CNS Spectrums

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The historical opposition to psychedelic research and implications for credibility in psychiatry

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Perspective

Cite this article: Koning E, Chu EM, and Brietzke E (2024). The historical opposition to psychedelic research and implications for credibility in psychiatry. *CNS Spectrums* **29**(5), 300–305.
https://doi.org/10.1017/S1092852924002141

Received: 15 April 2024
Accepted: 05 September 2024

Keywords:
psychedelics; psychotherapy; psychiatry; neuroscience; history; drug policy

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Abstract

Psychedelics are a group of psychoactive substances that alter consciousness and produce marked shifts in sensory perception, cognition, and mood. Although psychedelics have been used by indigenous communities for centuries, they have only recently been investigated as an adjunctive therapeutic tool in psychotherapy. Since the early twentieth century, psychedelic-assisted psychotherapy has been explored for the treatment of several neuropsychiatric conditions characterized by rigid thought patterns and treatment resistance. However, this rapidly emerging field of neuroscience has evolved alongside opposition in several areas, including the affiliation with mid-twentieth century counterculture movements, media sensationalization, legislative restriction, and scientific criticisms such as "breaking the blind" and "excessive enthusiasm." This perspective article explores the historical opposition to psychedelic research and the implications for the credibility of the field. In the midst of psychedelic drug policy reform, drawing lessons from historical events will contribute to clinical research efforts in psychiatry.

Introduction

The term *psychedelics* was named by psychiatrist Humphrey Osmond in 1957, an etymology that suggests a 'mind-manifesting' capability. Modernly, they can be defined as a group of substances that alter consciousness in a complex and subjective manner. The classical psychedelics include lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), psilocybin, and mescaline, which act primarily as a 5-HT_{2A} receptor agonist, especially in high-level cortical areas.[1,2] Nonclassic psychedelics include 3,4-methylenedioxymethamphetamine (MDMA), which nonselectively activates monoamine receptors and promotes serotonin neurotransmission as well as the dissociative anesthetic and N-methyl-D-aspartate receptor antagonist ketamine. Although there are a variety of origins and chemical structures, the perceived effects of psychedelics are relatively similar, including marked shifts in perception, cognition, and mood.[3] Mechanistically, psychedelics cause serotonergic stimulation and disrupt functional connectivity in brain networks such as the default mode network and between regions of the frontal cortex and subcortical areas.[1,4,5]

Psychedelics have been used for centuries by indigenous communities and have played a role in many cultures in the ancient Northern, Central, and Southern Americas.[6] In modern research, they are typically administered as an adjunct to psychotherapy, in a model known as psychedelic-assisted psychotherapy (PAP), with preparation and integration sessions occurring before and after dosing, respectively. The context for PAP is thoughtfully curated with relaxing music, a living-room ambience and psychological support from a therapist.[7] In this way, it has been investigated as a potential treatment for several neuropsychiatric disorders. For example, meta-analyses reveal large effect sizes of psilocybin-assisted psychotherapy on improved depressive and anxiety symptoms,[8–11] MDMA-assisted psychotherapy has demonstrated high rates of tolerability, clinical response, and remission in individuals with PTSD symptoms,[12] and the therapeutic effects of psychedelics have been preliminarily investigated in eating disorders, cluster headaches, and Alzheimer's disease.[13–16]

Throughout history, psychedelic research has evolved alongside opposition and controversy, including questionable scientific practices, exaggerated safety risks, and associations with counterculture movements that have contributed to stigmatization. Further, there is a long-standing debate over the dangers and therapeutic efficacy of psychedelics.

Twentieth century opposition to psychedelic research

The rapidly evolving timeline of psychedelic research, as depicted in Figure 1, was stimulated by the discovery of psychoactive properties of LSD by chemist Albert Hoffmann of Sandoz Pharmaceuticals in 1943.[17,18] Sandoz Pharmaceuticals contributed to a fertile period of

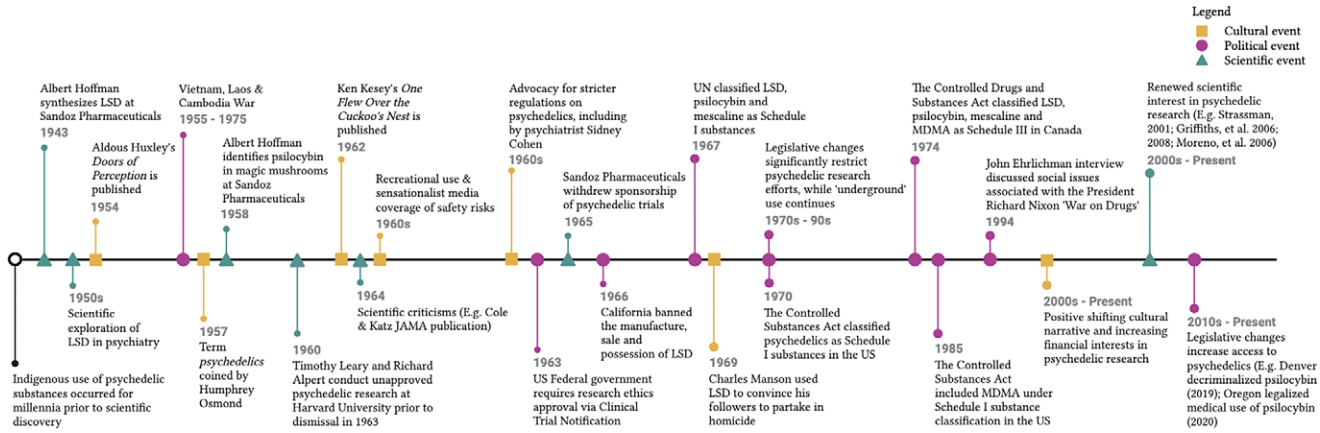

Figure 1. The timeline of notable historical events related to psychedelic research impacted the credibility of this emerging field in psychiatry. Abbreviations: LSD, Lysergic acid diethylamide; JAMA, Journal of the American Medical Association; US, United States; UN, United Nations; MDMA, 3,4-methylenedioxymethamphetamine.

psychedelic research in the 1950s, including the identification of psilocybin in magic mushrooms by Hofmann in 1958.[19,20] LSD was widely used as an adjunct to psychotherapy for a period of about 15 years and it was reported that up to 79% of mood disorder patients demonstrated subjective clinical improvement.[19,21] Throughout the 1950s, psychedelic research occurred with limited opposition or government oversight. In fact, over 130 clinical study grants were government-funded.[22]

Despite emerging therapeutic interest in psychedelics, many early trials faced skepticism. Major methodological biases were highlighted, including the lack of standardized measures, randomization procedures, adequate sample characteristics, and controlling which limited the validity of the results. Jonathan Cole, president of the American College of Neuropsychopharmacology (1965–66), was one of the first scientists to voice criticism of psychedelic research, emphasizing the lack of evidence for safety and efficacy.[23(p19),24] However, scientific opposition was not the only avenue in which psychedelic research was discredited.

During the early era of psychedelic research, recreational use increased substantially, especially amongst individuals engaging in the counterculture movement of the 1960s. The psychedelic-associated counterculture movement faced opposition by supporters of the U.S. involvement in the Vietnam, Laos and Cambodia war (1955–1975). Political figures such as President Richard Nixon and President Lyndon B. Johnson voiced opposition to the psychedelic counterculture, claiming the necessity of the war and the importance of upholding patriotic duty. The first major advancements in the development of psychotropic pharmacotherapies occurred around the same time, but these were not met with the same political opposition.[25]

Timothy Leary was a Harvard psychologist and prominent figure in mid-twentieth century psychedelic counterculture. After undergoing a personal experience with psilocybin in Cuernavaca, Mexico, Leary conducted research on the effects of psychedelics at Harvard University alongside colleague Richard Alpert, advocating for the ability of psychedelics, particularly LSD, to expand consciousness and promote psychological benefits. Leary conducted multiple unapproved projects and widely encouraged psychedelic use by the public, famously quoting "turn on, tune in, drop out." Both Leary and Alpert were dismissed for these actions from Harvard University in 1963, and the continued promotion of psychedelics eventually led to Leary's arrest in 1966.[1] President Richard Nixon referred to Leary as "the most dangerous man in America," with increasing concerns that recreational psychedelic use would pose health concerns and jeopardize war efforts in Vietnam. However, Leary was not alone in advocating for the psychedelic movement. Many other prominent figures including novelists Aldous Huxley and Ken Kesey as well as popular bands such as The Doors and The Beatles contributed.[26,27]

Despite emerging political and scientific opposition, the recreational use of psychedelics continued, often in uncontrolled environments. Further, there was an increase in the illegitimate use of psychedelics by sham psychiatrists.[28] The concept of the "bad trip" began to be recognized, referring to negative and distressing psychedelic experiences and contributing to the existing negative perception. However, this was not the first incidence of cultural opposition to psychedelics. Antipsychedelic views were often shared by several religious groups campaigning against Native American peyote use and referring to the substances as "addictive" and "insidious evil."[29]

Sensationalist media coverage of psychedelic medicines highlighted the emerging safety concerns associated with these substances, including reports of psychosis, accidental death, and suicide among users.[27] LSD was first banned in California in the mid-1960s as a result of these growing public concerns.[30] In 1969, the adverse public narrative of psychedelics was further perpetuated by the case of Charles Manson, a cult leader who used LSD to convince his followers to partake in mass homicide.[27] The concept of psychedelic neurotoxicity also emerged in which reports suggested that psychedelic users exhibit neurological or cognitive deficits.[31,32] Individuals advocated for stricter regulations on the clinical use of LSD in response to adverse events among patients undergoing psychotherapy.[28,27,33]

In 1963, the US Federal legislation increased restrictions on pharmaceutical research, requiring ethics approval in the form of a Clinical Trial Notification, which requires methodologically sound preclinical evidence of safety and efficacy.[34,35] In response to emerging controversy, Sandoz Pharmaceutical withdrew sponsorship of psychedelic trials in 1965.[17,34] At this point, psychedelic research was limited to studies funded by the National Institute of Health (NIH). The United Nations classified LSD, psilocybin, and mescaline as Schedule I in 1967, considering them as substances with no or very little medical purpose, a high potential for abuse, and a lack of accepted safety.[36] Similar political changes occurred in

https://doi.org/10.1017/S1092852924002141 Published online by Cambridge University Press

other countries, including Schedule 3 status under the Controlled Drugs and Substances Act in Canada.[36,37]

This political and legal opposition led to an unprecedented restriction on research efforts for decades, making it difficult for researchers to conduct studies using psychedelics, with limited funding and resources available. However, a few studies were conducted as supported by the Food and Drug Administration and NIH.[34,38] Nonetheless, the political opposition to psychedelic research that occurred was unprecedented in the field of psychiatry. This is especially true considering the growing body of positive findings that occurred leading up to scheduling and the relatively favorable safety profile of psychedelics in medically supervised contexts.[22,36,37]

The use and study of psychedelics largely occurred "underground" throughout the remainder of the twentieth century, leading to the conduct of methodologically and ethically questionable practices and therapeutic models. For example, some therapists conducted PAP with substances obtained from the illicit market.[39] Reports also include the use of therapeutic touch as a crucial aspect of practice, raising concerns about boundary violation and misconduct. Unethical conduct even extended to administering high doses of LSD to unprepared, restrained patients.[40]

Psychedelic research dwindled for decades until around the turn of the twenty-first century when a renewed scientific interest emerged in their therapeutic potential. Advancements in neuroscience such as neuroimaging techniques and psychopharmacological studies in healthy individuals contributed to the study of psychedelics in the modern age. In addition, small exploratory studies conducted at the early stages provided a base for larger investigations. For example, Rick Strassman and colleagues investigated DMT in the first government-approved study, which illustrated the importance of 'set' and 'setting.'[41] Roland Griffiths and colleagues demonstrated the profound and mystical nature of the psychedelic experience.[42,43] The first modern clinical trial was a pilot study conducted by Moreno et al (2006) on psilocybin for treatment-resistant obsessive-compulsive disorder. Significant reductions (23–100%) in symptoms occurred in all participants without adverse events, although the improvements did not last.[44] Many other impactful and pioneering studies occurred during this period of psychedelic research resurgence.[22]

Sociocultural factors impacting psychedelic research credibility

Despite significant cultural normalization, there remains a social stigma against psychedelics, amongst persisting antidrug views. The classification of psychedelic substances as Schedule I has been a contributor, which also includes an exaggeration of their risks and addictive potential, contrary to the evidence.[36] Ironically, psychedelics have actually demonstrated preliminary efficacy in the treatment of addiction and substance use disorders.[10,11,45] Previous work has shown that public views of high toxicity and adverse events are largely incorrect.[46–51] Further, the illegal status has contributed to the "underground" use of these substances, which further stigmatizes them in the public eye.

The medicalization of psychedelics as an adjunct to psychotherapy is contributing to a more positive cultural opinion. However, the "hype" surrounding psychedelic research is disproportionate to the available evidence and threatens public credibility if results do not follow through. Yaden (2022) described the "The Gartner Hype Cycle" in which novel scientific advancements trigger substantial public attention, leading to inflated expectations followed by a steep decline when expectations are not met in which public narratives may shift from overly positive to overly negative, before a plateau occurs.[52]

"Excessive enthusiasm" refers to the influence of personal use of psychedelics by researchers, potentially compromising scientific objectivity and promoting the biased reporting of results.[53] Cole & Katz (1964) were one of the first to describe "excessive enthusiasm."[24] Today, concerns of researcher bias persist, as discussed in a recent paper titled "Should we be leery of being Leary?"[53] "Excessive enthusiasm" may also impact the credibility of psychedelic research at the participant level. Individuals with past psychedelic experiences may be more likely to partake in psychedelic research, to expect positive results and to "break the blind." This may lead to a self-selecting study population, introducing bias into psychedelic research and ultimately jeopardizing credibility.

Political factors impacting psychedelic research credibility

Legislative restrictions of the 1960s and 1970s were largely made before a thorough understanding of the pharmacological effects of psychedelics was reached, leading to vague reasoning. Ongoing debates about the Schedule I classification of psychedelics highlight significant discrepancies in regulatory criteria, summarized by Nutt et al (2013).[36] Although preliminary interest in the therapeutic potential of psychedelic substances was identified by the 1960s, Schedule I criteria claims that there is no or very little medical purpose. At this point, there was evidence of safety for the use of psilocybin under medical supervision, and further investigations to determine the safety and efficacy cannot be conducted due to scheduling.[36] In this way, criteria for Schedule I status is paradoxically self-fulfilling as restrictions on research prevent the conduct of safety and efficacy studies that are necessary to challenge the classification.

While there are certainly unique risks associated with psychedelics, many argue that scheduling appears to be based on the assumption of extreme risk. Interestingly, an analysis demonstrated no relationship between the level of harm of psychoactive substances and legal status.[50,51] The "War on Drugs" launched by the Nixon administration disproportionately targeted marginalized groups and low-income communities, including selective enforcement, racial profiling, and over-incarceration with limited harm-reduction programs.[54] John Ehrlichman, the domestic policy chief for Nixon, was famously quoted in a 1994 interview stating that the administration's drug policies were intentionally crafted to disrupt and vilify certain communities, irrespective of drug harm. The political narrative of "protecting" the public from psychedelics is especially ironic considering the disturbing MK-Ultra project in which the CIA experimented if LSD could be used for "brainwashing" individuals.[55] In this way, legislative restrictions on psychedelics were made due to a confluence of factors beyond safety concerns or scientific evidence alone.

The scheduling of psychedelics from the 1970s persists in the majority of North America today. In Canada, LSD, psilocybin and psilocin, mescaline, and DMT remain as Schedule 3 substances, while MDMA and ketamine are Schedule 1, impacting the conduct of psychedelic research at numerous levels. For example, granting agencies may be reluctant to fund psychedelic research initiatives due to the misconceptions surrounding safety.[36] Further, the illegal status of psychedelics makes it difficult to gain approval for their use in clinical research. The Multidisciplinary Association for Psychedelic Studies took over four years to gain approval to investigate the therapeutic

https://doi.org/10.1017/S1092852924002141 Published online by Cambridge University Press

use of MDMA for PTSD, due to legislative hurdles enacted by Health Canada and institutional review boards.[36]

The status of these substances applies to any quantity, challenging research on submilligram doses, a fear that may be associated with the "leaking" of psychedelic substances into the recreational domain in the mid-twentieth century.[36] The restrictions extend to other 5-HT_{2A} agonists, limiting adjacent lines of research which may improve the mechanistic understanding of psychedelics.[4,43,56] Even once legislative hurdles are overcome, it is difficult to source pharmaceutical-grade psychedelics for research. Manufacturers face numerous hurdles in the development of psychedelics, leading to high costs of custom synthesis that is often too extensive for research grants, $12,000 per gram of psilocybin, for example.[56] Together, numerous political and legal barriers continue to impact the ability to conduct psychedelic research.

Scientific factors impacting psychedelic research credibility

The final area in which psychedelics have faced historical opposition and continue to impact the credibility of the field is through the level of scientific opinion. The "underground" nature in which psychedelics were studied and used throughout the latter half of the twentieth century contributes to skepticism about the scientific validity of the therapeutic claims resulting from this era of psychedelic research. Many early studies were later refuted and retracted.[32,57,58] As an evolving field of neuroscience, psychedelic research faces several challenges that are inherent to clinical, neuropharmacological, and psychotherapeutic research fields; in particular, adhering to the accepted gold-standard framework of the randomized controlled trial (RCT).

PAP clinical trials are typically conducted with relatively small sample sizes due to the amount of time and resources required. The absence of a control group is another limitation. Open-label, uncontrolled studies which report reductions in illness severity following PAP are not sufficient to prove efficacy. Another criticism related to sample characteristics is the often-extensive exclusion criteria, excluding participants with comorbidities, drug use, or a family history of psychotic disorders. While there are important safety precautions to uphold, it is argued that populations participating in psychedelic trials are easier to treat.[59] Further, participants of psychedelic studies are typically Caucasian with socioeconomic stability, limiting generalizability and external validity.[60] Many psychedelic studies have been conducted as a single session with minimal follow-up, threatening construct validity by making it difficult to determine if the benefit is persistent.[59]

Another methodological criticism is expectancy bias, a form of cognitive bias in which an individual's expectations about a process or outcome may influence the perception of their own or someone else's behavior.[61] Expectancy, including "excessive enthusiasm," may occur in psychedelic research at the level of the participant, investigator, or therapist and may be responsible for a portion of the therapeutic outcomes observed.[24,53] For example, therapist positive beliefs about psilocybin have been associated with greater openness to involving patients with PAP. Likewise, participants with positive beliefs about psychedelics are more likely to volunteer.[62] Expectancy may also contribute to negative outcomes if participants expecting a psychedelic experience in the control arm become disappointed upon being informed of their allocation.[63] Expectation bias in psychedelic research has not been fully investigated.[64]

In the RCT, expectancy is typically overcome through double-blinding, in which neither the researcher administering the substance or the participant is aware of their group allocation. However, blinding is particularly difficult to achieve in psychedelic research, due to perceptual distortions and hallucinations.[61] 'Breaking the blind' is a challenge across psychedelic research, which threatens internal validity as blinding cannot be achieved. Different study designs have attempted to overcome this limitation, such as employing multiple doses to standardize expectation and preparation procedures across study arms or including an active comparator, such as ketamine.[1,65,66]

The lack of mechanistic understanding of psychedelics is another scientific criticism that limits the credibility of the field. It is difficult to determine the components eliciting any therapeutic outcomes, threatening validity. For example, mysticism, interoception, and cognitive flexibility are prominent in the psychedelic experience but are difficult to isolate and measure objectively.[67–69] Furthermore, the psychedelic experience displays inter-individual variability and is context-dependent, producing different outcomes depending on expectancy, the environment and drug administration. Some argue that therapeutic benefits can be attributed, in part, to the music played during dosing or primarily from the psychological support.[22,70] It is possible that cognitive, psychological, and neurobiological changes elicited by psychedelics play independent or convergent roles in therapeutic outcomes.

Current ethical concerns include the ineffable and variable nature of the psychedelic experience, making it difficult to obtain fully informed consent.[71,72] Another concern is the state of high psychological vulnerability elicited by psychedelics. Historically, the inappropriate use of therapist power, including sexual misconduct, has occurred in psychedelic clinical trials.[59] It is important for specific PAP guidelines and regulatory frameworks to be developed for ethical conduct.

Together, numerous scientific criticisms limit the credibility of modern psychedelic research and efforts to address these methodological limitations remain largely unsuccessful.[73] As the field progresses, the increased compliance of psychedelic studies with rigorous clinical research protocols has and will contribute to the increased credibility of the field, something that is important to uphold and improve in future work.[7]

Conclusions

Although the historical events described here have and continue to impact the credibility of the field, advancements in psychedelic research continue. Rescheduling appears to be a logical next step to conduct research and determine the safety and efficacy of these substances, although there are numerous hurdles which need to be overcome. Nonetheless, legislative changes are occurring across North America. Denver was the first U.S. city to decriminalize psilocybin, and Oregan legalized the medical use of psilocybin in 2020. Twenty-five U.S. states have considered 75 bills in which 10 were enacted and 32 are still active regarding psychedelic legislation reform.[74] Regardless, the field is still in its infancy, and few high-quality studies have been conducted, raising concerns over the premature nature in which political changes may occur.[75–81]

At a crucial time in drug policy reform, it is important to consider how to minimize the risk for setbacks and further detriments to the credibility of psychedelic research. For example, there is a concern for how stakeholder interests could impact credibility due to increasing financial conflicts of interest in psychedelic research and reporting.[82] Simultaneously, if the commercialization model of psychedelics fails, then there is a concern that funding for research efforts will be halted, ultimately creating another setback

https://doi.org/10.1017/S1092852924002141 Published online by Cambridge University Press

for research efforts.[36,39,81,83] Culturally, inflated expectations and the sensationalization of psychedelic therapy may pose safety risks and contribute to disappointment in the field.[52] It remains to be determined how regulatory bodies will continue to control psychedelics upon reform and how political, legislative, and cultural factors will continue to impact credibility. In drawing lessons from historical events, legislative decisions should be conducted with public health and safety as a top priority, guided by methodologically sound evidence.

Acknowledgements. None.

Author contribution. Conceptualization: E.C.; Formal analysis: E.K.; Investigation: E.K.; Methodology: E.K.; Project Administration: E.K.; Supervision: E.B.; Writing–original draft: E.K.; Writing–review and editing: E.K., E.C., E.B.

Competing interest. None.

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