

VIEWPOINT

Psychedelics in Psychiatry— Keeping the Renaissance From Going Off the Rails

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There is a resurgence, some say renaissance, of clinical research on psychedelic substances after decades of dormancy. Recent studies have produced findings suggesting psychedelics may demonstrate substantial efficacy for serious psychiatric conditions such as mood and substance use disorders. As a result, ongoing clinical trials with the psychedelic psilocybin have been given the Breakthrough Therapy designation by the US Food and Drug Administration that could result in medical approval for major depressive disorder and/or treatment-resistant depression.

This new period of psychedelic research, ongoing since at least 2006, has now lasted for about the same length of time as psychedelic research in the 1950s and 1960s did before it ground to a halt. As contemporary psychedelic research results accrue, the field may be facing a fork in the road to clinical applications. One path forward allows for the same kinds of exuberance, utopian thinking, and uneven clinical approaches that contributed to ending the previous period of research. Combined with the contemporary tendency to politicize science, the possibility of a repeat of the 1960s represents a significant concern. Another path forward, a more careful and systematic one, involves the appropriate integration of psychedelic treatments into existing evidence-based psychiatric paradigms such as psychotherapy and pharmacotherapy.

This Viewpoint offers perspectives on how the psychedelic research renaissance can stay on the path that leads to the integration of these medications into the standard of care rather than recapitulating the ethical and sociopolitical problems that led to the previous period of research going off the rails.

History of Psychedelic Research

Psilocybin is a psychedelic compound in certain mushrooms, which have been used in sacred ceremonies among indigenous peoples in Mexico and elsewhere for centuries. Other psychedelic compounds, such as mescaline and DMT (*N,N*-dimethyltryptamine), have likewise been used for hundreds or thousands of years in ritual contexts. The psychedelic LSD (lysergic acid diethylamide), which the Swiss chemist Albert Hofmann synthesized in 1938, led to innovations in understanding serotonin pharmacology and, eventually (albeit indirectly), to the development of therapeutics that modulate serotonin function such as selective serotonin reuptake inhibitors.

During a period in the 1950s and 1960s, research established that psychedelic substances produce substantially altered states of consciousness. This era of research showed psychedelics as having considerable promise in the treatment of depression in patients with

cancer and alcohol use disorder. However, in the late 1960s, clinical research on psychedelics was functionally prohibited because of burdensome governmental regulations, the perceived association of the substances with an antiestablishment counterculture, misperception of risk resulting from negatively biased media coverage, and lapses in research ethics.

Recent Research

After several decades of inactivity in the US, psychedelic research in healthy psychedelic-naïve participants was restarted at Johns Hopkins in 2000. Studies have focused on the serotonergic psychedelics (especially psilocybin), so called because these compounds function as partial 5-HT_{2A} serotonin receptor agonists.¹ Many studies have confirmed the low toxicity and minimal addiction potential of serotonergic and other psychedelics.¹

The study most often cited as restarting the current period of psychedelic research was a double-blind randomized clinical trial that examined psilocybin administered in a supportive setting. The intervention resulted in long-term increases in positive mood, life satisfaction, and prosocial behavior in healthy participants.² Two double-blind randomized clinical trials on patients with life-threatening cancer diagnoses showed sustained decreases in anxiety and depression.^{3,4} Additional research in clinical populations has suggested efficacy for treatment of mood disorders and substance use disorders.⁵⁻⁷ These and other recent and ongoing studies suggest the potential for psychedelics to be used as new and effective treatments for a range of psychiatric conditions.

Dead Ends

Despite this promise, cultural forces such as those that occurred in the 1960s may threaten contemporary research progress and the clinical application of psychedelics. For example, numerous recent popular press books, websites, podcasts, and media reports have uncritically promoted presumed benefits of psychedelics. Patient demand is growing, as is interest in the general population, with the possibility that expectations are outpacing the current data on what outcomes can be confidently foreseen. Psychedelics are neither a cure for mental disorders nor a quick fix for an unfulfilled life and should not be portrayed as a panacea. Ominously, pro-psychedelic subcultures are increasingly fostering utopian visions for society based on research findings that, while intriguing, still must be considered preliminary.

If psychedelic research is going to avoid another period of prohibition, we must learn from the lessons of the past. It is critically important that the medical and

scientific communities be vigilant in opposing the conflation of science with larger cultural agendas, as occurred in the 1960s with the blending of psychedelics into the antiwar and other antiestablishment movements. The enthusiasms that attend such agendas should not be allowed to supersede the scientific and regulatory processes meant to carefully vet these substances and their application in a variety of mood and behavioral disorders.

A Way Forward

More randomized clinical trials are necessary to replicate and extend the promising findings of open-label trials and to better understand contraindications and other potential risks. Furthermore, additional studies will be required to better understand the mechanisms by which psychedelics exert their therapeutic effects, ideal dosing schedules, selection of the most effective compounds, and optimal clinical management. The lure of the approval of the clinical use of psychedelics raises the possibility that a vast array of eclectic and untested psychotherapeutic techniques may be applied in conjunction with medication administration. Considering that psychedelic experiences are known to be strongly influenced by expectations and the context (ie, set and setting) and that such experiences sometimes result in major shifts in worldview, adding psychedelics to fringe or unproven psychotherapeutic paradigms

may increase the risk of iatrogenic harm. The safest and most effective psychedelic treatment protocols will likely be those that integrate existing evidence-based interventions and psychotherapies.

Conclusions

Psychiatric treatments have seen only modest innovation for decades. Research on psychedelics is pointing to the potential for new treatment options for a variety of psychiatric conditions. However, as testing and clinical applications expand, it is still possible for researchers and clinicians to squander this opportunity. The word *renaissance* comes from the French word for rebirth; however, this may be somewhat of a misnomer as it has been more than 2 decades since clinical psychedelic research resumed in the US. We believe this new era of psychedelic research is no longer being reborn but rather coming into maturity. Whether this era of psychedelic research will conclude with another scientific and clinical dead-end period of prohibition or move ahead into a productive time of mainstream research and clinical application remains to be seen. We owe it to the next generation of researchers and clinicians, and to the millions of patients with mood and substance use disorders who may benefit from these treatments, to ensure that no exceptions be made in the standards of research or clinical application for psychedelics, regardless of their seemingly exceptional potential.

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