Psychedelic drugs fell from grace in the 1960s. Now, scientists are rediscovering them as potential treatments for a range of illnesses

By Kai Kupferschmidt
Should researchers try psychedelics themselves? And what can be learned from the drugs' controversial history?

THE PSYCHEDELIC ERA BEGAN with a bold self-experiment. On a Monday afternoon in April 1943, Albert Hofmann, a chemist at the pharmaceutical company Sandoz in Basel, Switzerland, took 250 micrograms of LSD. Hofmann had derived the compound from ergot, a fungus that grows on wheat, 5 years earlier in search of something to stimulate blood circulation and breathing, but it had shown few effects on rodents. Now, on a hunch, he decided to try it himself.

As Hofmann biked home, the world began to appear distorted and time seemed to slow. At home, the furniture turned into threatening forms, his neighbor appeared to him as a wicked witch, and he felt his sense of self dissolve. He thought he was losing his mind. “A demon had invaded me, had taken possession of my body, mind, and soul,” he later wrote. The next morning, however, he woke up with a clear head, feeling euphoric. “I was aware that LSD, a new active compound with such properties, would have to be of use in pharmacology, in neurology, and especially in psychiatry,” he wrote. Sandoz soon started producing the drug under the name Delysid and asked researchers all over the world to experiment with it.

Doctors and scientists embraced LSD. Some started giving patients single doses of up to 800 micrograms in hopes of inducing extreme experiences that might lead to permanent changes in behavior. Others gave psychotherapy patients repeated low doses as a way of “loosening their minds.” Researchers reported positive results in depression, anxiety, obsessive-compulsive behavior, and other disorders.

Most of the experiments were not up to modern standards, says neuroscientist Franz Vollenweider of the University of Zurich in Switzerland. Success was measured in vague terms, control groups were often lacking, or participants and experimenters weren’t blinded. Still, the studies were very suggestive, and some have stood the test of time, says Robin Carhart-Harris, who studies psychedelic substances at Imperial College London. A 2012 meta-analysis, for instance, showed that in randomized, double-blind trials done between 1966 and 1970, 59% of alcoholics who received LSD showed lower levels of alcohol misuse in the months afterward, compared with only 38% of those who received placebo.

The experiments of that era went well beyond potential treatments. Some researchers sought to instill mystical or religious experiences in volunteers or help resocialize criminals. Others gave the drugs to artists and studied how it changed their work.

Hofmann, meanwhile, conjured a second demon from mysterious mushrooms said to have been used for sacred ceremonies in Mexico for centuries. Neither mice nor dogs showed any reaction to the mushrooms, so Hofmann again turned to self-experimenting. By testing different extracts of the mushrooms on himself and co-workers and purifying those with a psychedelic effect, he managed in 1958 to isolate two equally active molecules, psilocybin and psilocin. Both are closely related to LSD, but psilocybin was the more stable one. Again, Sandoz began providing it to researchers worldwide.

IN A SMALL ROOM at a psychiatric hospital in Zurich, Martin is tripping. He shifts his position on the bed but feels, strangely, as if his body keeps moving. He sees a colorful mist swirling above the floor and the orange bedspread starts glowing. The student knows what that means: The five
unmarked capsules he was given 20 minutes ago contained not a placebo but rather 25 milligrams of psilocybin.

Martin is just one of hundreds of volunteers who have been sent on a psychedelic trip here over the years. The cradle of LSD and psilocybin, Switzerland is still a center for psychedelic research. Vollenweider started out in 1990, comparing the effect of LSD with that of ketamine and amphetamines for his Ph.D. thesis.

At the time, little was known about how psychedelics produce their extreme effects on the mind. Scientists had noticed, however, that their potency seemed to correlate with how strongly they bind to a class of serotonin receptors called 2A. In 1998, Vollenweider showed that blocking that receptor with the chemical ketanserin blocked psilocybin’s effects. Most researchers now agree that classic psychedelics like LSD, mescaline, and DMT—the key component in ayahuasca, a psychedelic brew from the Amazon—work by engaging this receptor.

Just how that unleashes such overpowering effects is unclear, however. Vollenweider has published studies showing an increase in brain activity, particularly in the frontal cortex. Flooding that part of the brain with too much information may lead to hallucinations and fracture the mind, he says. But in a recent brain imaging study, Carhart-Harris found that psilocybin actually reduced activation in important parts of the brain. He thinks psychedelic drugs activate a particular set of neurons that disrupt the regular pattern of activation in the cortex, the way a few irregular clappers can disrupt an audience clapping in synchrony.

The regular pattern is the basis of our sense of self, Carhart-Harris says: “When this organization collapses, the self dissolves.” Regions that are usually controlled by the cortex become more autonomous, which may explain why people on psychedelics can have ecstatic experiences as well as terrifying trips. “The emotion centers have been let off the leash, if you want,” Carhart-Harris says. Hallucinations may occur because the shift in brain activity seems to allow visual processing to be more easily influenced by someone’s beliefs.

An hour after he has taken the capsules, Martin is lying in a scanner and feels as if he is floating. “All my negative feelings were erased. I kept grinning,” he later recalls. On a screen, Martin is shown representations of himself and two other people playing a ball game together. After a while, the other two start excluding Martin from the game. In earlier studies, Vollenweider’s group showed that people who take psilocybin respond less strongly to negative images, such as photos of an accident. Now, the researchers want to find out whether the drug can ease people’s sadness about being excluded.

Vollenweider and Carhart-Harris both plan to give the drug to depressed patients. But they disagree on how it might help them. Vollenweider notes that an excess of serotonin 2A receptors in the frontal cortex is thought to contribute to depression; by binding to and overstimulating these receptors, psilocybin may trigger the brain to reduce their numbers, he says. On top of that, psilocybin may also trigger the release of a factor called BDNF, which can help neurons make new connections.

Carhart-Harris, in contrast, thinks the antidepressant effect is related to the drug’s ability to disrupt brain networks, in particular the so-called default network, which is active when people think about themselves.
Healing with a high?

A selection of recent and planned trials with psychedelic drugs

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>SUBSTANCE</th>
<th>INDICATION</th>
<th>TREATMENT</th>
<th>NUMBER OF PATIENTS</th>
<th>STATUS</th>
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<tbody>
<tr>
<td>Harbor-UCLA Medical Center, Los Angeles, California</td>
<td>Psilocybin</td>
<td>Existential anxiety related to cancer</td>
<td>Two experimental sessions a few weeks apart, one with psilocybin and one with placebo</td>
<td>12</td>
<td>Published in 2011</td>
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<tr>
<td>Private practice in Solothurn, Switzerland</td>
<td>LSD</td>
<td>Anxiety in patients with life-threatening disease</td>
<td>Psychotherapy, including two sessions on LSD</td>
<td>12</td>
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<td>Two independent clinics in Mexico</td>
<td>Ibogaine</td>
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<td>Ibogaine-assisted psychotherapy</td>
<td>30</td>
<td>Completed in 2012; unpublished</td>
</tr>
<tr>
<td>New York University, New York City</td>
<td>Psilocybin</td>
<td>Existential anxiety related to cancer</td>
<td>Nine preparatory psychotherapy sessions; two dosing sessions (one psilocybin, one placebo)</td>
<td>32</td>
<td>Ongoing since 2009</td>
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<tr>
<td>Johns Hopkins University, Baltimore, Maryland</td>
<td>Psilocybin</td>
<td>Existential anxiety related to cancer</td>
<td>Several psychotherapy sessions, including one on psilocybin</td>
<td>44</td>
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<tr>
<td>Johns Hopkins University</td>
<td>Psilocybin</td>
<td>Nicotine addiction</td>
<td>Several preparatory sessions, then three daylong sessions with psilocybin</td>
<td>15 in an open-label pilot; 80 in a controlled trial against nicotine patch</td>
<td>Pilot completed; paper under review</td>
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<tr>
<td>Imperial College London</td>
<td>Psilocybin</td>
<td>Depression</td>
<td>Psychotherapy with two sessions on oral psilocybin</td>
<td>12 in an open-label pilot; 60 in a controlled trial</td>
<td>Expected to start by the end of 2014</td>
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<tr>
<td>University of Alabama, Birmingham</td>
<td>Psilocybin</td>
<td>Cocaine dependence</td>
<td>Several preparatory sessions, then one daylong session with psilocybin</td>
<td>40</td>
<td>Expected to start by the end of 2014</td>
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<td>Source: ClinicalTrials.gov; participating researchers</td>
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Patients with depression spend too much time on self-reflection, Carhart-Harris says. “These people are stuck in their own heads, they cannot engage in the world.” Psilocybin may loosen that psychological spasm, he suggests. “It’s like taking a snow globe and shaking it.”

Florian Holsboer, director of the Max Planck Institute of Psychiatry in Munich, Germany, says both hypotheses are intriguing, but he is strongly opposed to treating patients with psychedelic drugs. “You can’t give patients some substance just because it has an antidepressant effect on top of many other effects. That’s too dangerous,” he says.

Holsboer says scientists should use psilocybin studies as a starting point to find similar substances that have antidepressant effects but aren’t psychedelic. Molecules that engage the serotonin 2A receptor but don’t cause a trip do exist, Vollenweider says; his group is planning to study some of them. But Carhart-Harris is convinced that for the treatment of depression, the psychedelic experience itself is essential. “This is not a chemical effect,” he says.

THE PSYCHEDELIC EXPERIENCE was the downfall of these compounds last time around, however, when enthusiasm for it got out of hand. To U.S. military and intelligence agencies, the new drugs seemed to offer exciting ways of fighting enemies both at home and abroad. In secret and sometimes highly unethical research, they tried to develop them into a truth serum and a psychochemical weapon that could disorient opposing armies. To millions of others, LSD and psilocybin seemed to offer the reverse: freedom and inner peace, escape from the material world, and heightened sexual pleasure. Harvard University psychologist Timothy Leary became the high priest of the cult, preaching a whole generation to “turn on, tune in and drop out.” Reports of drug parties at Leary’s home and allegations that he had given drugs to students led to his firing from the university.

As recreational use of psychedelic drugs spread in the United States—a trend that never really caught on in Europe—their dark side started to show. The drugs are very safe in a research environment, where subjects are carefully screened, prepared, and supported by therapists, but they can have horrific consequences in other situations, Ross says. Psychedelics can induce psychoses and make people agitated and violent toward themselves or others; people at risk of psychoses should never use them. In the ’60s, more and more users ended up in emergency rooms, and newspapers ran stories about people walking in front of a car or jumping out of a window because they believed they could fly.

LSD became a liability for its maker. In a letter in August 1965, Sandoz announced it would stop shipping the drug because its danger “has increased considerably and in some parts of the world has reached the scale of a serious threat to public health.” In 1970, former President Richard Nixon signed the Controlled Substances Act, which classified drugs into five schedules according to their dangers and medical usefulness; LSD, psilocybin, and other hallucinogenics were placed in schedule I. A year later, the United Nations adopted the Convention on Psychotropic Substances. Many countries adopted laws similar to those in the United States.

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Stephen Ross, Bellevue Hospital Center
In theory, the regulations allowed for scientific investigation of the substances, but there were many hurdles and funding was drying up. Moreover, the drugs had developed such a bad reputation that scientists on both sides of the Atlantic lost interest, Griffiths says. “The whole system shut down.”

WHEN TAMMY BURGESS WAS diagnosed with ovarian cancer, the tumor had already metastasized. A CT scan of her abdominal cavity showed many little growths. “It looked like oatmeal,” the 55-year-old New Yorker says. The cancer had also spread to her lungs. Paralyzed, Burgess laid on her couch for hours, watching old episodes of *The West Wing*. “This overwhelming sense of dread just permeates every cell of your body. You think about being ill, about not wanting to die,” she recalls.

Burgess had 9 weeks of chemotherapy, then a surgery—she calls it the decancering—then more chemotherapy. The treatment was very successful, and Burgess has had no recurrence. But as it neared its end, she got more and more depressed. She couldn’t sleep, couldn’t stand silence. The image of the cancer on an ultrasound stuck in her mind: “All these little tiny circles, seeing that menace floating inside of me, just gray and black, silent and eerie,” she says. “I don’t think I ever felt the kind of relief that my friends and relatives were feeling.”

Burgess enrolled in Ross’s study of psilocybin. An addiction specialist, Ross had become interested in psychedelics in 2006. “In psychiatry training, I had learned that these substances were banned, dangerous, and addictive. I didn’t learn anything about their history and all the research that took place from the ’50s to the early ’70s,” he says. To him, “the therapeutic application of mystical, spiritual states within psychiatry” was a completely new idea.

Ross and two colleagues formed a study group to educate themselves. They learned that a doctor named Rick Strassman at the University of New Mexico, Albuquerque, had scraped together funds for a DMT study in 1990. David Nichols, a pharmacologist at Purdue University in West Lafayette, Indiana, who had produced the DMT for it, had founded a nonprofit called the Heffter Research Institute in Santa Fe a few years earlier. By 1995, Doblin was 29 when he first tried 3,4-methylenedioxymethamphetamine (MDMA). The experience was life-changing, Doblin recalls. Thirty years later. At the time, some psychotherapists had started giving the drug to patients, claiming it helped them talk and fostered a more trusting atmosphere. Doblin—who took the drug privately—experienced all that and more; MDMA “helped open me up to my emotions and enabled me to feel deep and profound love,” he says. He decided to study clinical psychology and devote his career to giving MDMA a role in therapy.

Today, MDMA has become known primarily as the illegal party drug ecstasy—but Doblin has kept his plan alive. The Multidisciplinary Association for Psychedelic Studies (MAPS) in Santa Cruz, California, which he leads, has funneled millions into studies of MDMA as a treatment for post-traumatic stress disorder (PTSD), despite political headwinds and scientific skepticism. Two phase II studies have been completed, one with encouraging results, and several more are in progress.

Although often lumped together with psychedelics like LSD or psilocybin, MDMA has a different mode of action and doesn’t produce hallucinations. It activates brain receptors for dopamine and noradrenaline and releases serotonin from nerve endings, leading to the characteristic feeling of euphoria that made it popular in clubs and at dance events.

Its potential to help PTSD patients is clear, says psychiatrist David Nutt of Imperial College London. Such patients relive a psychological trauma again and again and are often plagued by fear and thoughts of suicide; therapists try to help them master their memory by revisiting it in a safe atmosphere without overwhelming emotions. MDMA might make that easier because it reduces fear and fosters trust, Nutt says.

But questions about safety have long dogged MDMA. Some clubbers using it died from dehydration, and there have been reports of brain damage; in 1985, the U.S. Drug Enforcement Agency (DEA) made MDMA illegal and ranked it among the most dangerous drugs. Many other countries followed suit. This kept MDMA out of psychotherapeutic practice but didn’t do much to stop its use elsewhere; almost 20 million people consumed the drug in 2011, according to United Nations estimates. And some scientists say the risks have been overblown. Nutt, for one, argues that using MDMA is safer than horse riding (Science, 31 January, p. 478).

Following DEA’s decision, Doblin changed career plans and studied public policy—and in 1986, he founded MAPS to pursue his dream. In 1992, the U.S. Food and Drug Administration (FDA) allowed a phase I safety study, which Doblin and psychiatrist Charles Grob of the University of California, Los Angeles, conducted from 1993 to 1995. They then started to prepare a study to treat cancer patients’ anxiety with MDMA, but in 1999, Grob decided to focus on psilocybin instead. FDA approved an MDMA study in PTSD patients in 2001, and it took 3 more years to get the green light from institutional ethics panels and DEA.

The study, finally published by Doblin and South Carolina psychiatrist Michael Mitrohefer in 2010, enrolled 20 patients, most of them female sexual assault victims. After 2 months, 10 out of 12 patients who had received MDMA along with psychotherapy no longer met the diagnostic criteria for PTSD, compared with only two out of eight patients who had received a placebo.

It was a small study, and another trial in Switzerland showed no significant effect. But MAPS is now funding further phase II studies in Israel, Canada, and the United States. The association, which has also funded some work on classic psychedelics, employs 14 people and took in more than $1.5 million in private donations last year. But with the current political climate and the small size of the patient pool, it will be “a long time before we find out if this is effective,” Doblin says. Science
PHOTOS: (TOP TO BOTTOM) ALAN ROCKEFELLER; DEA

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One Friday Morning, Burgess came into that room carrying a few personal things: a blanket, a picture of the house she grew up in. The therapists, a man and a woman, explained what would happen once more and went over the safety aspects. An antipsychotic medicine was at hand, Burgess was told, in case she wanted to end the experience. Then, she was handed a big chalice with the psilocybin capsule inside. She swallowed it with some water, lay down on the couch, and put on headphones and eyeshades.

Soon, Burgess started to float in a black space, surrounded by beautiful bright stars in various colors. “I kept hearing ‘Hi. Hi,’ ” she says. She heard herself saying “Hi. I’m Tammy from Earth ... ” Later, ancient stone faces appeared, crumbling to dust then taking shape again. She met a doctor and asked if there would ever be a cure for cancer. “It doesn’t matter,” he answered. “Everyone has to die.” That comforted her in a weird way.

By the time Burgess went home that night, she felt like something had lifted. At work, someone told her that she seemed her old self again. “I just got better,” she says. Ross says he has seen many similar experiences. “The first couple of years, I felt like I was in the wilderness; I was hanging out with a bunch of old dudes that had kept the flame flickering all these years but were tired,” Ross says. “I thought to myself, ‘This is the stupidest thing I have ever done.’” Now, he’s convinced he’s on to something.

The study is scheduled to finish later this year and Ross hopes to publish results soon afterward. “We have taken a peek at the data and there seems to be a very big treatment effect of psilocybin against placebo,” he says. A similar phase II study is going on at Johns Hopkins; Ross is already thinking about a phase III trial that might lead to Food and Drug Administration approval.

But Vollenweider is critical of Ross’s approach. He says it’s based on the idea that the more a patient’s self dissolves, the more mystical their experience is, the better. “For me that is not a medical concept. It is more like an interesting shamanic concept,” he says. Others have argued that the overwhelming sense of meaningfulness that Burgess and other patients feel is just another of the drug’s illusions. In his essay Return Trip to Nirvana, the writer Arthur Koestler describes listening to music after taking psilocybin. “I suddenly understood the very essence of music, the secret of its magic,” he wrote. The next day, he couldn’t even say what kind of music it had been. “I may just as well have listened to Liberace. ... [M]y soul was steeped in cosmic schmaltz.”

But to Burgess, the experience was real enough. “I believe that when I pass, this is what I will experience again,” she says. And Nichols says the debate about the true meaning of trips is irrelevant for most patients. “If it gives them peace, if it helps people to die peacefully with their friends and their family at their side,” he says, “I don’t care if it’s real or an illusion.”

donations in fiscal year 2013 alone.

Neurobiologist Franz Vollenweider of the University of Zurich in Switzerland calls the MDMA results “exciting,” but is critical of MAPS. “They annoy me, because they pretend to know all the results before a single study is done,” he says. “It’s a political organization” that hopes to decriminalize the drug, he adds. Vollenweider calls Doblin “a dreamer” who won’t be able to finance or manage a phase III trial.

Doblin concedes that he thinks the ban on MDMA should go. “I believe in people’s basic human right to use molecules to explore their consciousness,” he says. But he’s confident he can raise the $15 million needed for a phase III study in 400 patients. MDMA could become a prescription medicine by 2021, he predicts. “I might just get to start my psychedelic psychotherapist career shortly before I turn 70.”

later to support research into psychedelics. At about the same time, the Multi-
disciplinary Association for Psychedelic Studies had started a safety study of MDMA, better known as ecstasy (see sidebar). Ross and his colleagues learned that these events had kicked off a small research renaissance, which they joined.

Leary’s legacy lingers in the minds of modern-day researchers and regulators, however. Psychedelics researchers tend to avoid discussions about their own experiences. “I think psychedelic researchers should be neutral, bland, boring,” Ross says. “I am not interested in destroying my career.” Privately, many admit having tried the drugs. Vollenweider, who has taken psilocybin as part of a dosing study, says it is hard to understand the drug’s effects without firsthand experience. And patients may feel safer if therapists know the unusual terrain themselves, Ross says.

The reemerging field also struggles with some unresolved methodological problems. Many of the new studies are small, and the profound effects of psychedelics “make it virtually impossible to blind subjects,” says John Kelly, an addiction psychiatrist at Massachusetts General Hospital in Boston.

And there are other hurdles. Ross needed a license from the Drug Enforcement Admin-
istration, and he had to install a safe. “The security around it is a little bit ridiculous,” he says. Bellevue Hospital Center, where Ross works, is a city hospital, and some administrators feared that the scientists could be accused of testing psychedelic drugs on poor, dying minority patients. “There were many times that the project was almost finished,” Ross says. Eventually, the dental school offered to host the study. A room was decorated to make patients comfortable. It has a sofa bed and black-and-white photographs of paths snaking into the woods or toward the horizon. Small mushroom sculptures and a copy of the The Tibetan Book of Living and Dying make it feel like the cozy bedroom of a hippie aunt.

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