a patient takes psychedelics is still unclear—and that's what Sharmin Ghaznavi, MD, PhD, director of cognitive neuroscience and associate director of the Center for Neuroscience of Psychedelics at Massachusetts General Hospital in Boston, hopes to answer. The Harvard Medical School psychiatrist says she did not set out to study psilocybin; she started out looking for treatments to relieve rumination in patients.

Her colleague returned from a conference that included a presentation on psilocybin's effects on the brain and shared what he had learned, leading her to read more about psilocybin and design a study to look at its effects on rumination.

Now, after two years spent obtaining the necessary regulatory and institutional approvals, she has started recruitment for what will be a first-of-its-kind study.

"The interesting thing is that because these studies are so difficult to do, there actually aren't that many studies of neuroimaging in patients treated with psychedelics. In fact, there are many papers in the literature that are based on just a few data sets," Ghaznavi says.

Additionally, nearly all neuroimaging studies of psychedelic compounds in patients so far are in the resting state, in which the data are collected while patients are resting with their eyes open, or in some cases closed, but not engaging in tasks. "All the data is very preliminary—and it has generated very good questions, but there is a lot we still don't know."

Ghaznavi's study will image patients at baseline, then administer the dose of psilocybin and take a scan the day of administration—scanning in both a resting state and while the subject is doing a task—then at three weeks and again at 12 weeks to see how neural networks are affected.

"We're going to be the first study that I know of to image patients on psilocybin on the day of administration," she says. "It's a missing piece of the puzzle because the activity that's going on that day is going to tell us a lot about how these compounds work."

THE MICRODOSING APPROACH

While professional research is ramping up, so is popular acceptance. Colorado voters passed a ballot measure in 2022 to allow psilocybin to be used therapeutically, and Oregon will allow some state-regulated dispensaries to distribute psilocybin for therapeutic use beginning this year.

Meanwhile, "microdosing"—the use of small doses that users self-report are too small to cause a full psychedelic effect—made news in daily media such as *The Washington Post* and NPR in 2022.

"I think there's a tremendous need for better treatments—better-tolerated treatments—so I think people are rushing for what they see as the answer," Ghaznavi says. "But as a psychiatrist, operating on the principle of first do no harm, I want to see the evidence before recommending use."

Williams notes that microdosing could be a placebo effect as the evidence that such a small dose in the scant research done so far is unclear. In a November 2022 *New England Journal of Medicine* study of 79 people, a 1 mg dose of psilocybin was not effective. But there also didn't seem to be as much risk with the dose, he notes. "There is likely a psychedelic dose threshold that becomes therapeutic, and we do not know what that is, and it is likely different for different individuals."

That study, which compared 1 mg with 10 and 25 mg single-dose psilocybin treatment's effect (with psychological support) on depression at one, three and 12 weeks, showed results at higher doses. But, it also showed side effects of nausea, vomiting and dizziness in more than half of participants, and all participants experienced suicidal ideation and self-harm.

"What are the real harms and what are the real risks?" Williams continues. "It's unclear to me if microdosing is a risk or not because there hasn't been a great trial performed yet. Psychedelics at the currently described microdosing doses may be homeopathy for some and therapeutic for others. … It's curious. We don't yet know. We don't definitively know that any of the classic psychedelics are actual treatments yet, and determining that is the role of the FDA, not individual investigators."

Barrett agrees: "The current research literature has not provided any empirical evidence to support claims that have been made regarding microdosing," he says. "All controlled studies to date have been completed in healthy individuals, and none have been published in any patient population. It may be that the studies to date have not employed the most appropriate study design, or engaged the right populations, or included the most appropriate outcome measures, but that should not minimize the fact that no controlled studies have provided data supporting any benefit (often, any effect at all) of microdosing."

THE IMPORTANCE OF A THERAPEUTIC SETTING

For psychedelic therapeutic use, these experts emphasized that use within the therapeutic setting is important. "Not unlike every other kind of therapy, the alliance with your therapist matters," Ghaznavi says. "The alliance between patient and therapist, during times of distress, is part of what helps people get through."

Psychedelics Experts to Present at American Physiology Summit

Learn about therapeutic strategies involving the use of psychedelic substances to treat depression at the 2023 American Physiology Summit, which will be held April 20–23 in Long Beach, California.

The game-changer session "Rewiring the Brain to Treat Depression: Psychedelics and Novel Therapies" will feature Frederick Barrett, PhD, of Johns Hopkins University; Nolan Williams, MD, PhD, of Stanford University; and Olusola Ajilore, MD, PhD, of University of Illinois at Chicago.

It is one of several game-changer sessions, which will feature some of the biggest topics impacting life and health today. Learn more and register for the Summit at **www.physiology.org/APS2023**.

Williams says if there was a possibility of therapeutic drugs being derived from the current research it is years down the road, adding that one of the most important parts of therapeutic psychedelic use is "set and setting."

"You have to have the therapeutic environment controlled during these psychedelic sessions," he says.

Barrett explains that the setting can make all the difference. "Under supportive conditions and in properly screened individuals, one or two doses of a classic [serotonergic] psychedelic drug seems to have the capacity to substantially reduce depression severity or lead people to remission," he says. "One to three doses of a classic psychedelic under similar conditions also seem to have the capacity to support rapid and sustained behavior change in the form of abstinence from cigarettes and reduction in unsafe drinking habits.

"Psychedelics have also been shown to be safe in properly screened healthy individuals," Barrett continues, "with the majority of study participants indicating that their experience with a high dose of psilocybin in the laboratory was among the top five or single most personally meaningful and spiritually significant experiences of their entire lives."

He adds that he does not see a future where therapeutic psychedelic use will ever be outside the treatment setting.

PSYCHEDELIC ACCESS AND NEXT STEPS

What's next for psychedelic research? Ajilore says he hopes for an expansion of research and the number of studied psychedelic substances.

"I would like to see well-conducted clinical trials of psychedelics involving more diverse participants that may have not had prior positive experiences with psychedelics," he says. "I think this would make the clinical use of these agents more generalizable."

Williams says research into a range of psychedelic substances matter, especially when substances such as ibogaine and psilocybin have extended periods of psychoactive effects—with long periods of onset and taking hours to wear off—while substances such as DMT/5MeO-DMT have much faster psychoactive effects. The problem, he notes, are that all of these substances are tightly controlled by the U.S. government as Schedule I substances; the exception is the most studied rapid-acting psychomimetic substance, ketamine, a Schedule III drug, which Ghaznavi notes is not a classic psychedelic drug.

To work with these drugs in the lab, researchers must apply to the U.S. government under strict regulations, which can take years, and procure synthetic or semi-synthetic versions of the drugs from only a couple of tightly controlled labs that produce the compounds. The regulations of working with Schedule 1 compounds continue, Ghaznavi explains, as researchers then need to report their findings to the U.S. Food and Drug Administration.

"Barriers to the use of natural products include both characterization and standardization of dose within and between different batches of natural products, difficulty in maintaining purity of natural products, unknown influence of the hundreds of additional compounds that can be present in varying concentrations in natural products, and characterizing and maintaining the stability of compounds in natural products," Barrett says.

For researchers, says Williams—whose subjects used a semi-synthetic ibogaine from a lab in Mexico—the tight control on these drugs can delay or deter studies and make it difficult to get these drugs in the hands of scientists.

"There is a scientific need for psychedelics to be rescheduled lower than Schedule 1. If these substances prove to be efficacious in rigorous clinical trials, the responsibility to administer them should be placed back into the hands of clinicians. But it's going to take some time to get there," he says.

Then, Williams says, more research will be possible in a wider variety of substances on a wider variety of patients.

Williams' next steps with ibogaine? "If therapeutic efficacy is clear in the next planned randomized trials, along with a cardiac safe way to administer [ibogaine], we may be able to see it as a therapeutic option," he says.