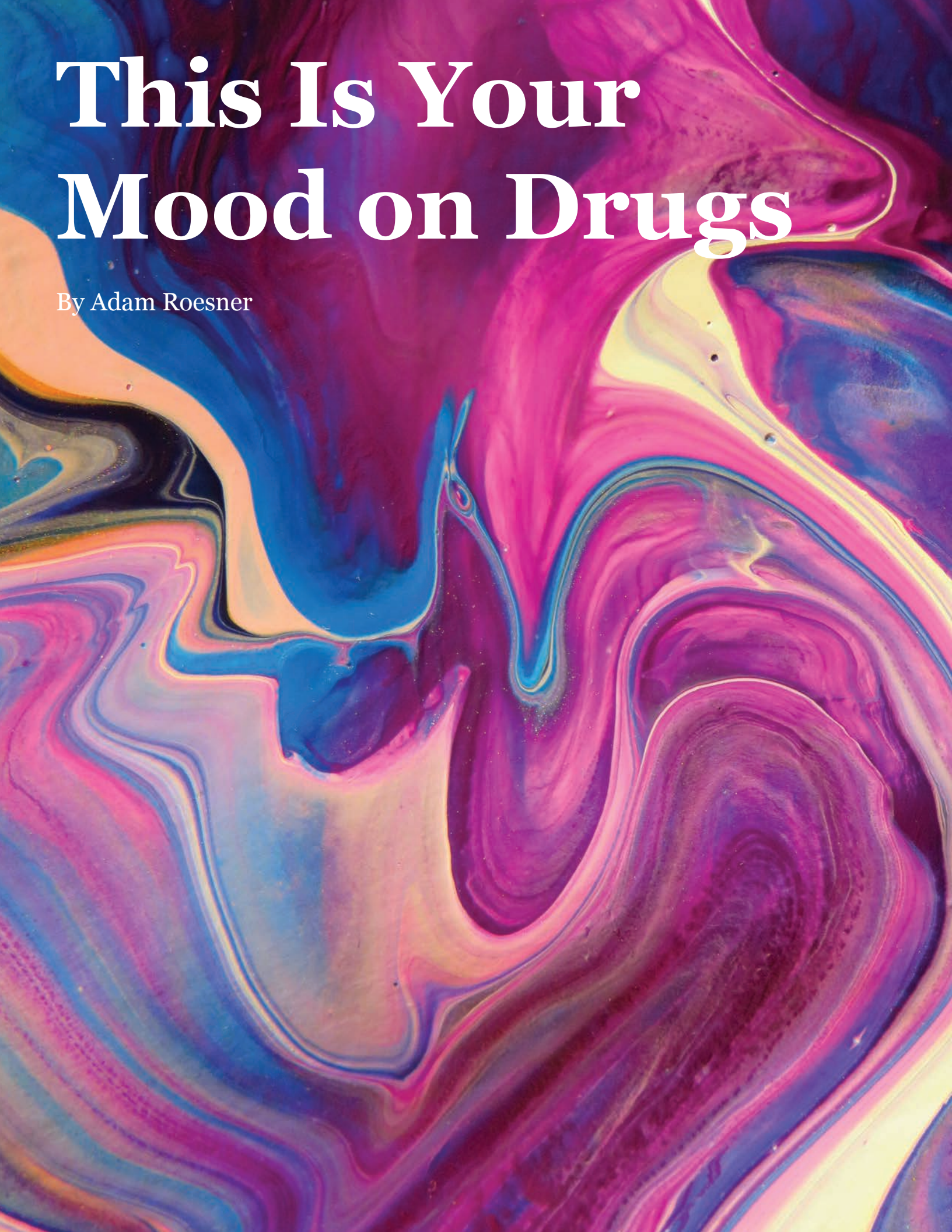
This Is Your Mood on Drugs

By Adam Roesner



Pharmacological science has produced many miracles in the last 70 years or so. From the invention of antidepressant drugs to Narcan, it is clear that major progress has been made towards the treatment of historically untreated or mistreated conditions such as depression, anxiety, and addiction. All is not perfect in the realm of psychiatry, however, as approximately 17.3 million American adults suffer from depression in a given year, approximately 40 million suffer from anxiety, and, in 2017 alone, approximately 19.7 million over the age of 21 suffered from a substance abuse disorder. What's worse, according to a study conducted by the Depression and Bipolar Support Alliance, about 50% of unsuccessful treatment for depression is due to medical noncompliance, meaning that patients are not taking their medicine as prescribed. The fight to treat mood disorders is not won yet, and it may be time to try approaches that were previously declared off-limits. Enter: psychedelics.

In 2006, researchers at Johns Hopkins University published a breakthrough study on the sustained qualitative effects of a single session of psilocybin (popularly known as magic mushrooms) use in a clinical setting[1]. The people that participated in this study were primarily college-educated, employed adults who reported not having used psychedelics in their lives prior to the study. Furthermore, the participants were not financially compensated for their participation in the study, which is quite uncommon. These participants made time in their busy schedules to participate in this study for the primary reason that they were interested in the psychedelic experience.

The researchers in this study were well aware that doing clinical research using psychedelics is not an easy sell, so they took many precautions they felt would protect both the participants and the researchers from the deleterious effects of conducting research with such substances. Participants met with the researcher that would monitor their session four times prior to taking the psilocybin and four times afterwards in order to establish a rapport with the researcher that would make them feel safe during the height of their psychedelic experience. The dosage of psilocybin was determined using data from several previous studies and intended to be a high-safe dose that would occasion a psychedelic induced hallucinogenic state, also known as a trip, but not so high that there would be any reason for concern about the patient. Participants and their monitors would spend the entire trip (an eight hour session, in total) in a special living room-style space arranged specifically for this study, complete with calming music and mood lighting. All of these steps were intended to minimize the chances that someone experiences the negative aspects of a trip, a carefully made decision that we will return to later.

Breaking the norms of psychedelic research, this study was the first of the new generation of research to explore the behavioral effects of psychedelics rather than just investigating their biochemical mechanics. What they found would lay the groundwork for those that would follow in their footsteps and pave a new path in the search for treatments for mood disorders. The team found in both the two-month and the 14-month follow-ups that individuals reported their experience had fundamental and overwhelmingly positive effects on their lives. The average participant reported that they had felt more altruistic and vastly more likely to be positive, in general as well as specifically about themselves. Moreover, the average participant, all of whom were reportedly new to psychedelics, rated this experience among the most significant spiritual experiences of their lives. And the real kicker: they rated this experience among the ten most meaningful experiences of their lives[2]. While this is only one study, it does cause one to wonder why more research isn't done in this area. To understand that, one has to look at the history of psychedelics in America.

The story of American psychedelic use begins, oddly enough, in the year 1943 in Switzerland, with a chemist by the name of Albert Hofmann. An employee of Sandoz Laboratories, Albert spent his days synthesizing derivatives from plants and fungi, and led an unremarkable life. But on April 16, 1943, Albert inexplicably decided to revisit a compound he had synthesized four-and-a-half years prior when he was working on derivatives of lysergic acid, a compound produced in wild ergot fungi. Specifically, he chose to revisit LSD-25, so named because it was the 25th compound he had derived from lysergic acid (LS) and because its characteristic shape included diethylamide (D). It was on this day that he accidentally absorbed some of it through the

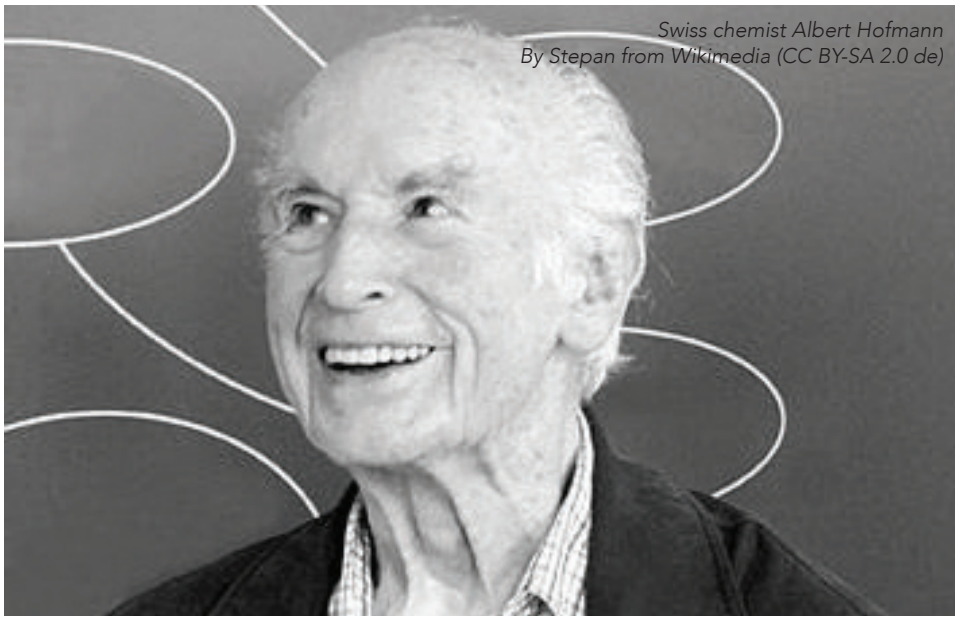
Psilocybin Mushrooms

tips of his fingers and began the first documented human acid trip.

This incident triggered a cascade of effects that went on to transform the face of American culture. In 1949, LSD made its way to America, where it was hailed as a psychotomimetic, or a simulator of psychosis. Regardless of the fact that the understanding of how the drug worked on a physiological level to produce its effects was limited, LSD was distributed by Sandoz to therapists in the states to facilitate more effective psychotherapy in patients with depression and/or anxiety, particularly related to death and alcoholism. A recent survey of the studies conducted during this period from 1949-1973 found that there were generally positive outcomes with respect to unipolar mood disorders (major depression or anxiety, for example), with 79.2% of patients judged to improve when treated with either LSD or mescaline, a psychedelic compound derived from the buds of certain cacti[3]. Another more recent review of the literature from this era found that patients seeking treatment for alcoholism had a significantly better chance to improve over a period of months when treated with LSD than those who were not[4].

At this point, you might be wondering how it is possible that these drugs that are heavily associated with socially deviant behavior like living in communes, dropping out of the workforce, and paranoid outbursts could possibly have a beneficial effect on an individual's life. Well, we'll talk about how these drugs that seemed to have such potentially positive effects came to be seen this way, but first a little discussion of the neuroscience of the situation.

Since it emerged in the late 19th century, neuroscience has been permeated by a belief that colors everything that it has been able to say about the mind: the mind is what the brain does. That means that all of the mood disorders that people suffer from are the results of things going askew in the brain. The brain is basically a big network of neurons and other cells working together to process stimuli from the outside world and turn that data into a response the body can then enact. The easiest way to distinguish the myriad different networks that exist in the brain when it comes to talking broadly about families of disorders is by talking about what messenger molecule these networks use, also known as neurotransmitters.



Swiss chemist Albert Hofmann
By Stepan from Wikimedia (CC BY-SA 2.0 de)

Now for Neuro 101 in a few sentences. Neurons communicate with one another by releasing neurotransmitters from one end of their body, called the axon, into what is known as the synapse. The synapse is a miniscule gap, just wide enough to allow for the flow of the fluid-matrix-of-choice for whatever type of neuron you are observing between the two neurons. The area of the next neuron that is specifically designed to receive the neurotransmitter signal is called the dendrite. The neurotransmitters are released from the end of one axon and they bind with the dendrites of the next neuron in their path. Due to the directionality of this interaction we call the neuron that releases the neurotransmitters the presynaptic neuron and the neuron that receives them the postsynaptic neuron. After a little while, the neurotransmitters that haven't bound to the postsynaptic neuron are dealt with in a couple of ways: they are degraded by special molecules in the synapse or they are reabsorbed by the presynaptic neurons. It's important to keep in mind that the things moving around are all inanimate particles which cannot, once sent into the synapse, decide to go anywhere of their own volition. Rather, these movements are entirely probabilistic, which is a challenge for those who would like to manipulate the behavior of these dang things. Right then, back to our discussion.

Generally, we in the neurosciences have been able to narrow down the disorders that affect your mood to the functioning of networks in your brain that all have one thing in common: they all employ the neurotransmitter serotonin. Serotonin is generally thought to be closely linked with mood regulation in the central nervous system[5]. It works by decreasing the likelihood that the neuron it communicates with sends

a signal of its own, also known as suppression. This comes in handy in areas where an increase in activity would cause you trouble. For example, when your amygdala isn't appropriately suppressed, you are likely to experience an unhealthy amount of anxiety that doesn't match the environment that you are in[6]. Healthy levels of serotonin help keep networks like this one quiet until it's time to get riled up for a good reason.

Drugs that are typically prescribed to people diagnosed with mood disorders can work on these networks in a variety of ways. The most well-known and common drugs prescribed to treat depression belong to the family of selective serotonin reuptake inhibitors (SSRIs). These drugs work by closing the channels on the presynaptic neuron that are designed to reabsorb the serotonin it released. This allows for the serotonin to stay in the synapse for longer and have a better chance of suppressing the postsynaptic neuron. Another class of these drugs, monoamine oxidase inhibitors (MAOIs), operate by inhibiting the molecule monoamine oxidase. Dear reader, it is only the intrepid biochemists among us that don't get a sense of dread from reading a name like that, but fear not: it is actually rather simple. All monoamine oxidase does is deactivate neurotransmitters known as monoamines, to which serotonin belongs. Most of the popular antidepressants operate by some variation of these two mechanisms, either inhibiting reuptake or inhibiting degradation of serotonin. They do not, on their own, increase the firing of the neurons that use serotonin. They simply improve the functioning of these neurons when they do fire.

So how do psychedelics fit into all of this? Well, as you might guess, they primarily act on systems that use serotonin. They do so, however, in a very different manner than any of the antidepressants discussed above. Rather than by simply facilitating and enhancing the normal behavior of these serotonin systems, they actually mimic the behavior of serotonin in the synapse and attempt to bind to and activate the same receptors that serotonin does. Notably, they do this even in microscopic doses (a normal dose of LSD ranges from 50-300 micrograms—millionths of a gram). While this difference may seem trivial at first, the implications for the brain—and mood—of anyone who takes these drugs are profound.

As opposed to typical antidepressants, these drugs don't have to wait for the serotonin systems to work on their own. Simply introduce a little LSD, or whatever your psychedelic of choice might be, to the brain and watch those circuits hum as though they were working all on their own. This helps to explain why the effects of psychedelics are felt immediately, whereas it takes several weeks in most cases for antidepressants to begin to have their behavioral effects. This is basically where the understanding of psychedelics got to before the public perception of them shifted and the political pressure mounted significantly enough to banish them from the minds of mainstream scientists. Researchers in the first wave were not able to successfully explain the long-term beneficial effects that were observed in a minimal number of exposures to psychedelics before the political tide turned against further exploration. Why did this come to pass? There are many factors at play, and it would be unfair to cast this at the feet of any one person, but it is useful to take up the story of one person and follow it through the end of the first wave of psychedelic research in order to illuminate some of the pitfalls of psychedelic research around which the current wave of researchers should take care. This character is one of the most infamous in the history of popular science: Timothy Leary.

If you've heard the expression "turn on, tune in, drop out," then you have been exposed to a significant aspect of what made Leary so polarizing. In 1962, Leary was a professor at the Harvard School of Psychology, and ran the Harvard Psilocybin Project. The problem with Leary was that he was a public preacher of the virtues of psychedelic experience before there was a solid grasp of the potential dangers of psychedelic use, the proper procedures of their administration, and the things that they might actually be able to treat. Amidst, albeit unverified, reports that LSD was causing people to leap from buildings believing themselves able to fly or committing horrible acts of violence, Leary was publicly espousing bad science. He entreated the populace to indulge in poorly understood chemicals without the supervision of trained researchers, paying no mind to the potential dangers. This drug was classified as a psychotomimetic when it first arrived in the US, after all. For his public pronouncements and failure to follow through on his obligations as a researcher, he was removed from his post at Harvard, and the Harvard Psilocybin Project was shuttered.

This didn't stop Leary from being a prominent public figure, much to the detriment of psychedelic research across the country. While there was certainly reason to think that psychedelics were a potent treatment for a wide variety of disorders, Leary's lack of discretion and scientific scruples were responsible for a large part of the change in public perception of these new drugs. Nixon once

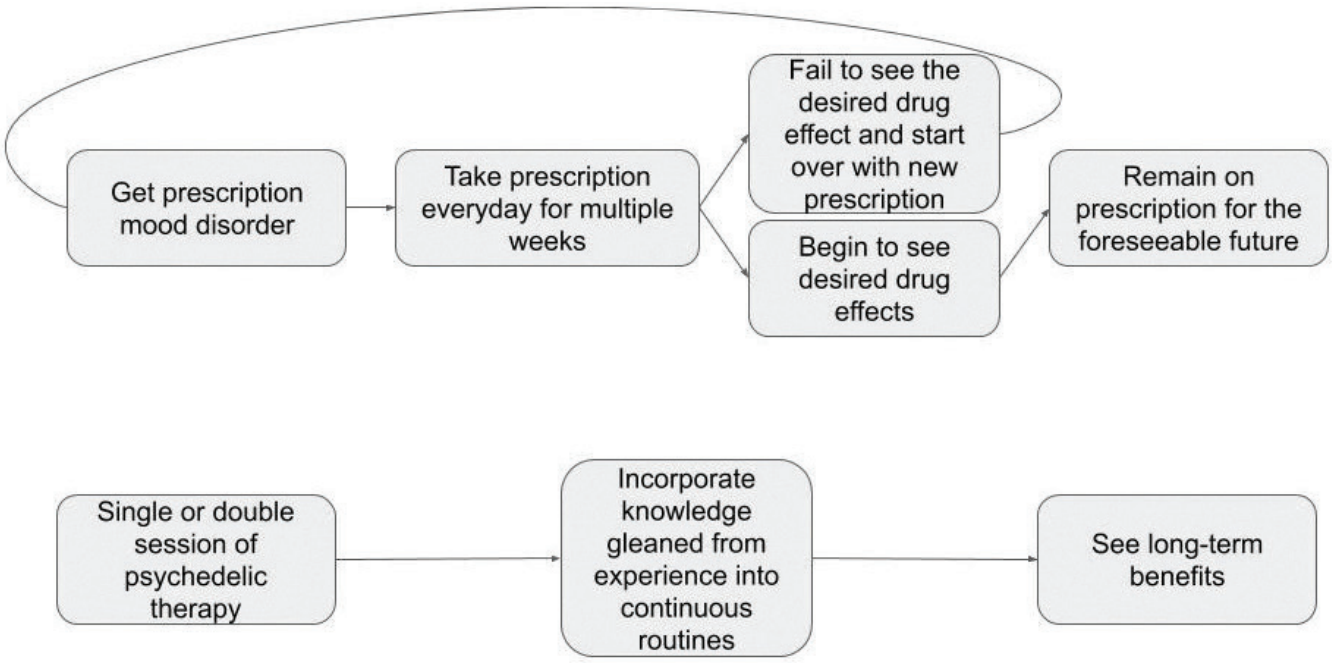


Figure 1. Comparison between mood disorder treatment with prescription drugs (top) versus psychedelics (bottom) Original image by Adam Roesner

called him "the most dangerous man in America." By 1970, psychedelics, including LSD and psilocybin, were declared to be of no medical use and to pose a high risk of abuse under the Controlled Substances Act. This marks the end of the first wave of psychedelic research. It would be a long time before we could come to a better understanding of how these drugs work to produce the therapeutic effects that had been unequivocally observed.

A minute amount of psychedelic research went on between 1970 and 2006, and almost none of it was focused on clinical applications of the drugs. This was due to a variety of reasons, but not the least among them that, due to the scheduling of these drugs, obtaining a license to conduct research on human participants was extremely difficult, and the stigma around doing this research was such that serious researchers who might be meritorious enough to receive one tended to shy away from it for fear of it staining their reputations. In 2006, Roland Griffiths became the first of the new wave of psychedelic researchers to put his well-connected neck out and reopen the American investigation of the behavioral effects of psychedelic compounds with the study that opened this article. But where has this new wave gone since then?

Since Griffiths cracked open the door to this area of research in 2006, a handful of studies have been published investigating the clinical effects of psychedelics have been done on a wide variety of conditions from anxiety related to terminal illness[7–9] to obsessive-compulsive disorder[10], with a strong trend towards positive outcomes. As the scope of the types of conditions that these drugs can treat expands, so too does our understanding of how these effects are achieved.

Some researchers have proposed that the reason psychedelics are so effective and efficient at engendering long-term improvements in behavior is related to the effect that they have on your brain's default mode network (DMN)[11,12]. This network is largely responsible for what you are thinking about when you aren't thinking about anything in particular[13,14]; that is, it turns off when you start to intentionally do something and turns back on when you stop and return to quiet repose. An advantage of doing clinical research in this modern era is that we have much fancier machines and we can take really high-def snapshots of brain activity during a psychedelic trip than we used to. One study endeavored to do just that and found that the DMN was significantly thrown out of its normal rhythms[11], which has previously been shown to be related to personality[15] and disorders of thinking[16]. While this is not a comprehensive explanation of how psychedelics function to achieve the effects that have been observed time and time again, it is certainly a step in the right direction.

"Okay," you might be thinking to yourself, "but what about those reports you mentioned earlier of people going crazy and doing heinous things while under the influence of these drugs?" Well, there's not a lot of evidence to back up these stories. One should always use caution when considering any new medical intervention and psychedelics are no different.

One study[17] asked nearly 2000 people about their worst bad trip experience after taking psilocybin and found that about 7.6% of people sought treatment for enduring psychological symptoms from their bad trip. Furthermore, three individuals reported sustained, impairing psychotic symptoms brought on by the bad trip, leading to diagnoses ranging from schizophrenia to bipolar disorder.

Despite this, 84% of respondents endorsed the experience as overall beneficial, and 60% said that it was among the top ten most psychologically and personally meaningful experiences of their life. The study also reported that the rates of these extremely challenging experiences are significantly lowered in laboratory research where drugs are administered in a controlled environment by experts (three of 250 participants reported negative impact on their life due to the experience, one of which was resolved within a week, one of which was undiagnosed hyperthyroidism, and one of which was resolved by the 5 month check-in). All of that is to say that there is some risk, however unlikely, associated with psychedelic use, and this article should not be taken as an endorsement of wanton psychedelic use. With more data we will more readily be able to say what the risk factors are. Until we can, any use of psychedelics without the supervision of experts carries an implicit risk.

The aggregate of the studies that have been conducted since 2006 yields some interesting data demonstrating the potential for psychedelic therapy to become a viable alternative to more standard medical interventions. In fact, there are some ways in which the benefits offered by psychedelics are preferable to typical drug courses, and a comparison between the two can be seen in figure 1.

We have reached the contemporary moment in the story of American psychedelic use. We're up to date. That means that we don't know where the story goes from here, and that we largely get to decide. When Albert Hofmann decided to take a dose of LSD, he had no idea where it was going to go either, but he braved the unknown and it changed the world. In that spirit, and in the absence of sufficient reason to act otherwise, we should move forward into the next chapter of the story not with fear, but with excitement and courage. Timothy Leary was right to be excited by the prospects of psychedelic therapy; let us learn from him and move forward with cautious optimism. The greatest advances in the history of human understanding were made possible by the intrepidation of those who chose to take them on, and great rewards were reaped for their fellow man in the process. ■

REFERENCES

1. Griffiths, R. R., Richards, W. A., McCann, U. & Jesse, R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* 187, 268–283 (2006).
2. Griffiths, R., Richards, W., Johnson, M., McCann, U. & Jesse, R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J. Psychopharmacol.* 22, 621–632 (2008).
3. Rucker, J. J., Jelen, L. A., Flynn, S., Frowde, K. D. & Young, A. H. Psychedelics in the treatment of unipolar mood disorders: a systematic review. *J. Psychopharmacol* 30, 1220–1229 (2016).
4. Krebs, T. S. & Johansen, P.-Ø. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J. Psychopharmacol* 26, 994–1002 (2012).
5. Charnay, Y. & Leger, L. Brain serotonergic circuitries. *Dialogues Clin. Neurosci.* 12, 471–487 (2010).
6. Forster, G. L., Novick, A. M., Scholl, J. L. & Watt, M. J. The Role of the Amygdala in Anxiety Disorders in *Amygdala - Discrete Multitasking Manager* (2012).
7. Gasser, P., Kirchner, K. & Passie, T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects. *J. Psychopharmacol* 29, 57–68 (2015).
8. Grob, C. S. *et al.* Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Arch. Gen. Psychiatry* 68, 71–78 (2011).
9. Gasser, P. *et al.* Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. *J. Nerv. Ment. Dis.* 202, 513 (2014).
10. Moreno, F. A., Wiegand, C. B., Taitano, E. K. & Delgado, P. L. Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder. *J. Clin. Psychiatry* 67, 1735–1740 (2006).
11. Muthukumaraswamy, S. D. *et al.* Broadband Cortical Desynchronization Underlies the Human Psychedelic State. *J. Neurosci.* 33, 15171–15183 (2013).
12. Carhart-Harris, R. L. & Friston, K. J. The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain* 133, 1265–1283 (2010).
13. Andrews-Hanna, J. R., Smallwood, J. & Spreng, R. N. The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann. N. Y. Acad. Sci.* 1316, 29–52 (2014).
14. Raichle, M. E. The Brain's Default Mode Network. *Annu. Rev. Neurosci.* 38, 433–447 (2015).
15. Adelstein, J. S. *et al.* Personality Is Reflected in the Brain's Intrinsic Functional Architecture. *PLOS ONE* 6, e27633 (2011).
16. Whitfield-Gabrieli, S. & Ford, J. M. Default Mode Network Activity and Connectivity in Psychopathology. *Annu. Rev. Clin. Psychol.* 8, 49–76 (2012).
17. Carbonaro, T. M. *et al.* Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *J. Psychopharmacol* 30, 1268–1278 (2016).