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The History, Legalization, and Potentials of Psilocybin-Assisted Psychotherapy

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HIGHLIGHTS

Therapeutic uses of the psychedelic compound 'psilocybin' show great promise but also raise important ethical and legal questions that require careful consideration.

ABSTRACT

The potential benefits and deficits of the chemical compound psilocybin, particularly when paired with psychotherapeutic interventions, have been increasingly apparent topics of interest in social, academic, and scientific circles. The unusual nature of psilocybin poses many questions in Western culture. Three of them, which will be discussed in the following review, are (1) What is psilocybin? (2) What is psilocybin-assisted psychotherapy? and (3) What are the potential advantages and disadvantages of psilocybin-assisted psychotherapy? Psilocybin-assisted psychotherapy is an innovative treatment that has not had the opportunity to be well-studied; as a result, the topic is currently shrouded in controversy and confusion. However, a recent series of clinical trials and research projects involving psilocybin-assisted interventions have yielded significant and beneficial results; indeed, additional trials are under way. The interventions studied include the treatment of end-of-life anxiety, depression, and existential distress in patients with terminal cancer, tobacco addiction, and treatment-resistant major-depressive disorder. Investigation into the known history, uses, relevance, and therapeutic effects of psilocybin-assisted psychotherapy require a careful inquiry, as these interventions are making an unavoidable and profound impact on contemporary American psychological culture as well as society in general. The current review attempts to describe psilocybin's shamanic roots, known history, legal controversy, psychotherapy, and contemporary neuroscience research.

KEYWORDS

Entheogens, psilocybin, psychedelics, psychotherapy

INTRODUCTION

The phenomenon known as *psilocybin-assisted psychotherapy* is gaining attention in the fields of Western medicine, neuroscience, pharmacology, psychiatry, and psychology. Psilocybin-assisted psychotherapy is showing a profound potential for confronting clients, moving them through their deeply held traumas, irrational belief systems, and psychological disorders.

The following discussion will explain and elaborate on the known history of psilocybin and its use. Subsequent sections will describe the discovery and synthesis of the chemical compound psilocybin in Western culture during the 1950s, as well as the earlier shamanic uses of psilocybin mushrooms, followed by the research and controversy in the West during the 1960s that led to psilocybin's classification as illegal under Federal law in 1970. Next, the historical events that allowed psilocybin and similar compounds to be studied again and to be employed legally in Western scientific and psychotherapeutic settings will be discussed.

Later sections will elaborate on both the potential

benefits and dangers of psilocybin-assisted interventions. They will discuss recent and relevant research and various psychotherapeutic approaches that are encompassing psilocybin, with an emphasis on humanistic and transpersonal psychotherapies.

Psilocybin

In 1955 an American mycologist, researcher, and vice president of J. P. Morgan, R. Gordon Wasson, discovered a species of mushroom in Oaxaca, Mexico, which produced powerful and peculiar effects. Wasson's curiosity led him to invite the mycologist and Director of the Musée National d'Histoire Naturelle in Paris Professor Roger Heim, to accompany him to Oaxaca to classify and describe these mushrooms of interest (Hofmann, 1959, p. 252). When Heim went to Oaxaca with Wasson in 1956, he obtained some of the mushrooms for further study. After transporting them back to his laboratory in Paris, he was successful in classifying as well as growing cultures of the mushrooms in question, naming the species *psilocybe Mexicana Heim*. In 1956 Heim sent a specimen to the Sandoz Research Laboratories in Basel, Switzerland, for chemical investigation (Hofmann, 1959, p. 252).

The term *psilocybin* was introduced in 1957 by Albert Hofmann; it is the name of the active principal molecule isolated from the *psilocybe Mexicana Heim* species of mushroom. It belongs to the *psilocybe* genus that includes more than 100 mushroom species discovered worldwide that contain psilocybin (Johnson & Griffiths, 2017, p. 735). After isolating the psilocybin molecule from the *psilocybe Mexicana Heim* in 1957, Hofmann and his team successfully synthesized a crystalline psilocybin compound in 1958 (Hofmann, 1959, pp. 251–253). Sandoz Laboratories marketed the synthetic under the name *Indocybin* for a brief period in the 1960s (Johnson et al., 2017, p. 144).

The chemical name for psilocybin is *4-phosphoryloxy-N,N-dimethyltryptamine*; it is known as an indole hallucinogen. When ingested, psilocybin dephosphorylates inside the body, converting psilocybin into the molecule psilocin (*4-hydroxy-N,N-dimethyltryptamine*) (Catlow et al., 2013, p. 481), which is a potent agonist at serotonin 5-HT1A/2A/2C receptors, with 5-HT2A receptor activation directly correlated with psychoactive effects (Grob et al., 2011, p. 71). The observed effects of psilocybin include the dilation of pupils, increased blood pressure and heart rate, nausea, auditory and visual hallucinations, distortion of auditory and visual stimuli, altered body sense, and alteration of temporal sense. The reported effects that contribute to introspection and often patients' increased receptivity to advice have led to its use in psychotherapy (Johnson et al., 2017, pp. 149–150).

In 1970, under orders of US President Richard Nixon and his administration, psilocybin and other so-called "hallucinogens" were placed in the Schedule I category of the United States Controlled Substances Act of 1970 (United States, 1970, p. 1236). In retrospect, this action seems to have been due to these substances' implicated involvement in and influence on the anti-war protests and counter-culture movements during the 1960s (Lee & Shlain, 1985, p. 93). All recognized "hallucinogens," including psilocybin, remain in Schedule I status to the current day. That status implies that the chemical has no accepted medical or therapeutic use and has an elevated risk of physiological and psychological dependence; moreover, there is an alleged lack of accepted safety for use of the drug or other substance under medical supervision (United States, 1970, p. 1247).

The initial name given to these compounds by researchers in the 1940s and 1950s was "psychotomimetic," because they assumed that these specific compounds induced a temporary psychosis (Pollan, 2018, p. 145). In this light, it was thought that, by having participants voluntarily ingest psilocybin or other "psychotomimetic" substances, psychotherapists could gain direct experiential, albeit temporary, understanding and insight into the psychological processes of patients suffering from psychotic disorders (Wasson et al., 1977, p. 138).

As inquiry and research pertaining to the nature of these compounds in the 1950s ensued, the assumption that they produced psychosis was ultimately ruled out by researchers, along with the term "psychotomimetics," when it became apparent that even though the effects of these compounds were powerful and disorienting, they did not produce psychosis (Pollan, 2018, p. 162). The term for these psychoactive chemicals, e.g., psilocybin, LSD, DMT, and mescaline, became known as *psychedelics*, a word derived from two Greek words meaning "soul manifesting" or "mind-manifesting." In 1956, Humphry Osmond was discussing the potentials of these substances with Aldous Huxley and how the unfortunate and ultimately misleading stigma related to psychosis involving these substances must be removed and the name changed (Pollan, 2018, p. 162). History shows that Osmond's term *psychedelic* won favor over Huxley's proposed term *phanerothyme* (p. 163).

The term and category of *psychedelics* has remained popular since its proposal in 1956. However, the term *entheogens*, which is derived from the Greek word *entheos*, was proposed in 1977 by Wasson et al., meaning "God (*theos)* within" (p. 139). Some of the terms used for centuries by many Native/Aboriginal/Indigenous shamans and healers, as well as many contemporary psychologists, for these chemicals in their unaltered plant forms, such as psilocybin mushrooms, are in English translation "sacred

mushrooms" (Carod-Artal, 2015, p. 45), "sacred plants," "sacred medicines," "plant medicines," "sacred plant medicines," or "entheogenic plant medicines" (Bourzat & Hunter, 2019, p. 27). Psilocybin is most commonly labeled as a "psychedelic," "hallucinogen," or "entheogen" in the current scientific research literature and legal documentation.

Shamanic Use of Psilocybin Mushrooms

The anthropological term *shaman* was initially introduced by the explorers and conquerors of eastern Siberia in the second half of the seventeenth century who had heard the term used by Tungusian tribes (Laufer, 1917, p. 361). Although the derivation of the term is uncertain, the Tungus word *saman* translates into "one who is excited, moved, or raised" (Casanowicz, 1924; Lewis, 1990, pp. 10–12).

The term *shaman* and the term for the shaman's practice of *shamanism* are both categorical Western scientific labels used to describe a variety of unique individuals. Harner (1990) stated that "shamans—whom we in the 'civilized' world have called . . . 'witch doctors'—are the keepers of a remarkable body of ancient techniques that they use to achieve and maintain well-being and healing for themselves and . . . their communities" (p. xix). Winkelman (1990) conducted a survey of some eighty societies, past and present, finding distinctions among four major groups: shamans and healers, mediums and diviners, priests and priestesses, and witches and sorcerers (p. 312).

The practices included within the term *shamanism* are as complex as they are controversial. The unique characteristics of shamanism, having been confirmed to appear in centralized societies as well as hunter–gatherer and fishing societies, suggest that shamanism was, and continues to be, a vital and versatile societal resource for survival and psychological development of the human species (Krippner, 2000, p. 94).

The technologies and techniques that produce so-called shamanic states of consciousness include the ingesting of entheogens, as well as focused concentration, chanting, dancing, fasting, drumming, running, jumping, sleep deprivation, "participating in sexual activity, refraining from sexual activity, [and/or] engaging in lucid dreaming" (Krippner, 2000). Additionally, rock and cave image-making may have served the function of recording the images elicited in shamanic states of consciousness (p. 107). In this light, shamanism can be seen as a venerable medical, religious, mystical, spiritual, and psychotherapeutic tradition (Walsh, 1989, p. 6). In 1620, the Roman Catholic church abolished the practice of shamanism in the lands that they controlled, as well as the use of entheogens, including psilocybin, declaring that their use was "an act of superstition condemned as opposed to the purity and integrity of our Holy Catholic Faith" (Pollan, 2018, p. 109). Many social scientists unfavorably viewed shamans as well, until their functions were more clearly understood (Walsh, 1989). There are a vast number of techniques and technologies in the shaman's repertoire, but, for the sake of the current review, our focus will be on the shamanic use of psilocybin mushrooms for healing and spiritual development.

The use of psychedelic mushrooms was widespread among Mesoamerican cultures, as there is archaeological evidence of mushroom use in Mexico, Guatemala, Honduras, and El Salvador, where so-called "'mushroom stones' . . . dated 3,000 B.C.E., have been found" (Carod-Artal, 2015, p. 42). A ritual bundle discovered in southwestern Bolivia contained traces of five different psychoactive compounds, including dimethyltryptamine (DMT). The bundle was radiocarbon dated to approximately 1,000 C.E. (Miller et al., 2019, pp. 11207–11210).

The shamanic use of psilocybin mushrooms in Mexico was considered to be of such importance that they had given more than two hundred different names, including the unusual and rare word *teonanacatl* ("divine mushroom") (Guzmán et al., 1998, p. 190). The use of the species *Psilocybe, Russula,* and *Boletaceous* fungi as sacred mushrooms have been reported among several aboriginal tribes in New Guinea (p. 191). Numerous species of neurotropic fungi have been found in the U.S., Mexico, Central and South America, Europe, Siberia, southwestern Asia, and Japan, showing a large distribution of the *Psilocybe* genus on all the inhabited continents (Guzman et al., 1998, p. 197).

Borovicka et al. (2012) added that a species of *psilocybe* mushroom is known to grow throughout the regions of Northern California, Western Oregon, Western Washington, and British Columbia became known as *psilocybe-alleni*, named after mycologist John W. Allen, who made the discovery in 2011 (p. 185).

Given the worldwide distribution and prevalence of psilocybe mushrooms, as well as documentation and information pertaining to their ritual use by many diverse tribes and shamanic cultures across the world, one might suggest that psilocybe mushrooms have been used for the purposes of survival, healing, and spiritual development since 70,000 B.C.E. and possibly earlier.

HISTORY OF PSILOCYBIN RESEARCH IN THE WEST

The initial appearance in Western scientific literature of psychedelics occurred in the late 19th century with the discovery of a cactus containing mescaline. In 1886, the German pharmacologist Louis Lewin published the first systematic study of the cactus, to which his own

name was subsequently given, *Anhalonium lewinii.* (Huxley, 1954/2011, p. 1). After chemists isolated and synthesized the mescaline alkaloid in 1886, mescaline research was conducted sporadically (p. 1). However, it never gained the serious attention from Western science, media, or culture that psilocybin and LSD achieved during the 1940s to 1960s.

In 1927, anthropologist William McGovern published ethnographic research in his book *Jungle Paths and Incan Ruins*, describing in detail a shaman's profound experiences after ingesting a psychoactive brew called *yage* (pronounced yah-hey), also known as *ayahuasca* (eye-uh-wass-kuh), along with tribal members in a Peruvian rainforest.

In 1934, Bill Wilson, who later co-founded Alcoholics Anonymous (AA), decided to try a remedy called the "belladonna cure" described as "infusions of a hallucinogenic drug made from a poisonous plant," during his fourth stay in a New York City detox center while struggling with alcoholism. Wilson did not believe in God at the time, but the treatment resulted in a first-hand experience with "God" or a "higher power," and it is said that Wilson never consumed alcohol again (Brooks, 2010, p. 1). In the 1950s, Wilson later went on to advocate for LSD in the treatment of alcohol addiction, attempting to include it in AA, but his recommendation was turned down by fellow board members (Pollan, 2018, p. 153).

In 1935 Albert Hofmann undertook the study of the fungus *ergot* (Hofmann, 1979/2009, p. 37), with the goal of synthesizing a chemical compound of a folk medicine used to facilitate childbirth. In the early 1930s, W. A. Jacobs and L. C. Craig of the Rockefeller Institute of New York had succeeded in isolating and characterizing the primary chemical compound from the ergot fungus, naming it *lysergic acid* (Hofmann, 1979/2009, p. 41). In 1938, Hofmann produced the twenty-fifth substance in the series of lysergic acid derivatives: lysergic acid diethylamide, abbreviated to LSD-25 for laboratory usage (p. 44). The objective of this compound was to obtain a circulatory and respiratory stimulant (an analeptic). This objective failed, and the project was discontinued until 1943, when Hoffmann intuitively decided to re-examine the compound (p. 44).

In 1938 Harvard botanist Richard Evans Schultes travelled to Oaxaca, Mexico, after becoming intrigued by fifteenth-century accounts of sacred mushrooms written by Spanish friars. Shultes discovered that the mushrooms were a vital resource for spiritual ceremonies among the Mazatec peoples of Oaxaca. Schultes published his findings and collected specimens but did not himself consume or experience the effects of the mushrooms (Sheldrake, 2020, p. 116).

Albert Hofmann and the LSD Experience

On April 16, 1943, while working on the final stages of repeating the synthesis of the LSD-25 compound, Hofmann became overwhelmed with vertigo and restlessness and could not concentrate on his work (Hofmann, 1959, p. 244). Hofmann noted that the faces of his associates as well as nearby objects underwent optical changes. While still in this state, he decided to go home and lie down, where, with his eyes closed, what he called "fantastic pictures of extraordinary plasticity and intensive colour" seemed to surge towards him (pp. 244–245). During the process of synthesizing the LSD-25 compound, Hofmann had unintentionally absorbed a minuscule amount of LSD-25 through the pores of his fingertips, causing these peculiar effects. This experience ignited Hofmann's curiosity and the decision to take a specific quantity of the compound (p. 245). This occurrence was the first human experiment with LSD. Hofmann later noted that he had chosen a dose that was five to ten times too high (p. 246), which led him to experience the fear that he was going out of his mind, even though he remained clearly aware of his condition (p. 245). In 1947, the first systematic study of LSD was carried out by W. A. Stoll, who examined its pharmacological and hallucinatory aspects (Hofman, 1959, pp. 246–247).

Aldous Huxley, *The Doors of Perception* (1954)

In 1952, a young British psychiatrist named Humphry Osmond was conducting research on LSD as well as mescaline at Weyburn Hospital in Saskatchewan, Canada (Lee & Shlain, 1985, p. 45). Osmond's primary interest resided in mental illness, especially psychosis, which attracted the attention of Aldous Huxley, the eminent British novelist who for years had been alarmed by the specter of drug-induced thought control (p. 46). However, Huxley also believed that drugs could have a profound and beneficial effect (p. 46).

In 1953, under Osmond's supervision, Huxley offered himself as a test subject, undergoing and later recording his firsthand experiences upon ingesting mescaline. The details of this experiment were later published in his book, *The Doors of Perception* (1954). Huxley then swallowed four-tenths of a gram of mescaline dissolved in half a glass of water and sat down to wait for the outcome, one that he later described as "without question the most extraordinary and significant experience this side of the Beatific Vision" (cited by Lee & Shlain, 1985, p. 46). He added that the mescaline experience "opens up a host of philosophical problems, throws intense light and raises all manner of questions in the fields of aesthetics, religion, theory of knowledge" (p. 46).

Huxley theorized that "the function of the brain and nervous system is to protect us from being overwhelmed and confused by this mass of largely useless and irrelevant knowledge . . . leaving only that very small and special selection" deemed to be practically useful (p. 8). Huxley believed that each human being was potentially a vast unrestricted ocean of consciousness that he referred to as "Mind at Large," claiming that it must be funneled through a consciousness-reducing valve in the brain and nervous system. This process during ordinary states of awareness consists of a minuscule trickle of consciousness that will help us to survive on the surface of this planet (p. 8). Huxley proposed that the mescaline experience impairs the efficiency of the cerebral reducing valve, adding that the mescaline experience is as near a finite mind can ever come to "perceiving everything that is happening everywhere in the universe" (p. 10). Huxley's explorations with mescaline, and later LSD and psilocybin, were self-directed and designed to explore consciousness; indeed, the success of his book attracted the attention of a large segment of the educated public to the existence of psychedelics for the first time in history (Lee & Shlain, 1985, pp. 46-47).

R. Gordon Wasson and Maria Sabina

In 1955, the decision to introduce the ancient, sacred, shamanic wisdom of the *psilocybe Mexicana* mushroom to the Western world was made by a remarkable shaman, or *sabia*, from Oaxaca, Mexico, named Maria Sabina. Sabina had felt called to become a *sabia* (i.e., "one who knows"), ingesting psilocybin mushrooms as a way of discovering the condition and treatment of her clients (Krippner, 2000, p. 94). Sabina claimed to have received a message one night while dreaming that it was her mission to share this sacred knowledge more widely. Soon after this dream, on June 29, 1955, a team of U.S. investigators headed by R. Gordon Wasson arrived at her home (p. 94).

Wasson had pursued a lifelong interest in mushrooms as a personal hobby, travelling around the world with his wife, Valentina, to learn about their roles in Indigenous societies (Leer & Shlain, 1985, p. 72). Wasson's travels in search of sacred mushrooms led him and his friend photographer Allan Richardson to the town of Huautla in Oaxaca, Mexico, where they met Maria Sabina. In 1957, *Life* magazine published a seventeen-page spread, complete with color photos, written by Wasson, titled "Seeking the Magic Mushroom." The article gives a straightforward and detailed account of the entire sequence of events that took place during this happenstance, yet profound, historical encounter.

Wasson (1957) explained that, directly after he and Richardson arrived in the Mixtec mountains of Mexico, he had found a *municipio,* or town hall, and approached the *sindico,* or official in charge, requesting to learn about the "divine mushroom." The officer agreed and then led them to the bottom of a ravine, where an abundance of the mushrooms was growing. After gathering some in a cardboard box, they were then taken to meet Maria Sabina at her home (p. 2).

Wasson went on to describe the events of the evening, explaining that, after gathering in the basement of the officer's house after 8 p.m. they were given chocolate to drink, as is often done ceremonially before ingesting the mushrooms. Around 10:30 p.m., Sabina cleaned the mushrooms, and, while praying, passed them through the smoke of resin incense. She then set aside 13 pairs of the mushrooms for herself, after which she handed Wasson and Richardson six pairs each. Then the ceremony took place in total darkness, after the mushrooms were eaten. Sabina snuffed out the flame from the only candle in the room, which remained dark until dawn. After 30 minutes of waiting in silence, Wasson and Richardson began to see visions, occurring whether their eyes were open or closed, and including harmonious vivid colors, art motifs that evolved into gardens and palaces, mythological beasts, and the development of philosophical ideas underlying imperfect images of life (p. 4).

Wasson then turned his attention to Maria Sabina, observing that, during the initial stages of the experience, they saw Sabina waving her arms rhythmically and beginning a low, disconnected humming that soon took the form of articulate syllables. Sabina's chanting then came forth in stages, "with a full-bodied canticle, sung as if it were very ancient music." After they fell asleep around 4 a.m. and awoke at 6 a.m., their hosts served them coffee and bread, and they went on their way to tell of the experience (Wasson, 1957, p. 6).

The historical significance involved in this happenstance encounter is reflected by Wasson (1957), who stated that "Richardson and I were the first white men in recorded history to eat the divine mushrooms, which for centuries have been a secret of certain Indian peoples. . . . No anthropologist had ever described the scene that we witnessed" (p. 2). Wasson, who was extremely well-connected, on a successive trip to Mexico in 1956 convinced Professor Roger Heim, the experienced mycologist, to accompany him, so that they could classify these mushrooms (p. 10). Heim was successful in doing so; later, Heim, along with his colleague Cailloux, succeeded in growing cultures of several of these mushrooms in his Paris laboratory, sending material from a particularly active fungus, *psilocybe Mexicana Heim*, to the Sandoz research laboratories in Basel for chemical investigation (Hofmann, 1959, p. 252). By 1957, Hofmann and his team were able to isolate the active compound from

the mushroom, giving it the name *psilocybin*; the following year, they successfully synthesized a crystalline psilocybin compound (Hofmann, 1959, pp. 252–253). Hofmann also conducted self-experiments with psilocybin, confirming the drug's psychoactive effects. In 1962, Hofmann accompanied Wasson on a return trip to see Maria Sabina. Hofmann offered Sabina pills of synthesized crystalline psilocybin and she accepted, swallowing two of the pills and confirming that they indeed contained the spirit [essence] of the mushroom (Pollan, 2018, p. 113).

Millions of people read Wasson's article in *Life* or saw a follow-up documentary about it on television. The success and attention given to Wasson's exciting and provocative encounter with Maria Sabina (given the name Eva Mendez in the *Life* article) and these remarkable mushrooms resulted in thousands of people, including celebrities and rock stars, flooding to Huautla in search of Sabina and the mushrooms. Sabina's decision to share the mushroom ceremony with Wasson was severely criticized by male elders in her village, who had kept knowledge of their sacred mushrooms secret; her decision violated the political power of her society's male hierarchy (Krippner, 2000, pp. 94–95). "Huautla had become first a beatnik, then a hippie, mecca, and the sacred mushrooms, once a closely guarded secret, were now being sold on the street" (Pollan, 2018, pp. 113–114).

The people of her village blamed Sabina for all the destructive and ruinous attention and damage done to Huautla, and she was briefly jailed, her home was destroyed (Pollan, 2018, p. 114), her grocery store was burned to the ground, and her son was murdered (Krippner, 2000, p. 95). Maria Sabina proclaimed that "from the moment the foreigners arrived the saint children [mushrooms] lost their purity. They lost their force; the foreigners spoiled them. From now on they won't be any good" (cited in Pollan, 2018, p. 114). The above circumstances demonstrate the initial controversy around psilocybin reaching Western culture, but this was only the beginning.

The Harvard Psilocybin Project

Shortly after Wasson's *Life* magazine story was published, Timothy Leary, who was a Berkeley-trained psychologist transitioning into his newly appointed lecturer position in clinical psychology at Harvard University in 1959, took an interest in Wasson's experience (Wark & Galliher, 2010, p. 235). Richard Alpert was a colleague of Leary's at Harvard's Center for Research in Personality. They initially became drinking buddies and later began teaching courses together (Ram Dass, 1971, p. 11).

Once Leary had settled in at Harvard in 1960, he traveled to Cuernavaca, Mexico, where he was introduced to an anthropologist and learned about the divine mushrooms and where they could be obtained from a woman in the mountains (Ram Dass, 1971, p. 12). Leary ate the mushrooms and had a profound experience, claiming, "It was above all and without question the deepest religious experience of my life" (cited by Lee & Shlain, 1985, p. 73). Leary also stated that he "learned more in six or seven hours of this experience than I had learned in all my years as a psychologist" (Ram Dass, 1971, p. 12).

In 1960, not long after returning to Harvard after his first experience with psilocybin mushrooms in Mexico, Leary decided to consult with Aldous Huxley. Leary and Huxley, along with a group of graduate students at Harvard, contacted Sandoz Laboratories, receiving a test batch of their synthetic crystalline psilocybin compound marketed under the name *Indocybin* (Johnson et al., 2017, p. 144). Alpert returned to Harvard from vacation, and was invited to join Leary's research program, the Harvard Psilocybin Project (Wark & Galliher, 2010, p. 235).

This project was established in 1960, signifying the beginning of serious academic research into psilocybin (Pollan, 2018, p. 140). Its first study, which took place in 1961 (Wark & Galliher, 2009, p. 235), consisted of evaluating the efficacy of psilocybin on recidivism rates of thirty-two inmates at the Massachusetts Correctional Institute in Concord, a maximum-security prison (Lee & Shlain, 1985, p. 75). The pilot study was successful in the short term, concluding that 25% of inmates who took psilocybin re-offended, as compared to the 80% that was the normal rate (p. 75).

In 1962, the project attempted to create a religious experience for twenty seminary students by giving them psilocybin inside a chapel, on a day of religious significance, namely, Good Friday, titling this study, "The Good Friday Experiment" (Wark & Galliher, 2009, p. 236). Leary, along with his assistant Walter Pahnke, who was a Harvard doctoral candidate, administered psilocybin to ten of the seminary students, giving another ten a placebo, setting in place a "double-blind" study (Lee & Shlain, 1985, p. 76). The results revealed that nine out of ten students who received psilocybin had an "intense religious experience," but only one individual from the placebo group claimed to have had a similar experience. Pahnke concluded his doctoral dissertation, based on this research project, by stating that the described experiences of individuals who had taken psilocybin were "indistinguishable from, if not identical with" the classical mystical experience (cited in Lee & Shlain, 1985, p. 76), including "loss of time sense; objects more beautiful; being able to operate at several levels at once; extreme pleasure, ecstasy, cosmic joy, paradise; feeling of being very wise; knowing everything; [and] feeling that nothing need be said" (Havens, 1964, p. 217).

At the beginning of their research project in 1960, Alpert and Leary were affiliated with Harvard's Department of Social Relations, which was a part of Harvard's Center for Research in Personality. Although understanding that psilocybin showed no indication of addiction, Harvard insisted that Leary and Alpert not give it to undergraduate students, on the ground that they had heard of students experiencing "acute psychosis" after taking hallucinogens (Wark & Galliher, 2010, p. 235).

In the summer of 1961, Aldous Huxley introduced Leary to a man named Michael Hollingshead, who had contacted Huxley, asking for existential advice as well as what he should do with an exceptionally large amount of LSD that he had in his possession. Huxley directed him to Harvard to meet Timothy Leary (Lee & Shlain, 1985, p. 83), who, after his first LSD experience, was so stunned that he wandered about dazed and confused for nearly two weeks until the point when his two closest associates, Richard Alpert and Ralph Metzner, were extremely concerned, believing that he had done himself severe psychological damage (p. 84). Eventually, curiosity led Alpert and Metzner to assess the substance themselves; Hollingshead then supplied all the members of the psilocybin project with LSD, and from that point on LSD was a permanent constituent of their research (p. 84).

During the fall of 1961, Leary and Alpert supplied many graduate students with psilocybin and LSD, inciting increasing hostility from Harvard faculty (Wark & Galliher, 2010, p. 235). In an attempt to increase knowledge of psychedelics, Leary and Alpert started a group called the "International Federation for Internal Freedom" (IFIF), asking undergraduate students to join and form research cells and allowing them access to psychedelic compounds. The IFIF published a journal called *The Psychedelic Review* and organ-ized a commune in Newton, Massachusetts. At this point, undergraduate students were obtaining psychedelics from an underground laboratory near campus or through the mail (Wark & Galliher, 2010, p. 236).

In late 1961, Harvard College Dean John U. Monro and the director of the Harvard University Health Services, Dana Farnsworth, M.D., demanded that Alpert and Leary stop using students as research subjects. Leary's LSD escapades had started to become a growing topic of conversation around Harvard, as an already existing negativity reached its bursting point in March 1962, when members of the Harvard faculty, during a meeting, insisted that Alpert and Leary alter their research methods or abandon the psilocybin project altogether. Leary's opponents charged that he had been conducting his drug studies in "a nonchalant and irresponsible fashion," noting that trained physicians were rarely present; moreover, they charged that Leary "got high with his test subjects" (Lee & Shlain, 1985, p. 86). The meeting and confrontational exchange appeared on the front page of Harvard's newspaper, *The Crimson,* the next day (p. 87).

In the fall of 1962, Monro and Farnsworth published a statement in *The Crimson* warning students about the dangers of psychedelics. Gradually, Harvard officials began to demean and discredit Leary and Alpert's research project in what some commentators called "a blatantly degrading level of intellectual respectability" (Wark & Galliher, 2010, p. 237). This led to the mass spreading of discrediting and often ridiculous rumors, ranging from holding alleged wild undergraduate LSD parties to selling psychedelics on the illegal market (Lee & Shlain, 1985, p. 88).

Leary was soon notified that a medical doctor must be present when the drugs were administered if he were to continue his research. Later, in a thinly disguised attack on Leary and Alpert, the U.S. Food and Drug Administration (FDA) maintained that LSD was too unpredictable and powerful to allow access to irresponsible individuals, especially when they advocated using it for drug-induced, "pseudo-religious," instead of medical or scientific, purposes. Alpert and Leary were soon ordered to surrender all their psilocybin to the university health service, and, at the end of 1962, the Harvard Psilocybin Research Project was permanently terminated (Lee & Shlain, 1985, p. 87).

Ironically, while Leary was being castigated, the CIA was engaging in the MK-ULTRA Project, an attempt to counter the "brainwashing" employed by Communist countries against imprisoned U.S. soldiers. The Project tried electroshock as well as LSD, the latter being administered to both volunteers and unwitting participants in settings as diverse as universities and hospitals, prisons, and brothels. The body of one unwitting participant, a CIA employee, was found on the pavement (having fallen off the roof of a building)—perhaps a suicide, perhaps not. His family sued the CIA successfully and President Gerald Ford, much to his credit, wrote a personal apology to the family (Talbot, 2015).

In April of 1963, Timothy Leary took leave from Harvard University without notice and was eventually fired for neglecting his teaching duties. On May 27, 1963, Richard Alpert was fired, when the Harvard Administration presented a student claiming that Alpert had provided him with psilocybin as an undergraduate in 1962 (Wark & Galliher 2010, p. 237). Following their dismissal from Harvard, Leary and Alpert were determined to continue their research in a completely unrestricted manner, conducting additional studies focused on evoking religious, philosophical, and spiritual practices during the psychedelic experience (Lee & Shlain, 1985, p. 96). They travelled abroad with the International Federation for Internal Freedom (IFIF) group, eventually being expelled from both Mexico and the

Caribbean Island of Dominica. In 1963, they started a commune and "psychedelic research center" for spiritual and religious seekers in a sixty-four-room mansion on a four-thousand-acre estate in Millbrook, New York (pp. 97–118).

In 1965, Leary and Alpert went their separate ways (Pollan, 2018, p. 205). Leary went on to live his life as a messianic media figure for the psychedelic counterculture, earning a place on the FBI's top ten most-wanted list and the title of "Public Enemy Number One" from President Richard Nixon. His numerous drug arrests, a prison escape, a subsequent absconding from the law, and constant provocation by the U.S. Government led to a stern prison sentence for Leary in 1973 (Lee & Shlain, 1985, p. 273). Alpert flew to the Himalayas on a spiritual journey, where he found a teacher who made a profound impact on his life. He then changed his name to Baba Ram Dass and returned to the U.S. as a spiritual teacher, author, and lecturer. His 1971 book, *Be Here Now*, described the Harvard days with Leary and his transformation from Richard Alpert to Baba Ram Dass.

The Harvard Psilocybin Project was the beginning and the end of serious academic research into psilocybin in the 20th century. What had been a remarkably fertile and promising period of research that unfolded during the previous decade in Saskatchewan, Vancouver, California, and England, and elsewhere was terminated (Pollan, 2018, p. 140). Some of the best minds in psychiatry had seriously studied these compounds in therapeutic models, some with government funding, only to have this body of knowledge effectively erased from the field (p. 142). Leary's notoriety obscured from view the role of a resolute but little-known group of therapists, scientists, and both professional and amateur researchers who were trying to develop a theoretical framework to understand these chemicals, and who devised therapeutic protocols to put them to use for healing.

Research and licit clinical use of psilocybin slowed down starting in the 1960s, as amendments in 1962 and 1965 to the 1938 U.S. Food, Drug and Cosmetic Act severely restricted its possession, use, and research (Johnson et al., 2017, p. 145). The societal backlash in the U.S. and other countries in the 1960s resulted in a ban on the possession and marketing of "hallucinogenic" drugs in 1965 in the U.S.; indeed, Sandoz Laboratories discontinued marketing and manufacturing *Indocybin* in 1966 (p. 144). The limitations to research and the sensational media accounts of adverse consequences from the use of psychedelics fueled the perception that psilocybin posed serious risks to patients and the public that were not outweighed by its benefits (p. 144). Since they had never gained formal approval from the FDA for therapeutic use, psilocybin and all other recognized "hallucinogens" were placed in the Schedule I category of the U.S. Controlled Substances Act (CSA) in 1970, where they currently remain (p. 144).

U.S. Controlled Substances Act

The Comprehensive Drug Abuse Prevention and Control Act of 1970, which was enacted by the U.S. Senate and House of Representatives during the presidency of Richard Nixon, was published and put into effect on October 27, 1970 (United States, 1970, p. 1236). This historical Act, also known as the U.S. Controlled Substance Act of 1970, placed psilocybin, as well as all other identified "hallucinogens," in the Schedule I category of the Act.

The United States government lists 64 opiate and opiate-derived compounds, along with 17 hallucinogenic compounds, in that category. The requirements for placement in Schedule I are as follows:

> SCHEDULE I. (A) The drug or other substance has a high potential for abuse. (B) The drug or other substance has no currently accepted medical use in treatment in the United States. (C) There is a lack of accepted safety for use of the drug or other substance under medical supervision. (United States, 1970, p. 1247)

A study carried out by Johnson et al. (2017) on the provisions of the Controlled Substances Act (CSA) concluded that psilocybin could provide therapeutic benefits that might support the development of an approvable New Drug Application (NDA), but further studies were required. The authors noted that adverse effects of psilocybin are manageable when administered according to risk management approaches, suggesting that placement in Schedule IV might be appropriate if a psilocybin-containing medicine were approved (p. 143).

Psilocybin is currently in the developmental stages for the treatment of depression and anxiety for patients with a life-threatening cancer diagnosis (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Moreover, promising "open label" results [meaning a study where both participant and researcher are aware of the psilocybin treatment] have been reported for treatment-resistant major depression (Carhart-Harris et al., 2016; Rucker et al., 2021), addiction to tobacco (Johnson et al., 2014), and alcoholism (Bogenschutz et al., 2017). The removal of psilocybin from Schedule I of the CSA can occur only if a medicinal product containing a Schedule I substance is approved for therapeutic use by the FDA (Johnson et al., 2017, p. 144). If it is determined to be reschedulable, the placement into the appropriate schedule will be subject to the FDA's abuse potential assessment, entailing detailed analysis into the eight factors of the Controlled Substances Act (p. 144),

namely: (1) abuse potential, (2) scientific evidence of pharmacological effect, (3) current scientific knowledge of the drug, (4) history and pattern of current abuse, (5) scope, significance, and duration of abuse, (6) risk to public health, (7) physiological or psychological dependence liability, and (8) immediate precursor of substance-controlled drugs (pp. 143–144).

The 2017 study by Johnson et al. concluded that all these eight factors, as well as other lines of evidence, when taken together, indicate the profile of a substance that is characterized by some level of abuse potential and potential risks. However, the evidence does not support placement more restrictively than Schedule IV (p. 161).

The Multidisciplinary Association for Psychedelic Studies (MAPS)

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit psychedelic pharmaceutical company (Emerson et al., 2014, p. 1). The origins and genesis of MAPS took place in 1972 through the initiative of its founder, Rick Doblin, Ph.D. At the age of 18, Doblin devoted himself to renewing legitimate psychedelic research, which had been universally halted. He was also determined to become a legal psychedelic psychotherapist (p. 1).

With the help of a manuscript copy of LSD researcher and psychotherapist Stanislav Grof's *Realms of the Human Unconscious* (2016), given to him by a guidance counselor at the New College of Florida, Doblin began to understand LSD's potential (Emerson et al., 2014, pp. 1–2). In 1984, Doblin and a few colleagues revived a non-profit organization known as the Earth Metabolic Design Lab (EMDL), which became a vehicle to coordinate the responses of the psychedelic psychotherapy community reacting to the apparent move by the Drug Enforcement Administration (DEA) to criminalize MDMA. MAPS was established in 1986 with the goal to facilitate research into the therapeutic uses of MDMA (p. 2).

The chemical name for MDMA is *3,4-methylenedioxymethamphetamine*. It was discovered and synthesized in Germany in 1917 (Gimeno et al., 2002, p. 1). During the 1950s, MDMA was briefly researched by the U.S. government but was forgotten until the mid-1970s, when it was rediscovered by the psychedelic therapy community (Emerson et al., 2014, p. 2). MDMA is not a classic psychedelic like LSD, psilocybin, DMT, or mescaline, but early observers noted that it triggered acceptance of self and others, increased tolerance of emotionally upsetting material, and improved the ability to address these issues without extreme disorientation or ego loss, all of which constitutes a common effect of classic psychedelics (p. 2). In the U.S., from the mid-1970s up to 1984, MDMA was used as an adjunct to psychotherapy by several psychiatrists and psychotherapists in the treatment of neuroses, relationship problems, and PTSD, and in 1984 the DEA placed MDMA in Schedule I of the Controlled Substances Act, criminalizing all uses thereof (p. 2).

In 1992, the MAPS Investigational New Drug (IND) Application for MDMA was filed and the FDA reviewed a MAPS-supported protocol submitted by Charles Grob, M.D., then at University of California Irvine, for a study of the use of MDMA in the treatment of pain, anxiety, and depression in cancer patients (Emerson et al., 2014, p. 3).

This action resulted in the FDA's Drug Abuse Advisory Committee recommending that the cancer patient study be postponed until a Phase 1 dose-response safety study was conducted first (Emerson et al., 2014, p. 3). The completion of this study led to the FDA's acceptance of its Advisory Committee's recommendation that human clinical research with psychedelics be resumed and reviewed with the same rigorous standards the FDA used to evaluate research with all other potential prescription drugs (p. 3). Grob's work was originally focused on MDMA, but, after the allowance of legal research with MDMA in cancer patients, a decision in which Grob played a crucial role, Grob decided to focus on psilocybin, instead of MDMA in treating cancer patients. His rationale was that psilocybin research would be less controversial than MDMA research; indeed, in 2003, Grob obtained approval for his psilocybin/cancer patient study (p. 4).

In 2007, MAPS extended its research to Switzerland, evaluating the safety and efficacy of LSD-assisted psychotherapy for patients with end-of-life anxiety secondary to life-threatening illness, receiving approval from the BAG (Swiss DEA), Ethics Committee (Swiss IRB equivalent), and SwissMedic (Swiss FDA equivalent) (Emerson et al., 2014, p. 5). The Swiss study was then accepted in 2008 by the FDA, which was finally open to the possibility of the therapeutic potential of LSD-assisted psychotherapy. With the IND in place, the FDA would accept data from the Swiss study (p. 5). Earlier, the FDA had approved research with MDMA, psilocybin, DMT, ketamine, and mescaline. LSD was the last of the classic psychedelic drugs to be accepted as a research tool. Therefore, acceptance by the FDA of the Swiss LSD protocol was a transformative moment in the psychedelic renaissance (p. 6). As a result of these efforts, MAPS earned a place in psychedelic history.

CURRENT SCIENTIFIC RESEARCH

The current body of scientific research into the potential therapeutic effects of psilocybin began its reemergence in the United States around the turn of the 21st century. Research publications since then have continued to ex-

pand, providing positive results for the treatment of a variety of psychological disorders and psychiatric conditions as well as the effects of psilocybin-assisted psychotherapy on personality structure (Erritzoe et al., 2018). See Table 1.

The current standard treatment model for therapeutic studies of psilocybin involves its administration as a catalyst, an intrinsic adjunct to structured psychotherapy, unlike most psychiatric medications (Johnson & Griffiths 2017, p. 735). Administered in a supportive environment, with preparatory and integrative psychological care, psilocybin has been used to facilitate emotional breakthroughs and renewed perspectives (Carhart-Harris et al., 2017, p. 1). This therapeutic regimen includes screening to exclude those with serious psychotic disorders who could be at possible risk. Moderate increases in blood pressure occur in patients receiving psilocybin, so those at high risk for cardiovascular problems also are excluded. Most of the risks involved in administering psilocybin are feeling psychologically overwhelmed, anxious, confused, and fearful, potentially leading to dangerous behaviors. However, session monitoring, participant preparation, and follow-up discussion about sessions are all thought to minimize the occurrence of such adverse reactions (Johnson & Griffiths 2017, p. 735).

The debut research article, utilizing the protocol described above and marking the revival of safe scientific inquiry into psilocybin, was published in 2011 under the title *Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced-Stage Cancer*. In it, Grob et al. (2011) explained that the objective of their pilot study was to explore the safety and efficacy of psilocybin in patients with advanced-stage cancer and reactive anxiety (p. 71). The study design consisted of a double-blind, placebo-controlled study of patients, meaning that half of the participants received psilocybin and half received a placebo; neither the researcher nor the patients were aware of what they received. Patients with advanced-stage cancer and anxiety functioned as their own controls, using a moderate dose (0.2 mg/kg) of psilocybin (p. 71). The setting was a clinical research unit within a large public-sector academic medical center, and the participants consisted of twelve adults with advanced-stage cancer and subsequent anxiety.

The main outcome measures in the study consisted of monitoring safety and subjective experience before and during experimental treatment sessions. Follow-up data included results from the Beck Depression Inventory (BDI), which consists of a series of questions developed to measure the intensity, severity, and depth of depression, as well as the Profile of Mood States (POMS) questionnaire, which describes individuals' moods during the past week including the present day. The POMS Brief, a shorter version of the original POMS Standard, was used for this study, in conjunction with the State-Trait Anxiety Inventory (STAI) questionnaire, a widely used self-report instrument for assessing both state and trait anxiety (Grob et al., 2011, pp. 71–73). The STAI evaluates the qualities of tension, apprehension, worry, and nervousness, differentiating between the temporary condition of *state* anxiety and the more general and long-standing quality of *trait* anxiety. For example, the STAI state anxiety subscale requests feelings at the moment of filling out the questionnaire, while the STAI trait anxiety subscale asks participants to indicate how they generally feel (pp. 71–73). The results, which were collected unblinded for six months after treatment, stated that safe psychological and physiological responses were documented during psilocybin treatment sessions with no clinically significant adverse events. The STAI trait anxiety subscale demonstrated significant reduction in anxiety at both one month and three months after treatment. The BDI showed an improvement of mood that reached significance at six months, and the POMS identified improvement in mood after treatment which approached but did not reach significance (p. 71).

The study noted that this design's limitations needed to be addressed in future research. Grob and his team concluded that despite these limitations this treatment may provide a model for treatment of the existential anxiety and despair that often accompany late-stage cancer (Grob et al., 2011, pp. 77–78).

Due to the careful and methodical standards to which Grob and his associates adhered, the revival of psilocybin research emerged for the first time since the 1960s, with a strong ethical and scientific foundation (Grob et al., 2013). The study initiated further detailed and disciplined research into incorporating psilocybin-assisted psychotherapy into palliative care.

Griffiths et al. (2016) studied the effects of psilocybin in 51 cancer patients, with life-threatening diagnoses and symptoms of anxiety and/or depression, using a randomized, double-blind, cross-over trial to investigate the effects of an exceptionally low, nearly placebo-like dose of psilocybin compared to a high dose. The results of the study demonstrated the efficacy of a high dose of psilocybin, when administered under supportive conditions, in producing large and significant decreases in symptoms of depressed mood and anxiety, along with increasing quality of life (Griffiths et al., 2016, p. 1194).

Ross et al. (2016) conducted a controlled double-blind, placebo, crossover trial involving 29 patients with cancer-related anxiety and depression, who were given either a niacin tablet (placebo) or psilocybin in conjunction with psychotherapy. Their results showed that psilocybin produced significant, immediate, substantial, and sustained improvements in anxiety and depression, leading to de-

TABLE 1. Selected Studies of Psilocybin-Assisted Psychotherapy

	Year	Diagnosis	N =	Placebo	Study Design	Follow-up	Results
Grob et al.	2011	Cancer-induced anxiety	12	Yes	Double-blind	6 months	Significant reduction in anxiety (STAI), depression (BDI) scores
Griffiths et al.	2016	Cancer-induced anxiety, depression	51	Yes	Double-blind	5 weeks	(80%) significant decrease in anxiety, depression
Ross et al.	2016	Cancer-induced anxiety, depression	29	Yes	Double-blind	6.5 months	(60–80%) anti-depressant, anxiolytic response
Agin-Liebes et al.	2020	Subset of Ross et al., 2016	15	Yes	Long-term follow-up	3.2-4.5 years	(60–80%) anxiolytic, antidepressant response, (71–100%) improved well-being
Carhart-Harris et al.	2016	Major depressive disorder	12	No	Open-label	1 week; 3 months	(100%) reduction, (67%) complete remission; (58%) reduction, (42%) complete remission
Johnson et al.	2014	Tobacco addiction	15	No	Open-label	6 months	(80%) abstinence
Johnson et al.	2017	Subset of Johnson et al., 2014	15	No	Long-term follow-up	12 months; 16 months	(67%) abstinence; (60%) abstinence
Erritzoe et al.	2018	Personality structure	20	No	Open-label	3 months	Significant Decrease in Neuroticism; Increases in Extraversion, Conscientiousness, Openness (NEO-PI-R) scores

creases in cancer-related demoralization and hopelessness, improved spiritual well-being, and increased quality of life. These improvements were sustained for 6.5 months in approximately 60–80% of participants (p. 1161).

Agin-Liebes et al. (2020) conducted a long-term, follow-up of fifteen patients, in treatment that had been conducted by Ross et al. (2016, as described above). The study reported reductions in anxiety, depression, hopelessness, demoralization, and death anxiety between 3.2–4.5-year followups. Approximately 60–80% of participants met criteria for clinically significant antidepressant or anxiolytic responses at the 4.5-year follow-up. Approximately 71–100% of participants rated the experience among the most personally meaningful and spiritually significant experiences of their lives (Agin-Liebes et al., 2020, p. 155).

Depression and anxiety in cancer patients have been associated with lowered treatment adherence, prolonged hospitalization, decreased quality of life, and increased suicidality (Griffiths et al., 2016, p. 1181). Ross et al. (2021) suggested that psilocybin-assisted psychotherapy may be an effective anti-suicidal intervention following a cancer diagnosis, due to its positive impact on hopelessness and demoralization, as well as its effects on meaning-making. Findings have also implicated psilocybin treatment as a potentially effective alternative to existing antidepressant medications (p. 553). Bossis (2021) explained that a major distinction between psilocybin and most other medications, including antidepressants and anti-anxiety agents, is that the latter must be taken daily to produce desired effects, whereas research into psilocybin demonstrates positive and sustained clinical benefits after only one or two sessions (p. 15).

Psilocybin-assisted psychotherapy, incorporated with palliative care, has been the most widely examined and researched avenue of intervention, due to the beneficial and effective results that have been discovered with reference to extremely fixed and difficult symptoms of treatment-resistant major-depressive disorder, anxiety, and existential distress. However, the range of clinical research studies and publications relating to psilocybin-assisted psycho-

therapy has continued to expand into the possible treatment of many psychiatric and psychological disorders.

Erritzoe et al. (2018) described their research into the effects of psilocybin-assisted therapy on personality structure in a study exploring whether psilocybin with psychological support modulates personality parameters in patients suffering from treatment-resistant depression (TRD). Results indicated that Neuroticism scores significantly decreased, while Extraversion increased following psilocybin-assisted therapy. Openness scores also significantly increased following psilocybin, whereas Conscientiousness scores increased somewhat, and Agreeableness did not change (Erritzoe et al., 2018, p. 368). These results indicate that subjective reports of psilocybin-assisted psychotherapy produced significant decreases in emotional instability; increases in mental, emotional, and psychological flexibility; increases in confidence and the desire to express oneself; as well as increases in focus and attention. The effects of psilocybin-assisted psychotherapy on personality structure provide primary examples of how breakthrough is made possible, enabling new ways of perceiving, thinking, and behaving to emerge.

The Default Mode Network (DMN)

The default mode network (DMN) is a large-scale network that functionally integrates distant brain nodes and mediates among other phenomena, such as wakefulness, awareness, memory, and a variety of related cognitions. It is referred to as "default" because it takes over when emphasis is on processing of internal stimuli rather than those perceived externally. Modulations of the cortical midline network structures involved in higher order mental processes such as self-referential processing may facilitate states of self-transcendence, a proposed key treatment mediator in psychedelic-assisted therapies (Smigielski et al., 2019, p. 208).

Pollan (2018) described the DMN as the tightly linked set of brain structures implicated in rumination, self-referential thought, and metacognition—thinking about thinking (p. 386), or, in other words, self-awareness. Rigid and extremely fixed personal views of ourselves and our relationship to the world rooted in negativity, defeatism, hopelessness, and meaninglessness are created and reinforced in this network. Getting fixated on or overly attached to these narratives, taking them as fixed truths about ourselves rather than as stories subject to revision, contributes mightily to addiction, depression, and anxiety (p. 388).

Psilocybin-assisted psychotherapy seems to weaken the grip of these narratives by temporarily disintegrating the parts of the DMN that reinforce them (Pollan, 2018, p. 389). Carhart-Harris and Friston (2019) explained that the DMN has been associated with arguably species-defining behavior such as mental time travel, moral decision making, counter-factual thinking, and self-consciousness. In simpler and more mechanistic terms, however, the human DMN can be considered to sit at the top end—or center—of a uniquely deep hierarchical system, i.e., the human brain (p. 322). The available evidence indicates that the functions of the DMN are never turned off, but, rather, carefully enhanced or attenuated (Raichle, 2015, p. 440).

Research suggests that psychedelics mediate their subjective effects by decreases in connectivity within the DMN, modulation of the anterior and posterior cingulated cortex, and whole brain integration (James et al., 2020, p. 3). The subjective mystical-type effects of psilocybin, including ego dissolution, have been at least partially attributed to disruption of the DMN and the prefrontal cortex, allowing ancient brain systems such as the mirror neuron system, which is located in numerous cortical regions, to occupy a more vital role in subjective awareness (p. 3). The profound and often mystical subjective experiences catalyzed by psilocybin are due to the stimulation of 5-HT2A neuron receptors in the brain, suggesting decreased activity and connectivity in the brain's connector hubs and permitting an "unconstrained style of cognition" (Carhart-Harris et al., 2012, p. 2142). This decrease in DMN activity, which allows for the emergence of unfamiliar brain connectivity and communication, apparently accounts for mystical-type experiences such as *ineffability*, the difficulty in putting experiences into words (Belser et al., 2017, p. 371); the experience of interconnectedness, which involves "the dissolution of normal identity often leading to a feeling of interconnection with other people, the entire planet, or even the universe at large" (p. 369); and experiencing meaningful closed-eye visual phenomena, with varying degrees of complexity; and/or reporting complex visual phenomena described as "visions," which often involve synesthesia (p. 372).

Alan Watts provided a wonderful depiction of the psychedelically evoked synesthesia, describing it as follows:

> The physical world is vibration, quanta, but vibrations of what? To the eye, form and color; to the ear, sound; to the nose, scent; to the fingers, touch. But these are all different languages for the same thing, different qualities of sensitivity, different dimensions of consciousness . . . shape becomes color, which becomes vibration, which becomes sound, which becomes smell, which becomes taste, and then touch, and then again shape . . . Light, sound, touch, taste, and smell become a continuous warp, with the feeling that the whole dimension of sensation is a single continuum or field. (Watts, 1962/2013, p. 20)

5-HT2AR Serotonin Receptor Signaling

Psilocybin is the predecessor of psilocin (4-OH-dimethyltryptamine), a non-selective serotonin 2A receptor (5-hydroxy-tryptamine-2A-Receptor, 5-HT2AR) agonist, meaning that it binds with these chemicals and neurons in the brain, thereby increasing the effects of these neurotransmitters. Both compounds are structurally related to the endogenous (naturally occurring) neurotransmitter serotonin (5-OH-tryptamine, 5-HT) in the brain (Carhart-Harris et al., 2017, p. 1). The 5-HT2AR receptors are primarily expressed in the cortex, especially in high-level association regions such as those belonging to the DMN (Carhart-Harris & Friston, 2019, p. 322). The role of serotonin, and, more specifically, 5-HT2AR signaling, in cognitive flexibility has been substantiated by numerous studies in humans and other animals. Psilocybin and other psychedelics have been found to promote divergent thinking—a key component of creative thinking—as well as expanded associative processing, while impairing conventional cognition (p. 325).

5-HT2AR signaling has also been shown to enhance neural plasticity, the capacity of the brain to adapt and change by making new synaptic connections and neural pathways (Carhart-Harris et al., 2017, p. 1091). Catlow et al. (2013) stated that chemicals that modulate serotonin (5-HT) synaptic concentrations impact neurogenesis, the production of new neurons (Catlow et al., 2013, p. 481). Along with the findings of neurogenesis in their study of the hippocampus on mice injected with psilocybin, Catlow et al. (2013) discovered that psilocybin facilitates extinction of the classically conditioned fear response, suggesting psilocybin's potential therapeutic effects on post-traumatic stress disorder (PTSD) (p. 481). Krediet et al. (2020) explained that the plasticity-promoting properties of psilocybin and other psychedelics may contribute to their rapid anti-depressant and anxiolytic effects (p. 391). Psilocybin has also been shown to decrease amygdala reactivity during emotional processing. As patients with PTSD often show heightened amygdala reactivity, this may increase the brain's ability to process traumatic memories (p. 391).

A pioneering research study conducted by Carhart-Harris et al. (2012) used psilocybin and a task-free functional MRI (fMRI) protocol designed to capture the transition from normal waking consciousness to the "psychedelic state" by mapping cerebral blood flow and changes in venous oxygenation before and after intravenous infusions of a placebo and psilocybin on human participants. Carhart-Harris et al. (2012) suggested, "It seems relevant therefore that activity in and connectivity with the mPFC is known to be elevated in depression and normalized after effective treatment" (p. 2412). The mPFC was consistently deactivated by psilocybin, with the deactivations correlating with the drug's subjective effects. Depression has been characterized as an "overstable" state, in which cognition is rigidly pessimistic, while trait pessimism has been linked to deficient 5-HT2A receptor stimulation, particularly in the mPFC. MPFC hyperactivity, in turn, has been linked to pathological brooding (Carhart-Harris et al., 2012, p. 2142).

PSYCHOTHERAPEUTIC APPROACHES

Brent and Kolko (1998) defined *psychotherapy* as a modality of treatment in which the therapist and patient work together to ameliorate psychopathologic conditions and functional impairment through focus on the therapeutic relationship; the patient's attitudes, thoughts, affect, and behavior; and social context and development (p. 17). After developing and establishing a solid therapeutic alliance between patient and therapist, problematic thought and/or behavior patterns, psychological issues, disorders, traumas, neuroses, etc., can then be addressed by incorporating the most appropriate, beneficial, and effective psychotherapeutic approach into the psychotherapy.

Sloshower et al. (2020) proposed that, while a variety of biological and psychological mechanisms of action for psychedelic therapy have been proposed, most researchers and therapists have operated under the assumption that the powerful subjective and experiential effects of psychedelic substances play a significant role in therapeutic outcome, in addition to their possible direct pharmacologic effects. It has become a well-established constituent of psilocybin-assisted psychotherapy that subjective effects are highly variable, apparently influenced by psychological and environmental factors, commonly referred to as "set and setting" (p. 12).

Set and Setting

The terms *set* and *setting* were introduced by Timothy Leary, Ralph Metzner, and Richard Alpert (Leary et al., 1964, p. 84). Most current research with psychedelics emphasizes the importance of set and setting to maximize safety, reduce the risk of harmful experiences, and enhance therapeutic responses (Sloshower et al., 2020, p. 13). The term *set* refers to the intention of the individual prior to the experience. It encapsulates hopes, beliefs, traumas, fears, temperament, and personality, as well as the client's fantasies and expectations about psychedelic experiences. The term *setting* refers to the therapeutic environment and physical space in which an individual experiences the psychoactive effects of the substance. This term encapsulates the ambience of the therapists or guides, as well as such factors as music, artwork, and safety equipment (p. 13).

A positive set and setting in psilocybin-assisted psychotherapy provides patients with an adequate sense of safety which allows them to become physically, emotionally, psychologically, and spiritually vulnerable during sessions. The lack of attention to set and setting may lead to detrimental psychological effects. Disturbing situations and/or surroundings, along with unethical or poorly trained practitioners also have the potential to put individuals in severe psychological and physical danger.

Bourzat and Hunter (2019) described a guide as "someone who walks ahead and knows the territory, aware of the potential perils of the terrain" (p. 40). The psychotherapist occupies a role similar to that of a guide, shaman, or curandera, and it is the therapist's task to facilitate and support the patient's inner transformation. In this way the therapist integrates psychological understanding with personal growth (p. 42).

Current psilocybin-assisted psychotherapy usually comprises three stages: initial preparation before dosing session or sessions, support during dosing sessions, and integration sessions afterwards (Sloshower et al., 2020, p. 16). It is necessary for the therapist to develop therapeutic rapport with individuals, while providing education regarding the therapeutic approach and the experience itself, as well as discussing logistics of the dosing session and the description of acceptable boundaries of interaction between therapist and participants. Moreover, the therapist needs to establish the participants' intention regarding what they are seeking to gain from the treatment (p. 16). The support stage takes place during the dosing sessions, which have a duration of approximately 4–6 hours and take place in living-room–like settings in research facilities. The patients, lying on a couch, will typically wear headphones, which play preselected, instrumental music, along with eyeshades to encourage them to direct attention inward to the unfolding changes in consciousness. The eyeshades also prevent distraction from any environmental stimuli, although participants are free to remove either or both the headphones and the eyeshades at any time if they choose (Bossis, 2021, p. 16).

During the dosing sessions, therapists or guides create and hold a "safe space," or maintain a "safe container," allowing the participants to be comfortable and vulnerable enough to fully embrace their unique experiences, while gently providing emotional support when difficult sensations, thoughts, feelings, or memories arise. The reassurance of safety and assistance for the participants are key components of the support stage. The integration stage, in most cases, begins the day following the dosing session, and involves a thorough review of the participants' experience during their dosing sessions, and, in some cases, applying therapeutic techniques, reinforcing important aspects of the experience, and working towards sustainable patterns of thought and behavior (Sloshower et al., 2020, p. 13).

Humanistic and Transpersonal Psychology

Charles Grob and Anthony Bossis have linked their interest in this topic to their backgrounds in humanistic psychology, a field established with the founding of the *Journal of Humanistic Psychology* (JHP) by Abraham Maslow and Anthony Sutich. Another milestone was the creation of the Association of Humanistic Psychology founded by Carl Rogers, Virginia Satir, and Maslow in 1961 (Grob & Bossis, 2017, p. 315). The humanistic perspective in psychology has a foundational basis that deviated from the models prevalent at the time that were considered to be overly deterministic and restrictive. This humanistic orientation emphasized human potential and its development; indeed, the goals of humanistic psychotherapy focus on facilitating personal growth and self-actualization (p. 315).

As Grob and Bossis (2017) explained, "as the 1960s unfolded, however, Maslow and others identified with the humanistic movement perceived an essential albeit often neglected and denigrated element of human nature, the spiritual dimension" (p. 315). Many psychedelic sessions were marked by profoundly transcendental, mystical, and spiritual effects. The field of transpersonal psychology was established in 1967 when a small group of psychologists, including Abraham Maslow, Anthony Sutich, Stanislav Grof, James Fadiman, Miles Vich, and Sonja Margulies, met with the purpose of creating a new psychology that would honor the entire spectrum of human experience, including various non-ordinary states of consciousness. During these discussions, Maslow and Sutich accepted Grof's suggestion to name the new discipline "transpersonal psychology" replacing the original name of "transhumanistic," or 'reaching beyond humanistic concerns"' (Grof, 2008, p. 47). Shortly afterwards, they established the Association of Transpersonal Psychology (ATP) and inaugurated The *Journal of Transpersonal Psychology* (p. 47). In its effort to fully understand the varying dimensions of consciousness, transpersonal psychology endeavored to integrate the ideas of Western psychology with the insights of Eastern spiritual traditions (Grob & Bossis, 2017, p. 316).

The work of Stanislav Grof, who had recently moved from Czechoslovakia to the United States, was profoundly influential. Grof, an early researcher of the range of therapeutic effects of psychedelics since their emergence in psychological culture, explored the value of the transpersonal model to understand the full range of human potentiality and to harness the potential of psychedelic experiences to facilitate powerfully positive treatment effects (Grof & Halifax, 1977). Grof (2019) explained that he had "observed

and experienced countless paradigm-breaking phenomena, indicating an urgent need for a radical revision of the most fundamental assumptions of mainstream psychiatry, psychology, and psychotherapy" (p. 106).

Where current medications target symptoms of these disorders, altering brain function to repress and numb unpleasant thought and behavior patterns, psilocybin seems directly to confront and disassemble the root foundation on which psychological disorders are formed and perpetuated, allowing for a direct confrontation with and an emotional breakthrough from long held and rigidly fixed thought and behavior patterns. After this process is complete, the ability to create, form, and embrace new and ultimately beneficial ways of thinking and behaving are made possible by implementing specific psychotherapeutic approaches and techniques.

Out of the many approaches available, it seems that practitioners with humanistic and transpersonal psychotherapeutic backgrounds have had the most experience in dealing with the powerful and profound subjective effects of psilocybin-assisted psychotherapy. Three key components of the humanistic and transpersonal approaches that are of crucial importance and benefit when facilitating, counseling, or guiding a psilocybin-assisted psychotherapeutic intervention include: (1) the importance of developing a genuine, supportive, and empathetic therapeutic alliance or relationship between therapist and client; (2) the conduct by the therapist or guide of psychotherapy sessions of practicing continuous unconditional positive regard, in which the therapist is fully accepting of the client, showing no aggressive, assertive, or passive-aggressive judgment such as verbally shaming, displaying disapproving body language and/or gestures, or using verbal sarcasm or sarcastic body language and/or gestures at any time with the client; and (3) responding by restating or rephrasing the client's statements in a way that highlights the client's feelings or emotions, sometimes known as the "reflection of feeling" (Pomerantz, 2016, p. 585).

When reflecting back, the therapist or guide should not be telling clients how they feel, but, instead, should be asking clients if their understanding is correct. Therapists should not become overly confident in their ability to read clients' emotions and should always acknowledge the clients' expertise on their own feelings (Pomerantz, 2016, p. 586). By adhering to the humanistic psychological technique of reflecting, practitioners do not interject their opinion on the matter or tell the patients how to solve their problems, but instead create and hold a safe space, and ultimately guide clients as they create their own solutions for their psychological dilemmas. This approach often results in patients' embodying a genuine sense of accomplishment, purpose, and meaning regarding having the confidence to trust their own individual critical thinking processes and creating their own solutions to their problems. Many individuals in Western culture believe that medical and mental health solutions are given by the practitioner or medical professional to offer a quick fix without working towards helping patients to create a healthier and more balanced physical and psychological lifestyle on their own. In this light, the humanistic approach seems to meet many crucially important criteria involved with safe, beneficial, and successful psilocybin-assisted psychotherapeutic interventions.

Sloshower et al. (2020) asserted that numerous forms of psychosocial interventions could be compatible or adaptable for use in psychedelic assisted therapies, provided there is some theoretical synergism with the pharmacological treatment to produce desired therapeutic outcomes (p. 13). The unique and defining characteristics of psilocybin-assisted psychotherapy reside in making sense of, finding meaning in, and/or discovering a purpose related to the highly specific and personal phenomenological and subjective material that individuals experience during psilocybin dosing sessions.

Bogenschutz and Forcehimes (2017) noted that it was not clear how to integrate the psychedelic experience into treatment models designed to have specific therapeutic effects, such as the amelioration of the symptoms of a specific disorder; in contrast, supportive models of psychedelic therapy are not linked to particular therapeutic orientations, nor do they target the specific disorder being treated. Instead, they provide containment, safety, and clear guidelines to help participants navigate their own psychedelic experience (Carhart-Harris et al., 2016).

CONCLUSION

Notable results of psilocybin-assisted psychotherapy have occurred in the treatment of tobacco addiction and treatment-resistant major-depressive disorder. The beneficial results of this research suggest that the profound and often mystical subjective experiences catalyzed by psilocybin are due to the stimulation of 5-HT2A neuron receptors in the brain, suggesting decreased activity and connectivity in the brain's connector hubs and permitting an "unconstrained style of cognition" (Carhart-Harris et al., 2012, p. 2142).

This unconstrained style of cognition facilitated by psilocybin, along with adherence to adequate and ethical psychotherapeutic treatment protocols, is showing breakthrough results in the treatment of some of the most difficult, treatment-resistant, psychological disorders, known in the field of mental health. This is due to the unique ability that psilocybin-assisted psychotherapy has to dis-

assemble pharmacologically structured and highly "overstable" neurochemical systems in the brain that sustain, and reinforce, pessimistic and rigidly fixed thought and behavior patterns (Carhart-Harris et al., 2012, p. 2142).

It is important to consider that the primary interest into psychedelics such as psilocybin is the potential that they hold to break individuals out of their fixed and rigid thought and behavior patterns, thereby allowing for a condition that viscerally reveals to the individuals that there is more to life than they had previously thought or believed. This revelation can result in new and beneficial ways of thinking, feeling, perceiving, and behaving. Currently, we face a severely unaddressed mental health crisis in the West. The COVID-19 pandemic and political events since the spring of 2020, have added cultural, societal, and economic upheaval, for which the existing approaches to mental health conditions and disorders are inadequate.

It is not only individuals in Western culture suffering from diagnosed psychological disorders who can benefit from discovering new ways of thinking and relating to consciousness. It is now unavoidably apparent that continuing to adhere to the existing ways of thinking, perceiving, and behaving are dangerously reckless and destructive to the human species and the planet. As Krippner (2000) observed, "shamanic epistemology drew upon perceptual, cognitive, affective and somatic ways of knowing that assisted early humans to find their way through an often unpredictable, sometimes hostile, series of environmental challenges" (p. 98).

Aldous Huxley was an enthusiastic advocate for the potential that psilocybin holds to expand consciousness, declaring that the experience "opens up a host of philosophical problems, throws intense light and raises all manner of questions in the field of aesthetics, religion, theory of knowledge" (cited by Lee & Shlain, 1985, p. 46).

On a parting note, it is difficult to deny the correlation between recent neuroscientific and phenomenological research and Aldous Huxley's theory of a reducing valve for "Mind at Large." Research indicates that psilocybin may have the ability to loosen the reducing valve of our limited perceptions of ourselves and the world around us, via the default mode network, allowing for the availability of a much less restricted degree of consciousness, ultimately heightening our perceptions as well as our ability to relate them to consciousness. Equally prophetic was Huxley's decision to have his wife, Laura, give him an intramuscular injection of 100 micrograms of LSD on his deathbed in 1963, signifying the first self-experiment with LSD for the treatment of palliative care. Huxley was in the terminal phase of throat cancer, and his doctors had explained to his wife Laura that she should prepare for a disturbing and dramatic end to her husband's life, given that the terminal phase of throat cancer is usually accompanied by convulsions and choking fits. Hofmann (1979/2009) explained, "in the morning, when he was already so weak that he could no longer speak, he had written on a sheet of paper: 'LSD—try it—intramuscular—100 mcg.' Mrs. Huxley understood what was meant by this, and ignoring the misgivings of the attending physician, she gave him, with her own hand, the desired injection" (pp. 181–182). On November 22, 1963, Aldous Huxley died serenely and peacefully (p. 181).

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