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Psychedelic Therapy: A Primer for Primary Care Clinicians—The Strengths, Weaknesses, Opportunities, and Threats of Psychedelic Therapeutics

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The reviews in this special edition have presented a primer on the state of the literature for 7 different psychedelic compounds and their plausible roles in medicine. In a common format underscoring strengths, weakness, opportunities, and threats (SWOT), this article addresses how psychedelic compounds fit into the broader health care landscape for indicated conditions. Historically, psychiatric pathologies have been treated with small-molecule compounds that have limited effect sizes and carry a variety of adverse effect profiles. Psychedelic medicines offer the opportunity to provide more potent and rapidly acting treatments. It is crucial to note that this is an emerging field of medicine, and only one of these compounds (esketamine) is currently Food and Drug Administration-approved for depression. The other compounds discussed are investigational, and this discussion is both imaginative and prospective in nature.

STRENGTHS

When taking into consideration the psychedelic class of medications, the strengths that are most elucidated share several features: potency, unique adverse effect profile, lack of known metabolic side effects, the potential for rapid onset and durability of effects, and opportunities for concurrent psychotherapy.

The overarching strength of the psychedelic compound class is that these therapeutics create potent sustainable change, with effect sizes that are much higher than those of existing small-molecule pharmacological treatments. The average effect size of antidepressants is $d = 0.3$,[1] but the effect size of psilocybin is as high as $d = 2.6$.[2] Psilocybin also outperforms all but one of the 19 existing treatments for alcohol use disorder that are examined in a recent meta-analysis; psilocybin has a rate ratio (incidence of heavy drinking days in participants who received the psilocybin treatment over the incidence in participants who got placebo) of 0.36, whereas the median rate ratio among the existing treatments is 0.82.[3] Across all 6 phase II trials, the effect size of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy was nearly 2 times higher than that of the Food and Drug Administration (FDA)-approved medication paroxetine and 3 times higher than that of

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the other FDA-approved medication sertraline.[4] Although only a third of patients remit from depression after taking antidepressants,[5] top-line results from a recent phase IIa trial showed that 57% of participants experienced remission 12 weeks after receiving a single dose of N,N-dimethyltryptamine (DMT).[6]

Owing to their swift therapeutic effects, dropout rates in clinical trials of psychedelics tend to be much lower than those of existing treatments. Dropout rates are 1.7 times lower for MDMA therapy than for the FDA-approved medication paroxetine and 4.1 times lower than for the other FDA-approved medication, sertraline.[4] Selective serotonin reuptake inhibitors have an average dropout rate of 28%,[7] whereas clinical trials that administered multiple doses of psilocybin reported dropout rates that were as low as 0% and as high as 7%.[2,8]

The therapeutic effects from just 1 to 3 sessions of psychedelic treatment seem to be highly durable. For instance, in 1 clinical trial in which participants received a single dose of psilocybin to treat end-of-life anxiety, 60%–80% of participants sustained a clinically significant antidepressant or anxiolytic response at a 4.5-year follow-up.[9,10] End-of-life anxiety was reduced in a similarly large proportion of participants (78%)—12 months after receiving a single high dose of LSD.[11,12] A longitudinal analysis of 6 phase II trials on MDMA actually found that the number of participants who no longer met the diagnostic criteria for PTSD increased from the end of treatment (56%) to the 1-year follow-up (67%).[13]

In addition, psychedelics seem to be very safe. Although ibogaine can induce heart arrhythmias, particularly in patients with preexisting cardiovascular conditions, the other psychedelics do not seem to carry any physiological risks.[14,15] The risks of fatal overdose and addiction are very low, especially when psychedelics are administered in a clinical context.[16,17] Although MDMA can be addictive, recent phase III trials reported that none of the participants abused or depended on MDMA after their treatment session.[18] Psychologically, psychedelics can cause anxiety, but feelings of mental discomfort typically subside once the acute effects are over, particularly when participants are actively monitored by trained therapists.[19]

WEAKNESSES

When psychedelics are used in recreational contexts without adequate supervision, they can lead to tragic outcomes.[20] There are rare reports of serious adverse effects, including psychosis and even suicide, arising from recreational use.[21] Methods for subduing so-called "bad trips" in recreational settings include potentially dangerous habits, such as taking benzodiazepines, which are known to be "trip killers."[22] That being said, large-scale population surveys have found no significant association between psychedelic use and mental health problems.[23,24] Nevertheless, many more people have ingested psychedelic compounds for recreational purposes than in monitored medical contexts, compared with any other group of novel therapeutics.[25] Therefore, the adverse effect profile of psychedelics remains unclear within a population of patients who are unlikely to imbibe these compounds recreationally.

Most problems associated with psychedelic use can be avoided in clinical settings where participants are screened and actively monitored by trained therapists. Long-term adverse effects have not been reported in contemporary clinical trials on psychedelics,[19] although transient adverse effects can be quite serious; for instance, in the largest clinical trial of psilocybin to date with 233 participants, there were 7 instances of suicidal ideation or self-injury from Day 2 to Week 3 after treatment.[26]

Furthermore, it is possible that, as psychedelics are deployed on a larger scale, there may be more reports of mental health problems, especially if adequate measures are not in place to monitor participants. Indeed, the number of double-blind, placebo-controlled RCTs on psychedelics is still relatively small (see *Part I* of this special edition for a list of all such RCTs), in large part because psychedelics have been Schedule I substances for decades. When sample sizes are small, rare adverse effects will be under-reported and under-addressed.[27] Psychedelic therapies require significant postmarketing surveillance to understand the complete adverse effect profile and variability between specific population cohorts.

Psychedelics can engender experiences of profound personal or spiritual significance,[28] yet these experiences are plausibly biasing to scientists. Scientists who have had experiences with psychedelic medicines will understand what they are capable of but may be inclined to believe that they are more powerful or have special properties compared with existing treatments.[29]

OPPORTUNITIES

Psychedelics not only are potent in treatment-resistant populations but also act very rapidly compared with existing treatments. For instance, the median length of antidepressant treatment is 2 years.[30] By contrast, psychedelics can lead to sustained remission from depressive symptoms after just 1 or 2 doses.[2,8,26,31–34]

If they become approved by the FDA, the limited dosing regimens of psychedelics would significantly decrease health care spending for underserved

populations. This reduction in cost to the medical system is a remarkable opportunity, especially in patient populations who have traditionally been the last to gain access to novel treatments because of socioeconomic constraints.[35,36] Psychedelics are therefore positioned to make quality treatment much more accessible for psychiatric patients, especially in Medicaid populations. The time an individual is enrolled on a Medicaid health plan can be scant, with the average duration approximating 10 months.[37] This leads to "churn" or frequent turnover between different health care plans, which can interrupt ongoing treatments.[38] If they were to receive psychedelic therapy, Medicaid populations would not have to face these disruptions to their treatment plans.

Rapid resolution of depression and other psychiatric conditions will also reduce the considerable loss of productivity that mental illness diagnoses, such as depression and PTSD, exert on the workplace. Psychedelic medications may have wider and more generalizable efficacy than existing antidepressant treatments; for instance, genetic polymorphisms are known to mediate the efficacy of selective serotonin reuptake inhibitors.[39]

THREATS

Although psychedelics require much fewer administrations than existing antidepressant medications, a trained therapist must be present throughout the acute effects of psychedelics, which can last up to 6 hours with psilocybin and up to 12 hours with LSD.[40, p. 200,41] In most clinical trials on psychedelics, a therapist has also provided psychological support to participants in the days after the treatment to help them integrate their experience.[42] Therefore, although psychedelic therapy will overall be less expensive, the cost per session will likely be higher than the cost per dose of antidepressant treatments, which typically do not involve therapists.

Well-trained therapists are of paramount importance in psychedelic treatments. Unlike existing medications, psychedelics are known to have heavy psychoactive effects that are capable of radically altering a person's worldview.[43] These changes can be highly beneficial, but they can also be very disorienting. A therapist must be able to help with "picking up the pieces" if a person's worldview is shattered after psychedelic treatment (Edward Jacobs, personal communication). In addition, a therapist must be trained to comfort participants in the event that they have a "bad trip" during the acute effects of psychedelics, which has, in rare cases, led to hospitalization in recreational contexts.[44]

The intense psychoactive effects of psychedelics also create opportunities for malicious therapists to take advantage of participants. There have been accusations of sexual assault by therapists during clinical trials of MDMA sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS).[45] In one case, the therapists used the patient's desire to heal from their sexual trauma as a pretense to inappropriately touch them during the MDMA session.[41] However, MAPS responded to this allegation by cutting ties with the therapists,[41] and allegations of sexual harassment during clinical trials of psychedelics have been very rare.

Legal and regulatory barriers may also impede the adoption and widespread use of psychedelic medicines. Currently, all psychedelics reviewed here except ketamine are Schedule I substances, so they cannot be legally prescribed for any purpose.[46] FDA approval would necessitate rescheduling of psychedelics to Schedule II or lower. However, efforts to deschedule other drugs, such as cannabis, have historically failed,[47] although a recent Congressional bill to federally legalize marijuana has passed through the House of Representatives.[48] The Drug Enforcement Administration (DEA) imposes limits on annual production of Schedule I substances,[49] which may restrict the accessibility of psychedelic treatments. Even if psychedelics are rescheduled, it may be challenging for insurance providers to authorize psychedelic therapy.

Because many psychedelics, such as psilocybin and DMT, are natural compounds, psychedelic companies have been racing to patent various aspects of their manufacturing process and therapeutic framework to guarantee a return on investment from large investors.[50] However, these patents may further drive up the cost of psychedelic therapy.

CONCLUSION

There has been a recent resurgence of research on psychedelics as medicines for mental illnesses, with highly encouraging results. Could this class of drugs create a paradigm shift in the way mindfulness therapy and mental health are approached? In this comprehensive primer, we investigated 7 compounds—LSD, DMT and ayahuasca, psilocybin, ibogaine, MDMA, and ketamine—as treatments for anxiety, depression, PTSD, and addiction. Readers are challenged to question their preconceived notions and judgments regarding this group of restricted drugs. There is mounting evidence to support the meaningful and durable benefits of psychedelics on mental health. Hence, in a recent survey of medical students, most participants agreed that psychedelics either have therapeutic potential or merit further

research.[51] Primary care physicians ought to be keen to understand the therapeutic effects of psychedelics despite their long-standing stigma.

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