PSYCHEDELIC HEALING?

Hallucinogenic drugs, which blew minds in the 1960s, soon may be used to treat mental ailments

By David Jay Brown

Mind-altering psychedelics are back—but this time they are being explored in labs for their therapeutic applications rather than being used illegally. Studies are looking at these hallucinogens to treat a number of otherwise intractable psychiatric disorders, including chronic depression, post-traumatic stress disorder, and drug or alcohol dependency.

The past 15 years have seen a quiet resurgence of psychedelic drug research as scientists have come to recognize the long-underappreciated potential of these drugs. In the past few years, a growing number of studies using human volunteers have begun to explore the possible therapeutic benefits of drugs such as LSD, psilocybin, DMT, MDMA, ibogaine and ketamine.

Much remains unclear about the precise neural mechanisms governing how these drugs produce their mind-bending results, but they often produce somewhat similar psychoactive effects that make them potential therapeutic tools. Though still in their preliminary stages, studies in humans suggest that the day when people can schedule a psychedelic session with their therapist to overcome a serious psychiatric problem may not be that far off.

The Trip Begins

Psychedelic drug research began in 1897, when German chemist Arthur Heffter first isolated mescaline, the primary psychoactive compound in the peyote cactus. In 1943 Swiss chemist Albert Hofmann discovered the hallucinogenic effects of LSD (lysergic acid diethylamide) at Sandoz Pharmaceuticals in Basel while studying ergot, a fungus that grows on rye. Fifteen years later, in 1958, he was the first to isolate psilocybin and psilocin—the psychoactive components of the Mexican "magic mushroom," *Psilocybe mexicana*.

Before 1972, close to 700 studies with psychedelic drugs took place. The research suggested that psychedelics offered significant benefits: they helped recovering alcoholics abstain, soothed the anxieties of terminal cancer patients, and eased the symptoms of many difficult-to-treat psychiatric illnesses, such as obsessive-compulsive disorder.

For example, between 1967 and 1972 studies in terminal cancer patients by psychiatrist Stanislav Grof and his colleagues at Spring Grove State Hospital in Baltimore showed that LSD combined with psychotherapy could alleviate symptoms of depression, tension, anxiety, sleep disturbances, psychological withdrawal and even severe physical pain. Other investigators during this era found that LSD may have some interesting potential as a means to facilitate creative problem solving [*see box on page 70*].

Between 1972 and 1990 there were no human studies with psychedelic drugs. Their disappearance was the result of a political backlash that followed the promotion of these drugs by the 1960s counterculture. This reaction not only made these substances illegal for personal use but also made it extremely difficult for researchers to get government approval to study them.

Things began to change in 1990, when "open-minded regulators at the FDA decided to put science before politics when it came to psychedelic and medical marijuana research," says Rick Doblin, a public policy ex-

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pert and head of the Multidisciplinary Association for Psychedelic Studies (MAPS). "FDA openness to research is really the key factor. Also, senior researchers who were influenced by psychedelics in the sixties now are speaking up before they retire and have earned credibility." Chemist and neuropharmacologist David E. Nichols of Purdue University adds, "Baby boomers who experienced the psychedelic sixties are now mature scientists and clinicians who have retained their curiosity but only recently had the opportunity to reexplore these substances."

Research Begins Anew

The efforts of two privately funded organizations have catalyzed much of the recent wave of research: MAPS, founded in 1986 by Doblin, and the Heffter Research Institute, started in 1993. Outside the U.S. there are groups such as the Beckley Foundation in England and the Russian Psychedelic Society. These seek out interested researchers, assist in developing the experimental design for the studies, and help to obtain funding and government approval to conduct clinical trials. They have initiated numerous FDA-approved clinical trials in the U.S., Switzerland, Israel and Spain. So far the agency has approved seven studies, with two under review and more on the way.

Current studies are focusing on psychedelic treatments for cluster headaches, depression, obsessive-compulsive disorder (OCD), severe anxiety in terminal cancer patients, post-traumatic stress disorder (PTSD), alcoholism and opiate addiction. New drugs must pass three clinical milestones before they can be marketed to the public, called phase I (for safety, usually in 20 to 80 volunteers), phase II (for efficacy, in several hundred subjects) and phase III (more extensive data on safety and efficacy come from testing the drug in up to several thousand people). All the studies discussed in this article have received government approval, and their investigators are either in the process of recruiting human subjects or have begun or completed research on human subjects in the first or second stage of this trial process.

Psychedelic drugs affect all mental functions: perception, emotion, cognition, body awareness and one's sense of self. Unlike every other class of drugs, psychedelic drug effects depend heavily on the environment and on the expectations of the subject, which is why combining them with psychotherapy is so vital.

"Psychedelics may be therapeutic to the extent that they elicit processes that are known to be useful in a therapeutic context: transference reactions and working through them; enhanced symbolism and imagery; increased suggestibility; increased contact between emotions and ideations; controlled regression; et cetera," says psychiatrist Rick Strassman of the University of New Mexico School of Medicine, who from 1990 to 1995 performed the first human study using psychedelic drugs in about 20 years, investigating the effects of DMT on 60 human subjects. "This all depends, though, on set and setting," he cautions. "These same properties could also be turned to very negative experiences, if the support and expectation for a beneficial experience aren't there."

Mechanisms and Targets

Scientists divide classical psychedelic drugs into two basic chemical groups: tryptamines (such as LSD, DMT and psilocybin) and phenethylamines (such as mescaline and MDMA). In addition, some people consider so-called dissociative anesthetics (such as ketamine and PCP) to be psychedelic drugs, although the way they affect the brain is quite different.

The exact mechanisms differ, but all the tryptamine hallucinogens—which make up the

FAST FACTS

Mind-Bending Therapies

1» **The drugs that put the "psychedelic" into the sixties are now the subject of renewed research interest because of their therapeutic potential.**

2» **Psychedelics such as LSD and the compound in magic mushrooms could ease a variety of difficult-to-treat mental illnesses, such as chronic depression, post-traumatic stress disorder, and drug or alcohol dependency.**

3» **Clinical trials with various substances are now under way in humans.**

majority of psychedelic drugs—selectively bind to specific serotonin receptors on neurons, mimicking the effects of the nerve-signaling chemical, or neurotransmitter, serotonin on these receptors. Phenethylamines mimic the chemical structure of another neurotransmitter, dopamine. They actually bind to many of the same serotonin receptors activated by the tryptamines, however. Serotonin is responsible for many important functions, including mood, memory, appetite, sex and sleep. It is such an essential neurochemical that any substance—such as a hallucinogen—that interferes with its action might be expected to produce dramatic changes in brain function.

How do the drugs create their perceptual effects? Neuroscientists believe that activation of a particular set of serotonin receptors, the 2A subtype, which are highly expressed (or present) in the cortex, the outermost layer of the brain, interferes with the processing of sensory information. Consciousness is thought to involve a complex interaction among the cortex, the thalamus and the striatum. Disruption of this network by activation of serotonin 2A receptors is now the most popular theory for the mechanism of action for tryptamine and phenethylamine psychedelics.

"There are at least two possible mechanisms for beneficial actions," Nichols says. "The first simply involves a change in the numbers of brain serotonin 2A receptors. Activation of serotonin 2A receptors by psychedelics causes the number of receptors expressed on the surface of neurons to decrease, a process called downregulation. For some disorders, such as OCD, it may be this receptor downregulation that could be therapeutic," he explains. "The other possible mechanism is a psychological effect that is harder to define but in some way produces changes in the way the subject perceives pain and distress. Psychedelics seem able to produce a profound cognitive change that provides the patient with a new insight—the ability to see the world from a new perspective—somehow reducing anxiety and raising the pain threshold."

MDMA (3,4-methylenedioxy-*N*-methylamphetamine) is also chemically classified as a phenethylamine, but its action in the brain is substantially different from that of other drugs discussed in this article. "In contrast to most psychedelics, MDMA does not directly stimulate serotonin 2A receptors but instead causes dopamine, serotonin and norepinephrine [another neurotransmitter] to be released from their stores in neuron endings," Nichols says. There is some controversy about whether MDMA has neurotoxic effects. Most researchers believe, however, that the occasional moderate use of MDMA at therapeutic doses would not be damaging. There have been no recent studies using mescaline, although MAPS plans to initiate some in the future.

In contrast to the traditional psychedelics, the dissociative anesthetics selectively bind to *N*-methyl-D-aspartic acid (NMDA) receptors, blocking the neurotransmitter glutamate from activating these receptors. "Because glutamate is an essential neurotransmitter that activates neurons, this blocking effect seems to prevent the processing of sensory information by the brain," Nichols states.

Psychedelic parade: the ergot fungus, which contains a precursor to LSD (*left*); tablets of LSD (*center*); and "magic mushrooms" (*right*).

Ketamine appears to hold particular promise as a psychedelic therapy because it is already among the selections in Western medicine's pharmacopoeia. In addition to being part of a different chemical class of drugs than the other psychedelics, ketamine is in a separate legal class as an FDA-approved schedule III drug. This designation means that any physician can administer it for an off-label use if he or she believes it will help the patient.

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(The Author)

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A Spark for Creativity?

Nobel Prize winners Francis Crick and Kary Mullis reportedly attributed part of their breakthrough scientific insights to psychedelic drugs. And architect Kyosho Izumi's LSD-inspired design of the ideal psychiatric hospital won a commendation for outstanding achievement from the American Psychiatric Association. Others scoff at the notion that the drugs deserve the credit. What do studies say?

In 1955 psychiatrist Louis Berlin investigated the effects of mescaline and LSD on the painting abilities of four nationally recognized artists. Although the study showed that the artists' technical abilities were hampered, a group of independent art critics judged the experimental paintings to have "greater aesthetic value" than the artists' usual work.

Under the influence: An abstract painting produced two hours after an artist ingested LSD for an experiment (*left*) and a Kachina doll painted before the drug experience.

Two years later Los Angeles psychiatrist Oscar Janiger asked 60 prominent artists to paint a Native American doll before taking LSD and then again while under its influence. A panel of independent art critics and historians then evaluated the results. Members generally agreed that the craftsmanship of the second set of paintings suffered, but many of those pieces received higher marks for imagination.

In 1965 psychologist James Fadiman and social scientist Willis Harman of San Francisco State College administered mescaline to workers in various fields as they sought a creative solution for a professional problem. After some psychological preparation, subjects worked individually on their problem throughout their mescaline session. Psychological tests, subjective reports, and the eventual industrial or commercial validation and acceptance of the finished product or final solution measured the output of each volunteer. Virtually all individuals produced solutions judged highly creative and satisfactory by these standards.

Psychologist Stanley Krippner of the Saybrook Graduate School and Research Center in San Francisco, however, remains skeptical. "It is naive to claim that psychedelics produce creative experience," he argues. "At best, they may be one of many factors that result in something new that comes into being." —*D.J.B.*

chedelic drugs may enhance suggestibility and certain aspects of psychotherapy, the benefits of dissociative anesthetics such as ketamine and ibogaine may simply be the result of enduring biochemical changes in the brain. For example, in 2006 Carlos Zarate of the National Institute of Mental Health published a study demonstrating ketamine's unusual antidepressant properties [see "Good News about Depression," by Walter Brown; Scientific American Mind, June/July 2007]. A single infusion of ketamine relieved symptoms of depression in some patients within a few hours, and that relief persisted for several days.

This was the third study that showed ketamine's powerful and enduring antidepressant effects. In an intriguing finding from one of the previous studies, subjects received the ketamine as an anesthetic for orthopedic surgery—so they were not even conscious during the mind-altering segment of the drug's action in the brain—and the antidepressant effects occurred postoperatively.

In other work seeking to help cure addicts, a preliminary ketamine study, in which psychiatrist Evgeny Krupitsky of St. Petersburg, Russia, treated 59 patients with heroin dependency, produced encouraging results. And the Iboga Therapy House in Vancouver, Canada, has recently begun a study that has so far successfully treated three out of 20 opiate-addicted subjects with ibogaine. The experimental procedure substantially reduced the withdrawal symptoms associated with opiate addiction, helping the addicts to recover and break their dependency on the drug.

OCD, Cluster Headaches and Cancer

In addition to the promising work with ibogaine and the dissociative anesthetics, progress is also being made in the study of conventional psychedelics. In 2006 investigators at the Johns Hopkins School of Medicine published the results of a six-year project on the effects of psilocybin, in which more than 60 percent of the par-

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ticipants reported positive changes in their attitude and behavior after taking the drug, a benefit that lasted for at least several months.

In another 2006 study, researchers at the University of Arizona, led by psychiatrist Francisco Moreno, found that psilocybin relieved the symptoms of nine patients with OCD. The patients suffered from a wide range of obsessions and compulsions. Some of them showered for hours; others put on their clothes over and over again until they felt right. All nine experienced improvements with at least some of the doses tested.

"What we saw was a drastic decrease in symptoms for a period of time," Moreno says. "People would report that it had been years since they had felt so good." Moreno cautions that the goal was simply to test the safety of administering psilocybin to OCD patients and that the true effectiveness of the drug is still in question until a larger controlled study can be conducted. Such a study is being planned, although there are currently no funds available for it. According to Moreno, however, no treatment in the medical literature eases OCD symptoms as fast as psilocybin does. Whereas other drugs take several weeks to show an effect, psilocybin worked almost immediately.

Preliminary results of a current study led by psychiatrist Charles Grob of the Harbor-UCLA Medical Center suggest that psilocybin may reduce the psychological distress associated with terminal cancer. This research seeks to measure the effectiveness of psilocybin on the reduction of anxiety, depression and physical pain in advanced-stage cancer patients. Grob's study is almost complete; 11 out of 12 subjects have already been treated. Although the formal data analysis has not been completed, "my impression," Grob says, "from just staying in touch with these people and following them is that some do seem to be functioning better psychologically. There seems to be less anxiety, improved mood and an overall improved quality of life. There also seems to be less fear of death."

The first studies of psychedelic drugs at Harvard University since 1965 are also now under way. In one study, psychiatrist John Halpern and his colleagues are looking into using LSD and psilocybin to treat the debilitating symptoms of cluster headaches. The researchers, who are in the process of recruiting subjects, will probably begin trials in early 2008.

Acute Anxiety and PTSD

Another study at Harvard, also led by Halpern, will look into MDMA-assisted psychotherapy in subjects with anxiety associated with advanced-stage cancer—similar to Grob's psilocybin study—using measures to evaluate anxiety, pain and overall quality of life. This study is also in the process of recruiting human subjects.

Psychiatrist Michael Mithoefer in Charleston, S.C., is running an MDMA study for treatment-resistant PTSD victims of crime, war or childhood sexual abuse. So far 17 out of 20 such subjects have already undergone the experimental therapy. "At this point the results are very promising," Mithoefer says. "I think we're seeing pretty strong, robust effects in some people. I hasten to add these are preliminary findings—we're not ready to draw conclusions yet. But assuming it keeps going this way for the rest of the study, it certainly seems that there's very good reason to go on to larger phase III trials."

Although we are still in the early days of psychedelic therapy research, the initial data show considerable promise. A growing number of scientists believe that psychedelic drugs may offer safe and effective help for people with certain treatment-resistant psychiatric disorders and could possibly help some people who receive partial relief from current methods to obtain a more complete healing. M

(Further Reading)

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- **MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder.** M. Mithoefer. Ibid.
- The Multidisciplinary Association for Psychedelic Studies (MAPS) publishes a quarterly bulletin that reports on the status of current scientific research into psychedelic substances: **www.maps.org**