The Role of Psychedelics in Medicine: 
Historical Context and Current Clinical Applications

WHITE PAPER

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1. INTRODUCTION

Psychedelics, also known as hallucinogens, entheogens, and psychotomimetics, are psychoactive drugs that have been shown to alter consciousness and cognitive processes. Though psychedelic plants and fungi were first discovered more than a few thousand years ago, the chemistry and pharmacology of psychedelics were not investigated in the context of modern science until the 1950s. Even as biomedical research began to show these compounds’ potential promise in treating various psychiatric conditions, sociopolitical opposition stemming from psychedelics’ illicit use by members of the 1960s and 70s counterculture slowed progress and hindered widespread acceptance. The situation shifted again in the 1990s and early 2000s, as rigorous new medical research gave rise to an evidentiary foundation upon which the modern era of psychedelic research would be based. This research has sparked renewed interest in the role of psychedelics in clinical settings, where they may potentially treat a variety of psychiatric conditions.

In this study, we conduct a comprehensive “meta-review” of the historical context and development of clinical applications of psychedelics. The review focuses on two primary questions. First, given the long history of psychedelics, how has research evolved, and how does it inform psychedelics’ present-day clinical landscape? Second, how are psychedelics currently being applied in clinical settings, and what are the origins of these applications? Both questions have been addressed in existing literature to some extent, but with two important gaps. First, despite the publication of several systematic literature reviews in recent years, there has not yet existed a “meta-review” of these systematic reviews, especially one focused on clinical studies. Second, existing studies generally do not tie together historical context and current applications. The chief objective of this study is therefore not to replicate or update prior systematic reviews, but rather to link together what are essentially two generations of thinking on psychedelics, a “discovery” era and an emerging “application” era, while maintaining historical perspective. Such an analysis helps to illuminate key issues that have surfaced in the recent public discourse on psychedelics. These include the extent to which prior knowledge from both formal and informal

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1 In this paper we have chosen to use the term widely used term “psychedelics,” though we note that several prominent early researchers criticized the term for “etymologically unsound.” Refer to R.E. Schultes, A. Hofmann, and C. Ratsch, Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers (Rochester, VT: Healing Arts Press, 1998).


sources has contributed to current scientific research and clinical practice, which may have implications for the legal assignment of intellectual property (IP) rights; and the extent to which the mainstream medical-therapeutic model of mental healthcare supports or limits psychedelics’ healing potential.

The review uses a “snowball” method, a qualitative approach in which (1) basic search terms are used to identify an initial comprehensive list of sources; and (2) a review of those sources is conducted to identify “leading” sources, generally defined as those which directly address the research questions and are frequently cited by other sources. The main search engines used were PubMed and Google. No time horizons were specified, but all sources had to include an abstract and English language full text to be included.

The paper is organized as follows. The next section reviews general background on the basic types of psychedelics and mechanisms of action. The remaining sections describe the review’s main findings, beginning with the historical context of psychedelics and concluding with a review of current clinical applications.

2. MECHANISMS

In this section we provide a brief review of psychedelics’ biochemical mechanisms of action, which have been described at length elsewhere. We also discuss the perspective that, in contrast to the effects of conventional psychiatric drugs, the psychological effects of psychedelics cannot be fully understood in terms of biochemical mechanisms alone, and necessarily reflect contextual and experiential influences.

Psychedelics are typically grouped into three broad categories based on their pharmacological profiles and chemical structures: (1) “classic” psychedelics, (2) empathogens, and (3) other psychedelics, including dissociative anesthetic agents and atypical hallucinogens. Classic psychedelics (also referred to as serotonergic psychedelics) include mescaline, lysergic acid

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8 See generally Collin M. Reiff et al., "Psychedelics and Psychedelic-Assisted Psychotherapy," American Journal of Psychiatry 177, no. 5 (2020). In this paper, we focus on classic psychedelics and empathogens as these have been the focus of the vast majority of clinical research.
diethylamide (LSD), psilocybin, N,N-Dimethyltryptamine (DMT), and ayahuasca (broadly described as a decoction of plants containing DMT, harmala alkaloids, and other agents according to local custom). Psychedelics share in common the stimulation of the serotonin 5-hydroxytryptamine 2A (5-HT\(_{2A}\)) receptor, which has been hypothesized to lead to an increase in glutamate release in the prefrontal cortex.\(^9\) Research in this vein dates first to 1953, when Gaddum revealed that LSD-25 antagonizes specific peripheral actions of the 5-hydroxytryptamine (5-HT) receptor, and then hypothesized that a similar antagonism to actions of serotonin in the nervous system produces altered state of consciousness.\(^10\) More recently, Carhart-Harris et al. used neuroimaging techniques to show that when visual cortex cerebral blood flow (CBF) increased, visual cortex alpha power decreased, causing a strong correlation between expanded primary visual cortex (V1) functional connectivity and visual hallucinations.\(^11\) The study demonstrated how intrinsic brain activity affects the visual processing of a participant, explaining the hallucinatory quality of LSD.

Empathogens, such as 3,4-Methylenedioxymethamphetamine (MDMA), are characterized by their effects on the inhibition and release of serotonin and dopamine.\(^12\) Structurally, MDMA resembles mescaline and amphetamine, though the dextrorotatory isomer of MDMA displays more activity in the central nervous system.\(^13\) The biochemical effect of empathogens is caused by the release of calcium-independent 5-HT, which leads to the expansion of 5-HT neurotransmission.\(^14\) Empathogens are known to produce euphoria and a sense of emotional connectedness and openness to others, in part due to their impact on monoamine reuptake inhibition and release.\(^15\)

Psychedelics’ novel biochemical mechanisms are associated with qualitatively different types of participant experiences from those associated with conventional psychopharmacological agents. These may include “an altered state of consciousness, closed-eyes imagery, changes in perception, mood and affect, [and] a weakened sense of self or ego.”\(^16\) Growing evidence suggests that effects such as these are not simply “side effects,” but may themselves contribute directly to clinical outcomes. For example, Griffiths et al. reported that “psilocybin can occasion mystical-type experiences having persisting positive effects on attitudes, mood, and behavior” among some

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12 Reiff et al.


14 Ibid.


16 Madsen et al.
participants, and Watts et al. found that psilocybin alleviated depression in some recipients by helping them move from “disconnection (from self, others, and world) to connection” and “avoidance (of emotion) to acceptance.” Carhart-Harris et al. pointed directly to the nexus between biochemical mechanisms and subjective cognitive experience, writing that “psychedelics initiate a cascade of neurobiological changes that manifest at multiple scales and ultimately culminate in the relaxation of high-level beliefs.”

The likelihood that psychedelics “may work via paradigmatically novel means” relative to conventional psychopharmacological and psychotherapeutic treatments has implications for how these substances might be administered to maximize therapeutic benefit. It has been recognized since at least the 1960s that “set and setting” – the mindset of the individual entering a psychedelic experience (set) and the environment in which the experience takes place (setting) have a profound influence on the nature and outcome of psychedelic experiences. In the late 1990s Eisner expanded this idea into the concept of the “matrix,” which includes consideration of the environment (1) from which an individual comes, (2) in which the individual lives during the time of the sessions, and (3) to which the individual returns after successful therapy – the everyday living space.

More recent research has developed specific psychotherapeutic techniques for use with patients undergoing treatment with psychedelics, in the form of Watts et al.’s ACE (Accept, Connect, Embody) model.

3. EARLY EVIDENCE

Few chemical compounds, if any, have as rich and deep a history as psychedelics, whose use in the form of plant and fungal hallucinogens likely dates to pre-historic times. In some cultures, shamans would conduct prayer or healing ceremonies by performing rituals featuring the use of

19 Carhart-Harris.
20 Watts et al.
psychoactive plant medicines.²⁴ It has even been argued that “the whole idea of the deity could have arisen as a result of the other worldly effects of these agents,” and that hallucinogenic plants were considered to be “gifts from the gods.”²⁵

Psychedelics were likely used in the Vedic religion in the mountains of Afghanistan as early as 1600 B.C. Mushrooms were used in the Yucatan before the time of the Mayans (c. 900 A.D.-1300 A.D.), by the Toltec and Nahua predecessors of the Aztecs.²⁶ Some evidence, however – including mushroom shaped-sculptures and etchings – suggests an even deeper history of the use of psychedelics in religion and medicine, perhaps dating as far back as 5000 B.C.²⁷

As an example, more than 3,500 years ago, Soma, an ancient Indian god, occupied an exalted position in the Aryans’ magico-religious ceremonies in the Indus Valley. The Soma cult devoted many holy hymns to a sacred narcotic that was later believed to be based on a fungus called Amanita muscaria (“The Fly Agaric”). The Soma’s sacred fungus is known to be one of the oldest hallucinogens used.²⁸ Similarly, in Aztec rituals, diviners were said to achieve inspiration during spectacular ceremonies featuring the ingestion of hallucinogenic mushrooms, which they called teonanacatl, or “god’s flesh.”²⁹ Some of these wisdom traditions, such as the Mexican Mazatec Indians’ ritualistic use of the hallucinogenic plant salvia divinorum, have endured for centuries.³⁰

4. SCIENTIFIC DISCOVERY

The earliest formal exploration of the “psychotomimetic paradigm” was described by Moreau in 1845, regarding hashish and the deliriants henbane, belladonna, and datura.³¹ This was followed decades later in 1898 when Arthur Heffter isolated mescaline from the peyote cactus of Mexican origins.³² But the most important scientific advancement in psychedelics came nearly four decades after Heffter, when in 1938 the Swiss chemist Albert Hofmann created LSD-25 at the Sandoz laboratories in Switzerland when testing alkaloids from rye ergot fungus.³³ After resynthesizing LSD-25 in 1943, Hofmann accidentally ingested a minuscule amount, and the experience that

²⁵ Schultes, Hofmann, and Ratsch.
²⁶ Grinspoon and Bakalar.
²⁸ Schultes, Hofmann, and Ratsch.
³¹ Hartogsohn.
followed helped him understand the potency and psychoactive properties of the compound. In 1947, to promote further research, Sandoz laboratories made LSD-25 (under the name “Delysid”) available to researchers and clinicians, which in turn helped initiate animal testing and experimental human use in the in the 1950s.\textsuperscript{34}

A decade after Albert Hofmann’s synthesis of LSD in the laboratory, the therapeutic application of psychedelics was explored in 1953 by A.M. Hubbard and continued by Humphry Osmond.\textsuperscript{35} Max Rinkel’s interest in experimental production of psychosis is also thought to be an important milestone in medical research on psychedelics in the early 1950s.\textsuperscript{36} In 1958, Hofmann identified psilocybin as a psychoactive compound in Psilocybe mushrooms, which was then synthesized and made available to researchers in 1959 by Sandoz laboratories as “Indocybin.”\textsuperscript{37} As research on psychedelics progressed, the underlying conceptual assumption of the application of psychedelics to mental health was that “if one traumatic event can shape a life, one therapeutic event can reshape it.”\textsuperscript{38}

During the 1950s and 1960s, and into the 1970s, more than 1,000 clinical papers were published on the therapeutic uses of psychedelics in a variety of mental health applications (Figure 1), resulting in the emergence of the field termed “experimental psychiatry,” mainly pertaining to research on the properties and effects of experimentally induced states of psychosis.

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Number of Publications Per Year with Keyword “Psychedelic” Indexed in PubMed: 1945-2020}
\end{figure}

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\textsuperscript{35} Grinspoon and Bakalar. & \\
\textsuperscript{36} Hartogsohn; Rinkel. & \\
\textsuperscript{38} Grinspoon and Bakalar. p.195 & \\
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The 1950s through the 1970s later became known as the “golden period” of experimental psychiatry psychopharmacology, and marked the beginning of what some called the “pharmacology of consciousness.”39 Some of the most important contributions of this time period were in gaining a more complete understanding of the biochemical and neurological properties of psychedelics,40 particularly their interactions with the brain's serotonin system.41 During this same time period, experiences with psychedelic drugs also “jumped the laboratory walls” through the work of Harvard research psychologist Timothy Leary and others, setting the stage for a sociopolitical backlash.

5. SOCIOPOLITICAL BACKLASH

Despite the rapid and promising advances in psychedelic research from the 1950s through the 1970s, psychedelic research suffered important setbacks toward the end of this period. In contrast to other promising medical compounds that fade away after underperforming in early clinical studies, the setbacks suffered by psychedelics were not generally associated with their performance in laboratory and clinical settings.43 Rather, they were generally attributed to three factors:44 (1) rising recreational use (and misuse) of LSD, which was linked by the mainstream media to a counterculture narrative perceived as threatening by a large segment of the population;45 (2) lack of understanding by the mainstream medical establishment of the value of psychedelics in medical applications; and (3) difficulties in designing randomized controlled trials (RCTs) to study clinical outcomes with an appropriate control substance (i.e., an active placebo).

Sandoz laboratories ended its distribution of LSD in 1966.46 Four years later, the United States Congress passed the Controlled Substances Act of 1970, which placed most psychedelic drugs on

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43 Grof.
44 S. J. Belouin and J. E. Henningfield, "Psychedelics: Where we are now, why we got here, what we must do," Neuropharmacology 142 (2018); Grof.
45 For example, Richard Nixon in 1971 described Timothy Leary as “the most dangerous man in America.” See Pollan.
“Schedule I,” signifying that they had a high potential for abuse and no legitimate medical use, and therefore could not be prescribed, dispensed, or administered. These restrictions were buttressed in 1971 by the United Nations Convention on Psychotropic Substances, which implemented restrictions on importing and exporting, and created additional rules limiting use to specific scientific and medicinal purposes. The overall effects of these restrictions on scientific research can be seen in Figure 1, which shows a precipitous decline in the volume of published material on psychedelics from the early 1970s through the 1980s.

6. SCIENTIFIC PERSISTENCE

Despite the prohibition on recreational and medical use of psychedelics, biomedical research persisted at a rate of over 300 publications per year from the 1970s to the 1990s, mainly at private research organizations and universities. The continuation of psychedelic research during this period resulted in several important contributions on biomedical properties and mechanisms of action, in addition to findings on potential therapeutic applications in a variety of mental health conditions, including depression, anxiety, and addiction.

Exploring applications in depression, Grinspoon and Bakalar in 1986 reviewed some of the existing case studies of the use of psychedelics to treat depression (primarily as an adjunct to psychotherapy), concluding that the research from the 1970s and 1980s had been very promising. One of the earliest controlled studies of psychedelic-like treatment of depression came in 1999, when Berman et al. conducted a double-blinded study of seven subjects with Major Depressive Disorder (MDD). Relying on a randomized, double-blind study design, patients underwent two days of treatment, separated by a week. Four randomly chosen participants received 0.5mg/kg of intravenous ketamine hydrochloride, and the remaining three received a placebo saline solution.

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47 Kyzar et al.
48 Michael Gabay, "The federal controlled substances act: schedules and pharmacy registration," Hospital pharmacy 48, no. 6 (2013).
50 Grinspoon and Bakalar; Pollan.
52 Grinspoon and Bakalar, "Can drugs be used to enhance the psychotherapeutic process?"
After three days of the treatment, the Hamilton Depression Rating Scale (HDRS, or HAM-D) scores decreased by 50% or more in the experimental group versus the control group.

The period of scientific persistence also included important research on the use of psychedelics to treat anxiety, particularly that which is attributable to life-threatening illness. For example, Grof et al. conducted study of 60 cancer patients, including a treatment group (administered 200-500µg of LSD) and a control group (administered 60-105mg of dipropyltryptamine). Post-treatment results showed that most patients experienced either substantial (26%) or moderate (42%) improvement in depression and anxiety in the treatment group.

During this time research on the use of psychedelics to treat addiction also gained a foothold. For example, in 1966 Smart et al. studied 30 participants in an inpatient alcohol treatment program, all of whom underwent psychotherapy sessions prior to receiving drugs. Participants were split into three groups of 10 each, the first of which received 800µg of LSD, the second of which received 60mg of ephedrine sulfate, and the third of which were not given any drugs. During the three-hour drug treatment sessions, patients were accompanied by a doctor and nurse, and were asked a wide range of questions. The LSD group experienced a 33.7% increase in abstinence, compared to 31.5% in the ephedrine group and 19.6% in the no-drug group.

7. CULTURAL RESURGENCE

The resurgence of psychedelic research began in the second half of the 1990s as the cultural imprint of the Leary era faded, and the global rave and festival culture embraced the use of psychedelics through the “psytrance” movement. In Silicon Valley, the popularization of the magazines Wired and Mondo 2000 brought some legitimacy to what was termed the “cyberdelic” movement, and also revived enthusiasm for the creative potential of micro-dosed psychedelic use. Fueled by modern media and the internet, renewed enthusiasm for the potential of psychedelics spilled over into the scientific community, reinvigorating research. In How to Change Your Mind, author Michael Pollan attributed the resurgence to the persistent work of Roland Griffiths, Bob Jesse, Rick Doblin and Bill Richards, and in particular Griffiths’ 2006 paper reporting on an RCT that showed sustained mental health benefits associated with psilocybin.

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60 Griffiths et al.
A decade later, the medicinal value of psychedelics began to receive tacit endorsements from some unlikely but influential sources. For example, a recent Netflix series chronicled the experiences of individuals employed by actress Gwyneth Paltrow’s Goop Lab company on a retreat featuring psilocybin treatments, where one employee revealed she felt she had “completed five years of therapy in five hours.” Other recent documentaries, such as Have a Good Trip: Adventures in Psychedelics, The Mind, Explained, and Fantastic Fungi have explored psychedelics from a social and culture historical perspective, while at the same emphasizing the potential of these drugs in treating a variety of mental health conditions. In addition to documentaries, an increasing amount of detailed information on psychedelics has become available on a variety of websites, such as Erowid, an online resource for psychedelic drug users, therapists, and other experts.

In sum, the historical trajectory of psychedelics is somewhat unique from the perspective of biomedical research. The era of scientific discovery was filled with promise, and Hofmann’s captivating “discovery narrative” was befitting of the enthusiasm surrounding psychedelics’ potential. But the harshness of the backlash, while not enough to completely derail psychedelic research, was certainly enough to impede its progress. The persistence of a handful of dedicated researchers maintained a place for psychedelics in mental health treatment research long enough for the turmoil of the 1960s to fade, allowing these substances once again to be considered a serious alternative to existing treatments, many of which have failed to produce promised results.

8. CURRENT APPLICATIONS

Resurgence of interest in psychedelics has resulted in what is now a rich and rapidly developing clinical research agenda. In the past two decades, numerous studies have demonstrated clinical effectiveness of psychedelics in the treatment of depression (MDD and Treatment Resistant Depression [TRD]), anxiety (e.g., cancer-related psychiatric distress/anxiety disorders), addiction (alcohol dependence and smoking cessation), and post-traumatic stress disorder (PTSD). In recent years, this research has been extended to other areas, including obsessive-compulsive disorder (OCD) and management of chronic pain. Between 1995 and 2010, the annual number

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61 K. Shapiro, "Netflix And Trip: Take A Psychedelic Adventure In This Star-Studded Documentary," (New York, NY2020).
62 J. Naftulin, "Gwyneth Paltrow sent her employees to take psychedelic mushrooms in Jamaica. One staffer said she felt like she'd undergone 5 years of therapy.," (New York, NY2020).
63 Shapiro.
64 See generally http://www.erowid.org
of scientific publications on psychedelics more than doubled, from about 350 to over 700 per year until the COVID-19 pandemic in 2020 (Figure 1). Many of the studies published in this era were more robust versions of the smaller case studies that characterized earlier stages of clinical research. Several systematic reviews and meta-analyses summarizing the main findings of these studies have also been conducted. In this section, we briefly review this work, focusing on the treatment of depression, anxiety, addiction, and PTSD.

Depression

In recent years there have been 11 published systematic reviews and meta-analyses focused on the use of psychedelics in the treatment of depressive disorders, mainly MDD and TRD. These reviews shared similar selection criteria, with the main inclusion criteria being RCT study design and treatments mostly consisting of various doses of LSD, psilocybin, or ayahuasca relative to a placebo. Results of these systematic reviews have been remarkably consistent, showing sustained positive effects of psychedelics as measured by a variety of commonly applied outcomes measures. In addition, meta-analyses by Luoma et al. and Romeo et al. found average effect sizes larger than those typically reported in studies of pharmacological and psychotherapy interventions. These findings were confirmed in a recent meta-analysis by Galvão-Coelho et al., which reviewed data from 12 RCT studies of the use of psychedelics (psilocybin, LSD, and ayahuasca) in treatment of depression. The results mirrored those of other similar reviews, finding moderate significant effect sizes in favor of psychedelics both short-term and long-term.


68 The COVID-19 pandemic resulted in a significant slowdown in clinical studies globally, due in part to the restrictions associated with general lockdowns, but also reluctance on the part of study subjects to interact with health providers for non-life-threatening health care services. See generally F. S. E. Ebeid, "COVID-19 effect on clinical research: Single-site risk management experience," Perspect Clin Res 11, no. 3 (2020).

Results on the clinical utility of psychedelics in treating depression have also been found to be robust to patient-reported outcomes and clinician-judged improvement. For example, Rucker et al. found that of 423 individuals in 19 studies, 79% showed clinician-judged improvement after treatment with psychedelics. In addition, none of the reviews found evidence of significant adverse events associated with psychedelic treatment for depression, and all reviews consistently found robust evidence of both short-term and long-term reductions in psychiatric symptomatology.

Anxiety

Seven of the reviews covering depression also included anxiety. They found consistent evidence of the efficacy of psychedelics in the treatment of anxiety, primarily in the context of cancer and other life-threatening diseases. For example, Griffiths et al. conducted a double-blind study of depression and anxiety in 51 cancer patients in a carefully constructed therapeutic context. Study participants received either a low dose of oral psilocybin (1-3mg/kg) in the first session and a higher dose (22-30mg/70kg) in a second session about five weeks (or the same dosages but in reverse order). Five weeks after the first session, 92% of the participants in the group that had received the higher dose first demonstrated a more than 50% decrease relative to baseline on the GRID Hamilton Depression Rating Scale (GRID-HAMD), while the other group exhibited a 32% treatment response rate. At six-month follow-up, 80% of participants continued to show improvement in depressed moods and anxiety.

Addiction

Research on the use of psychedelics to treat addiction – especially alcoholism – dates to the 1960s. More recently, five systematic reviews have assessed the results of clinical studies of the use of psychedelics to treat addiction. In a recent systematic review and meta-analysis, Krebs and Johansen reviewed six randomized trials on psychedelics to treat alcoholism, representing 536 inpatient alcoholic volunteers across the six studies. A total of 325 individuals were randomly chosen to receive a single high dose of LSD treatment. Overall, 59% demonstrated improved

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70 Rucker et al.
71 Also see J. S. Aday et al., "Long-term effects of psychedelic drugs: A systematic review," Neurosci Biobehav Rev 113 (2020).
74 Andersen et al; Breeksema et al; Dos Santos et al; Fuentes et al; T. S. Krebs and PØ Johansen, "Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials," J Psychopharmacol 26, no. 7 (2012).
effects by the first follow-up, resulting in a 1.96 odds ratio for improvement. Though the literature is somewhat less developed, addiction research with psychedelics has also been applied to smoking cessation. For example, in 2014 Johnson et al. reported on an open-label pilot study of psilocybin in the treatment of tobacco addiction.\(^{75}\) A total of 15 nicotine-dependent smokers participated in the 15-week study. Psilocybin was administered at weeks 5, 7, and 13, of which the first session included a 20mg/70kg moderate dose of psilocybin, and the other two sessions having a high dose of 30mg/70kg. Of the 15 participants, 12 completed all three psilocybin sessions; of these, 80% remained abstinent from smoking at 6-month follow-up. After 12-month follow-up, 67% remained abstinent, and after 2.5 years the abstinence rate had fallen only to 60%.

**PTSD**

Finally, PTSD has also been a focus of psychedelic treatment, with four recent reviews assessing clinical studies to date.\(^{76}\) For example, Varker et al. reviewed nine clinical studies, five with ketamine and four with MDMA, concluding that the MDMA evidence on PTSD was moderate but consistent. Important contributions to this literature were made by Mithoefer et al. In a 2011 study, the authors conducted a double-blind randomized study of 20 PTSD patients, 12 of whom received 125mg of MDMA with psychotherapy and the other eight of which received placebos along with psychotherapy.\(^{77}\) Participants were also given an optional dose of 62.5mg of MDMA 2-2.5 hours later, depending on their response to the first dose. Upon treatment, the MDMA group demonstrated a significantly greater improvement in the Clinician-Administered PTSD Scale (CAPS). In the MDMA group, a positive response was observed in 83.3% of the participants.

Mithoefer et al. more recently conducted a randomized, double-blind study of MDMA-assisted psychotherapy for PTSD in 26 military veterans and first responders.\(^{78}\) Seven participants received 75mg of MDMA and 12 participants received 125mg of MDMA. The control group consisted of seven patients who were administered 30mg of MDMA. Based on their CAPS-IV scores after treatment, the groups that were given 75mg and 125 mg demonstrated more significant decreases in PTSD symptoms than the control group. In just one month after treatment, the mean change in CAPS-IV from baseline was -58.3 for the 75mg group and -44.3 for the 125mg group. At the 12-month follow up, all treatment groups had maintained gains.

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\(^{77}\) M. C. Mithoefer et al., "The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study," J Psychopharmacol 25, no. 4 (2011).

\(^{78}\) Michael C. Mithoefer et al., "3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial," The Lancet Psychiatry 5, no. 6 (2018).
9. CONCLUSIONS

In this paper we have described the historical trajectory of psychedelics, from their millennia of use in indigenous societies and wisdom traditions, to the frenetic period of scientific discovery in the mid-20\textsuperscript{th} Century followed by sociopolitical backlash, to the resurgence of scientific research in the past two decades. While the richness of the history and current uses of psychedelics in mental health suggest several interesting insights and conclusions, there are three that we wish to emphasize.

First, psychedelics have an amazingly long history of medicinal and other beneficial uses. Unlike many pharmaceutical compounds, psychedelics (by whatever name) were first discovered by individuals with no formal training. Organic patterns of use and recorded outcomes over the centuries offer insights unlike those that any bench science or clinical trial would likely be able to offer. Albert Hofmann’s experience in the laboratory with LSD was indeed a discovery in the modern sense, but a version of this discovery had taken place many times before, outside of the laboratory and in astoundingly diverse cultures and settings. As recorded history moved from the walls of caves to paper and then the digital world, the human experience with psychedelics has told a remarkably consistent story. This story is compelling enough to have sustained the curiosity of scientists who understood psychedelics’ potential even in the face of a multipronged backlash. The fact that psychedelics sustained such keen interest over such a long period testifies to their great promise. Moreover, because the large knowledge base accumulated throughout this history necessarily informs current investigations and practices, it should be considered in current legal and policy debates concerning psychedelics, such as those over the role of IP.

Second, the resurgence of psychedelic research in the past two decades has already generated a large body of work that consistently points to the benefits of psychedelics in treating a variety of mental health conditions. The findings from recently published systematic reviews and meta-analyses of rigorously designed clinical research have added robust support to the earlier efficacy findings. While this research needs to continue, especially with more controlled studies featuring larger numbers of participants, those that have been published to date show clear benefits associated with psychedelic-assisted treatment. These benefits are remarkably consistent with the results of the smaller studies conducted in the 1960s and 1970s. Psychedelics may especially offer hope to patients who fail to adequately respond to existing psychopharmacological treatments.

Finally, because psychedelics appear to operate through fundamentally different mechanisms from those of conventional psychopharmacological and psychotherapeutic treatments, it is possible that their clinical use will rise to a new paradigm for understanding and producing mental health. There is clearly room for a new paradigm in mental health treatments, as existing treatments have generally struggled to rise above 50\% effectiveness. Early results from rigorous clinical research on psychedelics suggest a markedly higher response rate coupled with sustained longer-term benefits, positioning them as a potentially valuable component of a more effective mental health treatment model.
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