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Psychedelic Therapy: A Primer for Primary Care Clinicians—Historical Perspective and Overview

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Background: Psychedelic drugs have recently emerged as plausibly effective pharmacological agents for the management of depression, anxiety, and other neuropsychiatric conditions, including those that are treatment-resistent. The latter half of the 20th century marked a revolution in the treatment of mental illnesses, exemplified by the introduction of selective serotonin reuptake inhibitors and other pharmacological agents. Nevertheless, mental illness remains a major public health crisis, affecting nearly one billion individuals worldwide.

Areas of Uncertainty: Because of the decades-long status of several psychedelics as Schedule I drugs, there have not been very many large, double-blind, randomized controlled trials of psychedelics. Owing to small sample sizes, there may be rare yet serious adverse events that have not been reported in the clinical trials thus far.

Therapeutic Advances: Esketamine, a dissociative hallucinogen drug, was approved for the management of major depressive disorder by the Food and Drug Administration in 2019. As of January 2024, two Phase III trials of 3,4-methylenedioxymethamphetamine (MDMA), a synthetic drug that inhibits the serotonin transporter, have been completed; the results indicate that MDMA is superior to existing pharmacological treatments for post-traumatic stress disorder. A phase III trial of psilocybin, a naturally occurring serotonin receptor partial agonist, is currently underway. The following series details the current state of research in psychedelic therapeutics, including lysergic acid diethylamide (LSD), N-N-dimethyltryptamine (DMT) and ayahuasca, psilocybin, ibogaine, MDMA, and ketamine.

Limitations: While initial clinical trials of psychedelics for depression were very promising, trials of psilocybin with larger sample sizes (100+ participants) suggest that its remission rate is 25%–29%. This is about the same as the remission rate of antidepressants, which is roughly 30% according to the landmark STAR*D trial.

Conclusions: Psychedelic drugs and structural derivatives offer a great deal of promise for the management of a wide range of psychiatric morbidities. It is imperative that clinicians become familiar with these novel agents and learn how to integrate psychedelic therapy with the rest of their care through open communication and referral.

Keywords: psychedelics, LSD, DMT, ayahuasca, psilocybin, ibogaine, MDMA, ketamine, psychiatry, depression, substance use disorder, end-of-life anxiety, anxiety, PTSD, hallucinogenics

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CLINICAL CASE

A 29-year-old man with no significant medical history presented to his primary care physician for evaluation of progressively worsening insomnia, fatigue, and appetite loss of 6 months duration. The patient reported that he had previously enjoyed weightlifting and playing video games, but he had lost interest in most activities and found himself sleeping only 5 hours per night. A diagnosis of major depressive disorder was made, with a baseline Patient Health Questionnaire-9 (PHQ-9) score of 19, and the patient was started on 20 mg of fluoxetine once daily. The patient returned to the clinic 6 weeks later and reported only minimal improvement in his symptoms. The fluoxetine dose was increased to 40 mg once daily; 4 weeks later, the patient reported several adverse effects—including dry mouth and erectile dysfunction—but no improvement in his symptoms. Fluoxetine was tapered, and the patient was started on bupropion 150 mg once daily. Six weeks later, the patient reported that his depressive symptoms had worsened, with repeat PHQ-9 at 25. He was referred to the outpatient psychiatry clinic for further evaluation and management. The dose of bupropion was subsequently increased to 300 mg once daily. At a four-week follow-up appointment, the patient exhibited worsening anxiety (General Anxiety Disorder-7 [GAD-7] score: 19) with no improvement in depressive symptoms. The case was reviewed by the psychiatry team, who recommended a trial of intranasal esketamine 56 mg, titrated to 86 mg after the first dose, twice weekly. The patient returned for follow-up 4 weeks later, reporting a significant improvement in depressive symptoms (PHQ-9: 13) with remission of anxiety (GAD-7: 4). The esketamine dose was reduced to 56 mg once weekly for maintenance. The patient exhibited continued improvement at follow-up visits at 4, 8, and 12 weeks (PHQ-9: 7) with sustained remission at 1 year (PHQ-9: 5).

BACKGROUND

Mental illness is the defining public health crisis of the 21st century, causing an estimated 14.3% of deaths worldwide.[1] The COVID-19 pandemic exacted a devastating toll on mental health worldwide, resulting in markedly increased rates of depression, anxiety, and suicidality.[2–4] Psychiatric illness now represents the leading cause of disability worldwide, affecting as many as 1 in 5 adults and accounting for a global burden of disease rivaling that of cancer and cardiovascular disease.[5,6] Management of mental health disorders has become a public health priority requiring urgent attention from biomedical, social, and governmental institutions.

The current standard of care for mental illness broadly entails a combination of psychobehavioral and pharmacologic interventions. Psychotropic medications have undergone a continuous evolution over the past 75 years with increasing efficacy and tolerability in each successive generation. The development of the typical antipsychotic chlorpromazine in 1950 heralded the "psychopharmacological era." Small molecule drugs revolutionized the management of mental illness. These replaced psychosurgery and high-risk interventions, including lobotomy and induced coma, as the mainstay of management for schizophrenia.[7] The earliest second-generation antipsychotic, clozapine, was introduced in the early 1970s and produced markedly improved outcomes as compared with its first-generation counterparts.[8] Selective serotonin reuptake inhibitors (SSRIs) were developed less than a decade later. These novel agents were presented as a leap forward in the management of depression, promising increased effectiveness with fewer adverse effects and lower potential for toxicity as compared with the monoamine oxidase inhibitors and tricyclic antidepressants of the mid-20th century.[9]

However, despite some success, this psychopharmacology revolution has limitations. Clozapine is incontrovertibly effective for the management of schizophrenia, but it can induce life-threatening loss of white blood cells, or agranulocytosis, in a significant proportion of patients.[10] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial called into question the value of SSRIs, establishing that remission is achieved in only up to one-third of patients receiving a single agent.[11] The results of the STAR*D trial prompted an exhaustive investigation into the SSRI literature. A subsequent meta-analysis found an association between SSRI use and suicide attempts and concluded that "a more accurate estimation of risks could be garnered from investigators fully disclosing all events."[12] The risks, it seems, may occur later than with earlier agents, but the promise of vastly improved safety profiles is receiving ever more scrutiny.

The conclusions from landmark trials such as STAR*D and subsequent investigations are controversial. Psychiatrists and other mental health professionals are fighting a perilous battle with a limited arsenal. The paucity of highly effective treatment options presents an opportunity for novel alternatives.

Psychedelics have emerged as promising treatments for not only depression[13–28] but also a wide range of other psychiatric conditions, including substance use

disorder,[29,30] post-traumatic stress disorder,[31–36] and end-of-life anxiety.[37–41] However, there is little emphasis on psychedelics in medical education, and many physicians just feel unprepared to manage patients taking psychedelic medications in the setting of other acute and chronic conditions.[42] In the following series, we discuss the history of psychedelic compounds, as well as the current landscape of clinical research on psychedelics. We highlight mechanisms of action, clinical applications, limitations, and risks.

EARLY DAYS OF PSYCHEDELIC THERAPY IN THE WEST

The first reported "acid trip" occurred on April 16, 1943.[43] Several years earlier, Swiss chemist Albert Hofmann of Sandoz Laboratories had been tasked with developing a central nervous system stimulant for use in anesthesia. He had synthesized a new lysergic acid derivative known as lysergic acid diethylamide (LSD-25). He initially retired the compound from consideration when it proved not superior to existing analeptic agents. Hoffman decided to synthesize LSD-25 again 5 years later. This time, serendipity struck. Hofmann became the first to experience a powerful LSD-induced hallucinogenesis that would later be termed an acid trip.

Hofmann was deeply moved by his remarkable experience with LSD. Three days later, he performed the first of many LSD self-experiments as he attempted to further understand the nature of this mysterious new drug. Hofmann subsequently enlisted friends and colleagues who experienced similar effects after ingesting small doses of LSD. Animal testing began shortly thereafter with the support of Sandoz Laboratories. The first experimental use of LSD in psychiatry was described four years later by W.A. Stoll at the University of Zurich. Both healthy volunteers and patients with schizophrenia were observed after receiving low doses. General euphoria was present among *all* the study participants.[44] Stoll concurrently performed self-experimentation and described his experience: "I felt myself one with all romanticists and dreamers… Often I seemed to stand at the pinnacle of artistic experience; I luxuriated in the colors of the altar of Isenheim and knew the euphoria and exultation of an artistic vision."

Sandoz (now Novartis) began marketing LSD for use in analytical psychotherapy after the results of the Stoll experiment were published. The drug was a blockbuster in the medical community. In 1951, Humphrey Osmond at the Weyburn Mental Hospital in Saskatchewan began experimenting with LSD for the treatment of refractory alcoholism. Between 1954 and 1960, Osmond and his colleague Abram Hoffer used LSD to treat nearly 2000 alcoholics, 40%–45% of whom were in remission at least one year later.[45]

Meanwhile, LSD became popular as a source of creative inspiration for many artists, and it came to play a key role in the countercultural movement that would define the 1960s.[46] Unfortunately, LSD's association with the counterculture led to a politically motivated backlash against psychedelics, which culminated in Richard Nixon's War on Drugs.[47] The 1960s also saw a surge in the number of emergency department visits that were caused by LSD-induced episodes of psychosis. However, many reports of "bad trips" were sensationalized by the media which led to a moral panic about psychedelics.[48] In 1970, the US government classified LSD and psilocybin as Schedule I drugs which designated them as substances with no accepted medical use and high potential for abuse. This not only halted but also delegitimized all psychedelic research. Prominent figures in the scientific community became active opponents of psychedelics. Sidney Cohen, a renowned psychiatrist and one of the pioneers of early LSD research, testified to Congress that LSD was a "dangerous drug."[49] A pair of heavily promoted government-sponsored films entitled "LSD-25" and "Case Study: LSD" dramatized the dangers of LSD. It would be 50 years before research could resume.

THE GRIFFITHS REVOLUTION

A few small trials on mescaline, psilocybin, and N,N-dimethyltryptamine (DMT) were published in Europe in the 1990s, some of which viewed these drugs as models of psychosis[50–52]. However, these did not have the impact of the landmark studies by Hoffman and Stoll. The first double-blind randomized controlled psychedelic trial of the modern era was conducted in 2006 by Roland Griffiths at Johns Hopkins University.[53] This trial evaluated the psychological effects of psilocybin among 36 healthy volunteers. Psilocybin was not only deemed to be safe—adverse effects, such as anxiety, tended to be transient—but it also significantly engendered spiritual experiences of unity and sacredness. Remarkably, two months after the psilocybin session, 67% of participants ranked it as either the most meaningful experience or among the top five most meaningful experiences of their lives. Follow-up at 14 months confirmed that psilocybin did not induce any long-term adverse effects, and 64% of participants reported that it improved their well-being or life satisfaction.[54]

This study restored the academic validity of psychedelic research. Although stigma persisted, rigorously designed trials were initiated at academic centers throughout the world. These largely focused on four conditions: end-of-life anxiety, depression, post-traumatic stress disorder (PTSD), and substance use disorders. At the University of California, Los Angeles, a pilot study in 2011 found that psilocybin improved anxiety and mood symptoms among patients with advanced stage cancer.[39] In subsequent trials with larger sample sizes, up to 80% of participants experienced remission from depressive symptoms.[38,40] Furthermore, these effects were sustained up to 4.5 years later.[55] LSD also significantly reduced anxiety associated with life-threatening diseases, with 12 months of durable relief after single-dose administration.[37,41]

The largest clinical trials on psychedelics to date have tested psilocybin for major depressive disorder and treatment-resistant depression. Initial studies with sample sizes of fewer than 100 patients attributed a remission rate of more than 50% to psilocybin.[15,17,26] However, subsequent phase II studies that enrolled up to 233 patients found that only 25%–29% of participants experienced remission from depression.[20,25] Many clinical trials on DMT for depression have yet to be published, although topline results from one phase IIa trial in 34 major depressive disorder participants indicate a remission rate of 57%.[56] Ayahuasca, an Amazonian brew that contains both DMT and monoamine oxidase inhibitors, produced a remission rate of 34% in a double-blind, placebo-controlled trial of patients with treatment-resistant depression (TRD), but only 14 participants received ayahuasca in this study.[23] A phase III trial of ketamine in 174 TRD participants indicated that when dosing is incremented based on the participant's response rather than fixed, ketamine is associated with a significantly higher remission rate (19.6%) than midazolam, a psychoactive "placebo" used to preserve blinding (2.0%).[57] Esketamine is the only psychedelic that has been approved by the Food and Drug Administration (FDA) for a psychiatric indication. Racemic ketamine, already FDA-approved for use as an anesthetic agent, is similarly being deployed "off-label" for depression.

Aside from ketamine, 3,4-methylenedioxymethamphetamine (MDMA) is the only other psychedelic for which phase III trials have been completed. The results of the replicated phase III trials, which enrolled 90 and 104 participants, suggest that MDMA is highly effective for treating PTSD.[31,32] After three sessions of MDMA-assisted therapy, 67% and 71% of participants no longer met the diagnostic criteria for PTSD in the two phase III trials. So far, all clinical trials on MDMA have been sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS). Preliminary studies also suggest that ibogaine may be a useful treatment for PTSD. An observational study of 30 veterans showed that magnesium-ibogaine caused remission from PTSD symptoms in 86% of participants after one month; the associated effect size was very large ($d = 2.54$).[58]

Finally, psychedelics have also shown promise for treating substance use disorders. In a small open-label trial with 15 tobacco-dependent individuals, 80% of participants were abstinent six months after receiving psilocybin.[29] Psilocybin also reduced heavy drinking days by 13.9% relative to placebo in an RCT with 93 participants.[30] Preliminary data indicate that ibogaine is highly effective for managing opiate and cocaine addiction. An observational case series of 191 participants found that ibogaine significantly diminished heroin craving by 50.2%,[59] and an RCT of 20 participants demonstrated a 64.9% reduction in cocaine cravings 24 weeks after the treatment.[60]

It is worth noting that most of the contemporary clinical trials have administered psychedelics in conjunction with therapy, such as cognitive behavioral therapy or some form of "psychological support" in which the participant "integrates" or processes their psychedelic experience with a therapist.[20,30–32] Thus, psychedelic treatments are often referred to as "psychedelic-assisted psychotherapy," highlighting the crucial role that professional supervision plays in the therapeutic effects of psychedelics.[61] Although the therapy or psychological support both elevates the clinical outcomes and mitigates the safety risks of psychedelics, they do significantly add to the financial burden of psychedelic therapy due to the cost of training new therapists.[62]

Emerging evidence suggests that psychedelics may have far-reaching effects that extend beyond the realm of mental health. In particular, psychedelics may affect the microbiota–gut–brain axis and play an important role in the modulation of inflammatory and neuroinflammatory processes.[63] Psychedelics may also be beneficial for cardiometabolic health—individuals who have used psychedelics at least once in their lifetime are at lower risk of heart disease and diabetes as compared with age-matched controls.[64] Although psychedelics have previously been used for the management of pain, new data suggest that they are more efficacious than previously believed and may offer benefit to patients with refractory headaches or migraines.[65,66]

While the existing clinical data are favorable, there are only a small number of published RCTs on psychedelics in clinical populations during the contemporary era of psychedelic research: two for LSD,[37,41] zero

for DMT (although there are top-line results from 1 Phase IIa trial[56]), one for ayahuasca,[23] nine for psilocybin,[15,17,20,25,26,30,38–40] one for ibogaine,[60] and six for MDMA.[31–36] (Note that, for some psychedelics such as MDMA, there are more trials that were never published.) Most of these studies enrolled fewer than 60 participants. As mentioned above, psilocybin studies with larger sample sizes of 104 or 233 participants observed remission rates that were only about half as large as those of smaller studies.[20,25] These results point to the need to enroll more participants in clinical trials on psychedelics. That being said, some clinical outcomes—specifically, the percentage of participants who no longer met the diagnostic criteria for PTSD—actually improved as sample size increased in trials of MDMA.[31,32,67]

Moreover, double-blinding clinical trials are challenging given the marked perceptual effects of psychedelics. In one clinical trial of psilocybin, more than 90% of participants correctly guessed the treatment group that they were assigned to, despite the purportedly double-blind study design.[30] Unblinding may create expectancy effects, thereby inflating the reported clinical outcomes of psychedelic therapy.[68] However, some have noted that other types of therapy, such as physiotherapy, have built a strong evidence base despite difficulties with blinding participants.[69]

The mechanisms underlying psychedelic therapies also remain poorly understood, raising concerns about possible unforeseen long-term adverse effects. In addition, many psychedelic therapies require close supervision, limiting their use in the outpatient setting. Nevertheless, psychedelic therapies have continued to show a great deal of promise, ultimately garnering serious attention from major pharmaceutical companies. Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson, invested heavily in research and development of esketamine. In 2019, esketamine became the first psychedelic agent to receive approval by the FDA.[70]

The approval of esketamine by the FDA, as well as the FDA's designation of MDMA and psilocybin as breakthrough therapies in 2017 and 2018,[71] marked a paradigm shift in the perception of psychedelic agents. In 2021, the National Institutes of Health awarded the first federal grant for psychedelic research in over 50 years, funding a study on psilocybin for treating tobacco addiction.[72,73] Prescription use of psilocybin and MDMA may become a reality within the next few years.[71] The stigma and skepticism that once surrounded psychedelic therapy may soon give way to a new era of rigorous, high-quality research and widespread clinical use.

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