VIEWPOINT

The Current Status of Psychedelics in Psychiatry

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In the 1950s, the Swiss pharmaceutical company Sandoz, which employed the chemist Albert Hofmann, who discovered lysergic acid diethylamide (LSD) and the similar serotonergic psychedelic psilocybin, made these drugs available to the psychiatric research community as the products Delysid and Indocybin, respectively. By the 1960s, these drugs had caused a revolution in brain science and psychiatry because of their widespread use by researchers and clinicians in many Western countries, especially the US. Before LSD was banned, the US National Institutes of Health funded more than 130 studies exploring its clinical utility, with positive results in a range of disorders but particularly anxiety, depression, and alcoholism. However, the displacement of LSD into recreational use and eventual association with the anti-Vietnam war movement led to all psychedelics being banned in the US. This ban became ratified globally under the 1971 UN Convention on narcotics. Since then, research funding, drug production, and the study of psychedelics as clinical agents has been virtually stopped. Until very recently, no companies would manufacture medical-grade psychedelics, which made getting regulatory approval for clinical research—especially clinical trials—very difficult and in some countries (eg, Germany) impossible.

The past decade has seen a resurrection in human psychedelic drug research, especially involving psilocybin. There were 2 drivers to this. The first was the discovery by Griffiths et al[1] that a single high dose (25 mg) of psilocybin, given in a psychotherapeutic setting, produced enduring positive changes in mood and well-being in people who do not have depression. The second was our series[2] of neuroimaging studies in healthy volunteers, which revealed that psilocybin produced profound and meaningful alterations in brain function, especially of the default mode network, consistent with an antidepressant effect. These findings suggested the possible utility of psilocybin for treating depression and initiated the launch of studies in the UK and US that further supported an antidepressant outcome from a single, 25-mg psilocybin dose in people with resistant depression[3] and those with anxiety and depression symptoms provoked by life-threatening cancer diagnoses.[4,5] There have also been open studies showing efficacy in both alcohol and tobacco dependence.[6]

Based on these positive findings, at least 2 companies have been set up to take psilocybin to the clinic by funding multicenter, dose-finding studies of psilocybin in depression, and a search of ClinicalTrials.gov (in April 2020) revealed that more than 30 psychedelic drug trials are registered (mostly with psilocybin, although a few are with LSD). These include studies in anorexia, obsessive-compulsive disorder, and addictions, as well as depression. At least 2 of the depression trials[7,8] (those of COMPASS Pathways and Usona Institute) are randomized clinical trials compatible with the US Food and Drug Administration and European Medicines Agency registration processes and have been given fast-track status in this field. Many of the trials in other disorders are open-label designs to gather feasibility and safety data to underpin subsequent double-blind randomized clinical trials. Once these regulatory-standard trials have been conducted, if the outcomes are positive, then it seems plausible that psilocybin will become a licensed medicine for some forms of mental illness when used in an approved treatment model.

In the depression trials, the treatment model is becoming standardized as a 4-stage process: assessment, preparation, experience, and integration. Assessment determines if the patient is suitable for psychedelic therapy, both from a mental and physical perspective. Currently, people with a personal or family history of psychosis and bipolar disorder are excluded, as are those with significant health issues (eg, hypertension) because psychedelics transiently increase blood pressure. Certain medications need to be stopped or at least reduced before the treatment, because they can block or attenuate the effect of the psychedelic. Specifically, medicines that block 5-$HT2_A$ receptors (eg, amitriptyline, olanzapine, quetiapine, risperidone, trazodone) need to be withdrawn, and serotonin reuptake inhibitors ideally stopped or, if that is not feasible, tapered down, because they produce subsensitivity of the 5-$HT2_A$ receptor.

In modern studies,[3-5] preparation sessions typically take place the day before the drug administration, the participant is prepared for the experience by at least 1 trained therapist, who are often referred to as *guides*, based on the analogy of the psychedelic experience being a psychological journey. An overview of the dynamics and nature of psychedelic experiences is explained, including how it can be challenging for many people, how any such challenges can be best confronted, and how the participant can get the most out of the experience. During the psychedelic experience, the individual is offered eyeshades and earphones to listen to a music compilation that has been prepared in advance (which they can specify) because music seems to enhance the therapeutic process. For oral psilocybin, the sessions last 4 to 5 hours. Verbal engagement with the therapists is not expected, and most patients go deep into their own visions, thoughts, and memories and do not want to be disturbed. But the guide or guides are present, and with permission, they can hold the patient's hand to reassure the person that he or she is being looked after. The next day is the integration session—during which the same guide or guides talk through the experience and help the patient make sense of it. Ideally, a small number of standard, talk-based psychotherapeutic sessions are further available for issues that emerged during the psychedelic experience to be processed,

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insights to be further integrated, and guidance given on how best to cultivate positive cognitive and lifestyle changes.

In all of the treatment studies conducted so far, the psychedelic is given just once or twice over a few weeks with psychotherapeutic input (which, in the case of addictions, can be a standard 10-week to 20-week abstinence-based program). In this regard, psychedelic treatments are being considered as a new paradigm in psychiatric medicine—that of drug-facilitated psychotherapy.

Why might psychedelics work in such a wide range of disorders? We suggest this may be because these conditions are all internalizing disorders. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addiction, drug craving drives behavior that is specific, narrow, and rigid; individuals with addiction ruminate on the drug, including where to get it, how to pay for it, etc. In obsessive-compulsive disorder and anorexia, there is excessive rumination about threats to the person, from contamination or the effects of eating or overeating, respectively. Neuroimaging studies reveal that psychedelics probably work by disrupting brain systems and circuits that encode these repetitive thoughts and behaviors. The psychedelic experience opens a therapeutic window that disrupts entrenched thinking and allows insight, which with psychotherapeutic support can lead to a recalibration of one's spectrum of associations.[9]

So far, the published trials of psychedelic therapy have yielded promising tolerability and efficacy data. Effect sizes have generally been greater than those of current treatments,[3-5] although confirmation biases may be inflating these. Retention rates are excellent, and few adverse effects have been reported. Head-to-head comparative efficacy studies with current treatments are necessary to fully gauge how promising psilocybin therapy is in comparison with current treatments. In this vein, our research team will report the results of our psilocybin vs escitalopram comparison in major depression later this year.

Perhaps the major challenge is how to scale the treatment up. The current model is time and therapist intensive, and even though only a couple doses of medicine are required, this is currently costly because of the many regulatory challenges associated with psychedelics still being scheduled as very dangerous, illegal drugs under the UN Conventions and all Western governments' drug laws. Another issue is how to provide enough psychedelic-trained therapists and ensure good practice through structuring, manualizing, monitoring, and delivering quality training and practice. Several of the centers currently researching psychedelic therapy are offering training under the supervision of more experienced therapists; for example, Kings College in London, in the UK, has successfully piloted group training of potential therapists, some of whom also received psilocybin as part of this course (though self-experience is not required). If this form of therapy does become more widely used, more formal training of large numbers of therapists will be required.

ARTICLE INFORMATION

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REFERENCES

1. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)*. 2006;187(3):268-283. doi:10.1007/s00213-006-0457-5

2. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143. doi:10.1073/pnas.1119598109

3. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry*. 2016;3(7):619-627. doi:10.1016/S2215-0366(16)30065-7

4. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*. 2016;30(12):1165-1180. doi:10.1177/0269881116675512

5. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*. 2016;30(12):1181-1197. doi:10.1177/0269881116675513

6. Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs: past, present & future. *Neuropharmacology*. 2017.

7. ClinicalTrials.gov. A study of psilocybin for major depressive disorder (MDD). Published March 7, 2019. Accessed July 1, 2020. https://clinicaltrials.gov/ct2/show/NCT03866174

8. ClinicalTrials.gov. Psilocybin vs escitalopram for major depressive disorder: comparative mechanisms (Psilodep-RCT). Published February 12, 2018. Accessed July 1, 2020. https://clinicaltrials.gov/ct2/show/NCT03429075

9. Carhart-Harris RL, Nutt DJ. Serotonin and brain function: a tale of two receptors. *J Psychopharmacol*. 2017;31(9):1091-1120. doi:10.1177/0269881117725915

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