Psychedelic medicine at a crossroads: Advancing an integrative approach to research and practice

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Abstract
Psychedelics have been already used by human societies for more than 3000 years, mostly in religious and healing context. The renewed interest in the potential application of psychedelic compounds as novel therapeutics has led to promising preliminary evidence of clinical benefit in some psychiatric disorders. Despite these promising results, the potential for large-scale clinical application of these profoundly consciousness-altering substances, in isolation from the sociocultural contexts in which they were traditionally used, raises important concerns. These concerns stem from the recognition that the mechanisms of therapeutic action of psychedelics are not entirely dependent on neurobiology, but also on the psychological, social and spiritual processes for their efficacy. For these reasons, physicians or psychotherapists involved in psychedelic-assisted psychotherapy need training in ways to accompany patients through this experience to promote positive outcomes and address potential side effects. Psychedelic therapies may foster the emergence of a novel paradigm in psychiatry that integrates psychopharmacological, psychotherapeutic, and cultural interventions for patients with mental health issues.

Keywords
Psychedelics, LSD, psilocybin, ketamine, psychotherapy, consciousness, culture, context

Mind-altering substances have been used in ceremonial and religious contexts for millennia (George et al., 2021; Guerra-Doce, 2015; Miller et al., 2019). However, it was only in the 20th century that psychedelic compounds (such as the serotoninergic N, N-Dimethyltryptamine, lysergic acid diethylamide-LSD and psilocybin), glutamatergic dissociative anesthetics (such as ketamine) and empathogenic compounds (such as 3,4-Methylenedioxy methamphetamine-MDMA) were isolated from mushrooms and herbs or chemically synthesized (Nichols & Walter, 2021). Following an initial wave of scientific interest in the 1950s and 60s, psychedelic substances were scheduled as illegal by the U.S. Drug Enforcement Agency, and the field of psychedelic research underwent an almost total hiatus of nearly 50 years (Carhart-Harris & Goodwin, 2017; Hall, 2022). The last 15 years have seen a resurgence of interest and biomedical research assessing their therapeutic potential (Sessa, 2012; Tupper et al., 2015). Although this reassessment is still at an early stage, there are already new treatments emerging with claims of unique efficacy. Esketamine, a ketamine-derived enantiomer, was recently approved by the FDA as a first-in-class antidepressant for treatment-resistant depression (Kim et al., 2019), and there is increasing evidence that MDMA-assisted psychotherapy can be a safe and

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Two recent randomized trials with psilocybin reported large effect sizes in reducing symptoms of major depressive disorder (Davis et al., 2021), though one of these studies did not find superiority over conventional SSRI treatment on the primary outcome (Carhart-Harris et al., 2021).

Despite efforts to uncover neurobiological mechanisms, our understanding of the therapeutic action of psychedelics remains limited. Psychedelics have effects on neuroplasticity, neuroimmunomodulation, neurotransmission (especially a synergistic action between serotonergic and glutamatergic systems), and epigenetics— all of which could contribute to therapeutic efficacy (Inserna et al., 2022; Inserna, De Gregorio, & Gobbi, 2021; Vollenweider & Prller, 2020). Psychedelics differ from other psychotropic drugs in their capacity to profoundly alter the phenomenology of consciousness through effects on neural circuitry including thalamo-cortico-thalamic pathways, which are critical for integrating external and internal stimuli (Doss, Madden, et al., 2022; Inserna, De Gregorio, Rezai, et al., 2021; Müller et al., 2017). However other pathways may also be implicated in the alteration of consciousness induced by psychedelics such as the hippocampal-cortex loop and the cortico-claustro-cortical circuit (Doss, Madden, et al., 2022). Psychedelics have also been shown to generally increase the functional integration of large-scale brain systems, encouraging synchronization of disparate brain regions and networks that are typically less connected to each other (Carhart-Harris & Friston, 2019). Increases in global functional connectivity have been correlated with altered phenomenology under psychedelics, including reports of “ego-dissolution” (Tagliazucchi et al., 2016). With respect to therapeutic mechanisms, a recent analysis of two fMRI studies investigating psilocybin-assisted psychotherapy found that pre–post increases in global brain network integration reliably correlated with improvements in depressive symptoms, even if the interpretation of the results has been challenged (Daws et al., 2022; but see preprint from Doss, Barrett, & Corlett, 2022).

Psychedelics have potent effects on perception, cognition, self-awareness, and consciousness. These could be incidental to the therapeutic effects at the level of brain circuitry, but there is evidence that the actions of psychedelics also depend on compelling experiences and changes in outlook and sense of meaning that may be socially mediated (Carhart-Harris, Erritzoe, et al., 2018; Kettner et al., 2021; Lifshitz et al., 2018; Majić et al., 2015). A prominent model of psychedelic brain action proposes a mechanism by which the effects on neurobiology may operate synergistically with contextual factors to facilitate deep changes in experience and behaviour. This “anarchic brain model,” proposed by Carhart-Harris and Friston (2019), suggests that psychedelics may generally loosen habitual patterns of predictive processing that the brain uses to build up models of the self and the world in which it is embedded. By rendering the brain less rigid and more malleable in its predictions about the world, psychedelics may make people particularly sensitive to contextual factors such as social cues, expectations, and other kinds of symbolic meanings, suggestions and affordances in the environment (Carhart-Harris, Roseman, et al., 2018). For example, based on his ethnographic study of the use of Ayahuasca in a Westernized treatment centre and among Indigenous healers in the Peruvian Amazon, Dupuis (2022) argues that the cultural worldview and social milieu in which the experiences took place shaped the specific visual and auditory content of the psychedelic experiences, so that people came to see and hear the spirits that they expected to encounter. These sensory experiences of the presence of spirits were deeply meaningful to participants and helped them to concretize and embody their cultural worldview and ontology (i.e., a world in which spirits can help guide human action) in ways that they often described as transformative.

In Western contexts, psychedelics drugs are often said to produce “mystical” experiences—sometimes described as episodes of ego-dissolution (Nour et al., 2016)—that many individuals report to be “life changing” or “transformational”. These experiences seem to allow people to take on fresh perspectives and reinterpret past negative experiences and traumas, potentially providing relief from suffering, depression, and distress (Griffiths et al., 2011) by enhancing acceptance, compassion, and a new perspective on past experiences including traumatic events. The prominence of experiences described as spiritual or self-transcendent was already reported in the well-known Marsh’s Chapel experiment with psilocybin in the 1960s, where mystical-type experiences were observed in healthy volunteers, many of whom reported never having experienced such states before (Doblin, 1991). Building on these early studies, several modern clinical trials with more rigorous methodology have replicated the finding that psychedelics can engender mystical-like states and, in some instances, have linked such experiences to therapeutic benefits (Griffiths et al., 2018; Johnson et al., 2019). A recent post-hoc analysis of a landmark clinical trial comparing psilocybin to escitalopram showed that having a psychedelic-induced mystical experience in the second session of the psychotherapy mediated reductions in depression symptoms (Murphy et al., 2022). This study also found that having an emotional breakthrough in the first session mediated depression outcomes, and that both mystical experiences and emotional breakthroughs were predicted by the strength of the therapeutic alliance reported by the patient.

The evidence of the importance of context and relationship in the efficacy of psychedelics points to a fundamental issue: psychedelics differ from the way other psychiatric medications are used, in that they are typically understood to act as catalysts for psychotherapeutic processes, rather than as standalone therapies. As recent trials have pointed
out, social and psychological support are likely critical to maximizing the benefits and reducing potential psychological harms of psychedelic experiences (Carhart-Harris, Roseman et al., 2018; Watts & Luoma, 2020). Research on psychedelics thus underscores the need to advance an integrated approach to therapeutics in mental health that emphasizes the interconnections between neurobiology, psychology, social-cultural context, and meaning-making.

Outside medical settings, psychedelic use has traditionally been embedded in ritual and ceremonial practices (Metzner, 1998). In some countries, such as the USA and Canada, psychedelic plant preparations such as Ayahuasca or peyote are legally permitted for sacramental use by Indigenous and syncretic religious communities. The disembedding of these substances from ceremonial settings raises questions about whether beneficial effects will be maintained and whether, in the absence of skilled guidance, the altered psychological states induced by psychedelics pose potential safety risks. Importantly, the traditional dispensers of these compounds, who often undergo extensive training before being “qualified”, usually have a well-defined role in accompanying the participant throughout the experience, and are well-acquainted with strategies to help participants navigate states of psychological or physical distress. This raises a critical issue for implementing this novel approach in psychiatry, suggesting that practitioners administering psychedelics should receive specific training that encompasses not only the clinical pharmacology of these compounds, but also the complex ways in which changes in neural functioning interact with patients’ personal, psychological, and cultural backgrounds (Penn et al., 2021; Phelps, 2017; Phelps & Henry, 2021). As psychedelics may amplify both beneficial and harmful psychological and interpersonal processes, their use requires close clinical attention and expertise, particularly when administered to individuals already suffering from significant mental health problems, including but not limited to, trauma, addiction, and depression. A growing number of organizations have begun developing programs to train practitioners in the skills necessary to navigate the complex and intense psychological processes catalyzed by psychedelics, including the processing of traumatic life events, the integration of new insights, and changes in one’s sense of self (Timmerman et al., 2022). Given the resource-intensive nature of psychedelic therapies, many questions remain about how such training can be delivered at scale. These questions are important and timely because, without adequate support and guidance, the same processes that may promote rapid healing, could instead cause significant harm.

In general, there is evidence that the casual, recreational or ceremonial use of psychedelic drugs is not associated with an increased prevalence of mental health problems (Argento et al., 2017; Barbosa et al., 2012; Hendricks et al., 2015; Schlag et al., 2022; St. Arnaud & Sharpe, 2022; Zeifman et al., 2022). Despite this preliminary evidence of physical and psychological safety, there are also reasons for caution. Psychedelics have varied pharmacology and our understanding of potential health effects and abuse liability remains limited. There is, therefore, legitimate concern that both acute and chronic use of psychedelics can have negative effects on mental health:

1. Although no association has been found between lifetime psychedelic use and psychosis in epidemiological studies or controlled trials (Hendricks et al., 2015; Johansen & Krebs, 2015), there is anecdotal evidence that psychedelics may trigger psychotic episodes, including paranoid, manic or depressive states, especially in vulnerable individuals with a family history of schizophrenia or bipolar disorder (for a review see: Dos Santos et al., 2017).

2. While psychedelics are currently being explored as treatment for post-traumatic stress disorder, there is still some concern that psychedelics can trigger or intensify the recollection of traumatic stress disorder, and give rise to a traumatic experience in their own right (Rossi et al., 2022).

3. Chronic hallucinogen use may be associated with persistent symptoms, including perceptual distortions in vision, hearing, touch, changes in sense of self and time perception, paranoia, mood changes (depression or mania) (Martinotti et al., 2018).

More epidemiological research is needed to assess the incidence of adverse effects and potential neurotoxicity arising from exposure to the different classes of psychedelic and empathogenic compounds during adolescence and adulthood, especially after repeated doses. Understanding the physiological mechanisms involved with specific psychedelic substances and identifying individuals at risk for negative effects remains an important research priority.

Several regulatory agencies and jurisdictions have already or are considering decriminalizing or even legalization of the possession and use of psychedelic compounds for personal use or self-medication (Smith & Appelbaum, 2021). If MDMA-assisted psychotherapy for PTSD receives FDA approval in the next several years, as is expected, this would mark the first time that a U.S. regulatory agency specifically approves a drug–psychotherapy combination. In Canada, the Special Access Program implemented in late 2021 permits emergency access to psychedelics such as psilocybin and MDMA for various conditions, including mental health disorders, when other therapies have failed, are unsuitable, or are not available in Canada (Government of Canada, 2022).

If psychedelics are legalized, adequate support should be provided by the government and health institutions to avoid potentially negative outcomes which could result in backlash and a renewed revalidation of these promising interventions to the status of “illicit drugs” with no clinical utility. Developing such support would benefit from a
comprehensive assessment to identify effective harm reduction strategies (such as access to psychological support or safe spaces in which to consume the substances). Guidelines and appropriate training and implementation resources, which take into account the issues raised here, should be carefully designed and established, before legalization.

A plethora of new pharmaceutical companies are developing therapeutic uses of psychedelics for neuropsychiatric disorders; others are searching for novel psychedelic-based medicines without hallucinogenic effects or cardiac toxicity that might be further developed and approved by regulatory agencies.

The renewed interest in psychedelic treatments has created an opportunity for advances in pharmacotherapy in psychiatry, at a time when innovation has been lagging. However, many questions crucial to the future of any therapeutic use remain unanswered. The neurobiological mechanisms of psychedelic effects on cognition and experience are an important focus of current research. In addition to the putative neurobiological mechanisms, to what extent are the experiential changes induced by psychedelics (e.g., alterations in perception, mood and self-awareness) essential for their therapeutic effects? What is the incidence of negative, deleterious or psychopathological effects? What are the clinical predictors of therapeutic benefit or potential harm? Most importantly, given the likelihood that psychedelics work best in the context of psychological therapy and/or social accompaniment, we need to know more about the essential elements and dynamics of this relational context (Timmermann et al., 2022).

Future directions for research needed to guide clinical applications of psychedelics include: i) studies of the mediating role of cultural meaning and practices on the therapeutic effects of psychedelics; ii) identification of social, psychological, and biological predictors of positive and negative treatment outcome; iii) implementation of large-scale clinical trials to further elucidate safety, effectiveness, and mechanisms of therapeutic action; iv) the development of non-psychedelic analogues to maintain therapeutic effects; and v) studies of the long-term benefits and potential side effects of psychedelics. Together, these research efforts could lead to a better understanding of the complex interactions of neurobiology, mind, culture, and spirituality.

Despite many open questions, psychedelic therapies are undoubtedly encouraging mental health practitioners to consider novel paradigms of integrated neurobiological-psychosocial treatment and care. The history and ethnography of cultural practices associated with these compounds strongly suggest that their clinical use should be understood in terms of processes of psychological transformation that consider human beings as persons, integrating brain, mind, social, cultural, and spiritual meaning and values. Psychedelic research is thus bringing psychiatry to a crossroads: we either think through our uses of these substances in supportive psychological and spiritual contexts by well-trained clinicians and expert guides or follow naïve enthusiasms that may create yet another drug crisis built on the exaggerated—though perhaps lucrative—hope and false promise of a quick fix.

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