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The Role of Psychedelics in Treating Mental Health Disorders: A Mini-Review

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Abstract:
Psychedelic substances are gaining attention as potential alternative or adjunct therapies for mental health disorders such as major depressive disorder and post-traumatic stress disorder. Traditional approaches do not work all the time, and they can cause serious side effects; thus, we need to look for other treatment options. In this paper, we analyze the past and present use of psilocybin, MDMA, ketamine, and other psychedelics in medicine, science, and research. It gives historical background for psychedelic studies early on to the research in the mid-20th century and speaks about the present-day research into their neurobiological effects and how they echo past findings. Also, the essay talks about the ethical and legal problems with the use of psychedelics. Moreover, it says why the past is important in the modern development of science. The conversation also considers how early exploration of psychedelics mirrors present-day surveying on their psychotomimetic and consciousness-altering properties. This work aims to address both scientific and ethical concerns to depict the therapeutic potential of psychedelics and the implications of their prohibition. In conclusion, this essay proposes directions for future research on the legal and ethical issues involving such therapies.

INTRODUCTION

Mental health has a profound effect on a person's life, and mental illnesses are challenging to treat effectively (Breeksema *et al.*, 2020). Recent studies have suggested that an alternative treatment using psychedelics could have a positive outcome (Nutt and Carhart-Harris, 2021). Since the late 1980s, dedicated researchers have conducted studies focusing on the effects of psychedelics (Ailani *et al.*, 2021). Lately, due to an increasing global crisis, the curiosity for alternative treatment options is high (Yaden and Griffiths, 2020). For decades, there have only been two treatments for mental health disorders: psychotherapy and antidepressants (Zhu *et al.*, 2022). In treatments using antidepressants, 20% of the patients report no improvement after trying many different kinds of remedies over an extended period (Schlag *et al.*, 2022). Considering this, new and alternative methods are necessary and quite promising (Vollenweider and Preller, 2020).

Psychedelics have been the subject of many writers and films in the past, and societal perceptions of psychedelics have been widely associated with delusional artists, distorted celebrities, and hippies on their personal, spiritual journeys (Kalfas *et al.*, 2023). This psychosocial bias has influenced the research on psychedelics (Kolasa and Faron-Górecka, 2023). Furthermore, psychedelics have also been subject to laws and regulations that have overshadowed their history (Muscat *et al.*, 2021). Nowadays, modern breakthroughs have justified the research and use of these psychoactive substances (Maggio *et al.*, 2023). Special studies of psilocybin, a property of psychedelics found in 'magic mushrooms,' have shown encouraging results regarding the effectiveness of treatment-resistant depression. Furthermore, it could also ameliorate anxiety and depression (Dewhirst, 2023). In the upcoming section, this piece of writing will focus on the historical context of psychedelics, followed by the therapeutic effects on individuals mentally disturbed by psychedelics (Falchi-Carvalho *et al.*, 2024). Subsequently, the explicit neurobiological processes of psychedelics' effects and the ethical norms regarding this area will be discussed (Dewhirst, 2023). Finally, the reflection piece will concern the latest insights from early researchers in the last few years, which will be discussed and reflected upon (Falchi-Carvalho *et al.*, 2024).

Historical Context of Psychedelics in Medicine

Psychedelics, or hallucinogens, have been a part of medical and religious practices for centuries (Breeksema *et al.*, 2020). These substances are known to induce a state of altered consciousness, which can lead to an "ecstasy" or "mystical" experience in sensitive individuals (Wheeler and Dyer, 2020). Indigenous groups in South America, North America, and Africa have used drugs of this type as sacramental tools for thousands of years (Chi and Gold, 2020). In the 1950s, when the chemical structures of many naturally occurring neurotransmitters and modulators had been unraveled in the brain, laboratory synthesis led to the creation of a large number of new drugs, and many of these had properties similar to natural products such as serotonin, phencyclidine, and mescaline (Ko *et al.*, 2022). Self-experimentation was common among investigators, and the study of psychedelics as potential psychiatric treatments was undertaken following reports of altered consciousness and "mind expansion" (Ko *et al.*, 2023).

Psychedelics inspired some psychiatrists to develop alternative models for the study of psychopathology, which bore little resemblance to the experimental paradigms that developed around the use of animal models and psychometrics (Vargas *et al.*, 2021). They have been used in the treatment of many psychiatric syndromes, including neurotic and depressive disorders, as well as in forecasting outcomes of psychiatric syndromes (Reiff *et al.*, 2020). During

the 1970s, when their use as an adjunct to psychotherapy became controversial, the United States Drug Enforcement Administration and the World Health Organization ruled that psychedelics were not drugs of abuse and that they were considered acceptable for medical use (Nichols and Walter, 2021). Psychedelics fell out of favor with researchers for more than three decades because of strict employment restrictions, political issues, and funding cutbacks that limited access to research-grade substances. In the late 1990s, a revival in clinical interest in psychedelics occurred. Limitations on research began to ease, and regulations that had greatly limited laboratory research and clinical trials were relaxed (Krediet *et al.*, 2020). Drug companies competed to develop psychedelics that complied with FDA requirements, setting up the first phase 1 and phase 2 trials of these drugs in 30 years (Galvão-Coelho *et al.*, 2021). The involvement of major academic medical centers, public and private granting agencies in the development of psychedelics as treatments for addiction, depression, and PTSD has been key to these drugs being evaluated in large numbers of patients with psychiatric disorders. Research in the natural history of psychedelics has also attracted social scientists, historians, and neuroscientists to document and investigate the benefits of occasional hallucinogen use, the risks of prolonged use, and potential clinical applications in basic science research and human volunteers (Mertens and Preller, 2021).

Neurobiological Mechanisms of Psychedelics in Mental Health Treatment

A key area of interest in understanding the role of psychedelics in mental health treatments, indeed therapy in general, is the neurobiological one. This line of study is less focused on understanding an eventual underlying pathology, rather pointing to the biological changes psychedelics induce in the brain (Császár-Nagy *et al.*, 2022). At a molecular level, we know that, among other things, psychedelics interact with the serotonin receptor system, which is central to the endogenous and exogenous regulation of mood disorders. At the same time, the phenomenon of psychedelics' subjective effects, such as adjacent sensory perceptions or moments of intense cognitive clarity, provides a way into discussion (Lowe *et al.*, 2022). There are physiological repercussions to the influence of setting on state, particularly setting—here defined as the patient's immediate physical and social "environment," which includes the therapist or therapists and a well-designed room away from everyday stressors, away from other distracting noises, and in fact with an eye towards some moments of beauty, like the characteristics of plants and artwork to be gradually looked at (Borroto-Escuela *et al.*, 2021).

At least from 2006 on, a consistent number of MRI and PET scans have been conducted during psilocybin, LSD, ketamine, or DMT administration in a pure laboratory or clinical setting during the time of its therapeutic application (Cumming *et al.*, 2021). The data is limited to less than 100 participants, depending on the study. Surprisingly, if not 'anomalously', the data paint a fairly uniform picture, at least with regard to possible reduction at a structural level of the symptoms of these conditions (Castelhano *et al.*, 2021). Hallucinations here looked at in the lump, can be understood as a hermetically lived isolation within, not from, the self. Here, psychedelics may break open the rigid narrative of self/other, inner/outer, and open a possible threshold to the outside again (Linguiti *et al.*, 2023). This is typical of the dimensions of a retreat, here indeed at this stage meant in a religious as well as in a poetic sense (Madsen *et al.*, 2020). The taken break, the crack open (Nadig *et al.*, 2022). Without possible perception at the moment, withdrawal would not be an option (Agarwal *et al.*, 2023).

Current Research and Clinical Trials on Psychedelics for Mental Health Disorders

In recent years, there has been a surge in interest in the use of psychedelics to treat various mental health disorders (Maggio *et al.*, 2023). A range of studies have demonstrated the potential of psychedelic substances such as psilocybin to reduce symptoms of disorders such

as resistant depression, PTSD, anxiety, addiction, and schizophrenia (Davis *et al.*, 2021). There is robust evidence from two large open-label studies showing that psilocybin when used in conjunction with therapy, can provide a sustained antidepressant effect for patients with resistant depression (Rosenblat *et al.*, 2023). Over time, many more studies have contributed to the development of a growing evidence base that outlines the potential role of psychedelic substances in mental health treatments (Rosenblat *et al.*, 2024). The data that has now come together has been sufficient to support a change in legislation in Australia to allow the rescheduling of psilocybin for use in certain mental health clinical indications (Goodwin *et al.*, 2023).

The case for using psychedelics to treat mental health disorders: findings from clinical trials and research institutions. Only in the last few years has the significant potential of psychedelic substances come back onto the radar of mental health research (Aday *et al.*, 2022). With changes in regulations around the direct supply and usage of psychedelics, many countries are now providing the environment for the use of these substances to be rigorously tested in clinical trials (Colloca and Fava, 2024). All research work in this area is ultimately designed to support the availability of these substances to treat patients (Kurtz *et al.*, 2022). The field of psychedelic-based therapeutics is increasingly being supported by a number of research institutions across the world (van Elk and Fried, 2023). In Australia, this area of research is still emerging, with the first clinical trials conducted in NSW, complemented by further preclinical research at the University of Sydney (Humphreys *et al.*, 2024).

Ethical and Legal Considerations in the Use of Psychedelics for Mental Health Treatment

The use of psychedelics in treating mental health disorders is associated with ethical and legal considerations across a range of issues: 1. Stigmatization of psychiatric disorders (Pilecki *et al.*, 2021). There is a historical and widespread stigma attached to mental health disorders in general and several psychiatric disorders, along with rehabilitation, have been stigmatized (Dos Santos *et al.*, 2021). This can have a negative impact on therapeutic progress; patients may decline participation due to clinical suspicion, and the public and regulatory authorities may assume more mundane motives for treatment (Nutt and Carhart-Harris, 2021). Regulatory challenges. In some jurisdictions, the pharmaceutical regulations governing the use of certain substances require additional precautions to be taken before treatment of the most acutely ill patients can be permitted (Smith and Appelbaum, 2021). This can slow down the approval process because regulators require a license application to reflect a robust understanding of substances' safety profile, risks, and potential for abuse (Ailani *et al.*, 2021). In every healthcare context, the principal concern is patient welfare (Celidwen *et al.*, 2023). Psychedelic research is motivated by the possibility of developing treatments where existing ones struggle to provide relief (Siegel *et al.*, 2023). In a broader translational paradigm, an improved understanding of the pharmacodynamic dimensions of psychedelics is also a valid research goal, but the focus remains on the patient population in the psychiatric setting. While a comprehensive toolkit sometimes lags behind modern operative environments, which present unconsidered challenges, acceptable solutions in the treatment setting should be developed through consultation with all involved stakeholders, including clinicians, patients, healthcare service managers, academics, legal professionals, and regulatory authorities (Celidwen *et al.*, 2023). Ongoing dialogue between these similarly diverse sectors of society will be critical in creating an effective and ethically responsible healthcare environment (Breeksema *et al.*, 2020). In summary, the ethical and legal considerations of the pharmacological treatment of psychiatric patients with psychedelics are considerable and interrelated. The need for protection of treatment recipients is paramount in all areas, and across various domains, extra precautions will be required because of the unique psycholegal status created by the abuse potential and societal history of psychedelics. However, if a balanced and reflective approach

can combine existing knowledge, patient yearning, and healthcare resource constraints, then such difficulties could be reduced and even transformed into opportunities to develop knowledge, treatment, and well-being for meaningful patient cohorts (McNamee *et al.*, 2023).

Conclusions and Future Directions

In conclusion, psychedelics represent one of the most promising novel approaches to addressing the global, chronic burden of mental health disorders (Scangos *et al.*, 2023). Ongoing research and clinical trials indicate that psychedelics may be applied safely, often just once, to achieve rapid and substantial relief from some of the most refractory clinical disorders known to science (Nichols and Walter, 2021). These substances have a lengthy and occasionally illustrious medical history (Scangos *et al.*, 2023). However, the prospects of psychedelic-assisted therapy as a regimen that can be offered to individuals seeking relief from otherwise difficult-to-treat mental health disorders have already outgrown subcultural enthusiasm and post-shamanic rhetoric about consciousness. The further development of this therapeutic modality is a historical inevitability (Császár-Nagy *et al.*, 2022). There are still many important questions to be answered definitively about the acute and long-term effects of psychedelics, as limited research has taken place since prohibition and design restrictions until very recently (De Gregorio *et al.*, 2021).

In its immediate future, the field of psychedelic-assisted therapy will and should interdigitate with the new clinical landscape of psychiatry that is grounded in a priori knowledge about brain-mind function and pathophysiology as partially elaborated by neuroimaging, molecular neuroscience, and genetics (De Gregorio *et al.*, 2021). Eventually, controlled trials will be informed by an increasingly intricate understanding of the neurobiological and phenomenal effects of psychedelics in humans, offering maximally efficacious treatments anchored in the principles of biologically guided integrative psychiatry (Kwan *et al.*, 2022). Equally, investigators not working directly in therapeutic studies can advance preclinical models that carefully analyze the molecular, cellular, and circuit mechanisms by which classic psychedelics exert their purported alterations of brain-mind function (Arnout and Alkhatib, 2019; Kelly *et al.*, 2021). Such data will in turn be used to further inform translational research and enrich our clinical grip on psychiatric and neurological diseases that remain extraordinarily challenging to understand and manage (Krediet *et al.*, 2020). It is precisely such multilevel data convergence that will signal a full maturation of the approach advocated, in time informing reasoned discussions of the truly future-forward possibilities for psychedelic science and technology while grounding early clinical initiatives in well-grounded data derived from modern scientific discovery (Arnout *et al.*, 2019a; Arnout *et al.*, 2019b; Hosanagar *et al.*, 2021).

CONFLICT OF INTEREST

Author hereby declares that he has no conflict of interest.

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