VIEWPOINT

Psychedelics as Therapeutics—Potential and Challenges

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With depression being one of the leading causes of disability, and crises of suicide and drug overdoses claiming unprecedented numbers of lives each year, there is an enormous unmet need for new approaches to treating mental illnesses including substance use disorders. Although existing pharmacologic treatments such as antidepressants and medications for opioid use disorder are valuable for many people with these conditions, a large proportion are not helped by those treatments. In this context, psychedelic drugs represent a promising psychotherapeutic frontier.

Classic psychedelics like psilocybin, lysergic acid diethylamide (LSD), and dimethyltryptamine (DMT) (ayahuasca's psychoactive ingredient) interact with the serotonin signaling system principally as agonists to the serotonin 5-HT_{2A} receptor. Recent preclinical research suggests they rapidly enhance cortical neuroplasticity and dendritic growth by directly activating intracellular 5-HT_{2A} receptors.[1] (Serotonin, which is unable to cross the cell membrane, cannot access these receptors.) The neuroplastic amplifying effects of psychedelics (sometimes called *psychoplastogens*) have been associated with their potential for therapeutic benefits, which are sometimes reported to persist for at least 3 weeks after 1 or 2 administrations.[2] Additional mechanisms thought to be connected to their potential therapeutic effects include reconfiguration of brain functional networks and psychological mechanisms driven by the altered mental state that triggers changes in emotions, cognition, and beliefs.[3]

Overall, the therapeutic evidence for classic psychedelics remains limited and is strongest for the use of psilocybin as a fast-acting antidepressant in patients with severe depression.[4] Some evidence from small trials has also shown beneficial effects of psylocibin for the treatment of alcohol and nicotine use disorders. When used in the treatment of substance use disorders, it is noteworthy that classic psychedelics work on neurotransmitter systems unrelated to the drug in question and not through dopaminergic effects, and that psychedelics are not themselves addictive.

Despite the promising early results, it is clear that psychedelics are not wonder drugs, but the hype has gotten ahead of the science. This is reminiscent of what happened with medical cannabis: regulations pertaining to its medical use were approved, promoting a booming cannabis industry, despite lack of scientific evidence for its therapeutic efficacy.

Unfortunately, adverse events like suicidal behavior, while rare, have been reported in psilocybin trials.[5] Much remains unknown about how psychedelic compounds work, how to administer them most effectively and safely, and how to identify which patients are the best candidates and which are at risk of adverse outcomes. As of this writing, the science policy office of the National Institute on Drug Abuse tallies the current active projects on therapeutic use of psychedelics funded by the National Institutes of Health at more than 70.

Research Questions

An important research question is whether the subjective experiences associated with psychedelic drugs are intrinsic to or separable from their therapeutic effects. There is evidence to suggest that psilocybin's therapeutic efficacy is tied to the mystical-type experiences it commonly precipitates.[6] This connection remains controversial, however,[7] and researchers are exploring whether desired (eg, depression-ameliorating) neuroplastic effects can be decoupled from the cognitive and sensory distortions that raise questions about the safety of psychedelic drugs.[8]

A unique feature of psychedelics is the significant role played by contextual factors. The individual's mindset going into the experience along with characteristics of the setting ("set and setting") influence whether the individual has a positive or a negative experience.[9] In all studies, these substances are administered by 1 or 2 clinicians in a supportive setting, but no standard protocol yet exists to prepare the patient for the experience, support them during it, and help them process it afterward. Some have suggested that the clinician's time and attention accounts for a nontrivial component of psychedelics' therapeutic effects, but there have been no rigorous tests of that hypothesis, to our knowledge. Research must clarify wherein the therapeutic efficacy lies and establish what other contextual components are needed.

Conducting clinical trials on psychedelics faces unique challenges, including administrative hurdles resulting from their Schedule I status. The lack of placebos indistinguishable from the drug is another challenge; participants can usually tell if they have been given a psychedelic vs a placebo. Some propose extremely low doses of the active psychedelic as a placebo. Greater standardization and harmonized protocols for clinical trials are needed so that results can be compared, along with longer follow-up studies to understand long-term outcomes. To gain US Food and Drug Administration (FDA) approval, a risk evaluation and mitigation strategy will be needed to promote maximal benefits with the fewest risks. Finally, to facilitate access to future psychedelic-assisted therapies that are FDA approved and reimbursed, it will be helpful for regulators and payers to articulate the evidence required for drug approval and reimbursement determinations so that researchers can design responsive trials.

Current psychedelics research carries the baggage of past ethical transgressions, including egregious experimentation with LSD on unwitting study "participants" including individuals with disabilities and those who were incarcerated in the 1950s. It places a unique burden on

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researchers to be transparent in their aims and methods and to establish a firm grounding of trust with study participants. Because of that dark history, people from racial and ethnic minoritized groups may be particularly hesitant to participate in research. Yet inclusion of diverse study populations is necessary to ensure that findings are applicable across individuals with varying demographic characteristics. Also, since patients are particularly vulnerable during a psychedelic experience due to altered perceptions, an increased posture of openness, and potential for the clinician to be imbued by the patient with medical and spiritual authority, the clinical staff's role needs to be structured in ways that prevent possible abuses.[10]

It is crucial that psychedelic-assisted treatments, if they become available, are available to everyone. That means they should be affordable. And given how time intensive the therapy may be, there should be accommodations for people with work, family, or transportation challenges. Answering the open questions and developing necessary structures will be a prerequisite to the eventual FDA approval, scaling-up, and reimbursement of these treatments, so research must be designed with that end in mind. Based on the experience with cannabis, it is also likely that psychedelics will be used for therapeutic purposes even without FDA approvals and that if states legalize their use for medical purposes, there will also be an increased use for wellness or recreational purposes. Research that informs about benefits and risks from such patterns of use will be necessary to guide public health policies.

Challenges notwithstanding, the promise of psychedelics research goes beyond the promise of new pharmacotherapies. Declining life expectancy among US residents in recent years has been tied to despair—overdoses, suicides, and diseases attributable to alcohol misuse all reflect large swaths of society feeling increased pain and loss of connection. We know a great deal about what goes awry in the brains of people with mental illnesses including substance use disorders, but we know less about what goes right in the brains of people whose lives are full of meaning and connection and who may be more resilient to the development of psychiatric conditions. Better understanding of the mechanisms by which psychedelics may increase resilience could be highly valuable. Besides telling us about the neurobiology of resilience, such research might facilitate development of alternative treatment modalities (eg, neuromodulation) that could produce similar benefits for patients.

ARTICLE INFORMATION

Published Online: July 26, 2023. doi:10.1001/jamapsychiatry.2023.1968

Conflict of Interest Disclosures: None reported.

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