[1] Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JX, UK

[2] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

[3] Patient and public representative, Oxford, UK

Correspondence to: R De Giorgi
riccardo.degiorgi@psych.ox.ac.uk

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Psilocybin for depression

Current evidence leaves more questions than answers

Riccardo De Giorgi, [1,2] Roger Ede[2,3]

Psilocybin and other psychedelics are under investigation for use in several mental health conditions, including depression.[1] Psilocybin, a prodrug that naturally occurs in "magic" mushrooms (genus *Psilocybe*), has been used for ritualistic purposes by indigenous populations of Central-North America for thousands of years.[2] Its active metabolite, psilocin, targets 5-hydroxytryptamine type 2A receptors, whose potent activation of serotonergic pathways is largely responsible for producing psychedelic effects.[3] Both rapidly induced changes in neuroplasticity[4] and immediate "psychedelic" experiences[5] are thought to contribute to the rapid antidepressant effects seen after just one or two doses of psilocybin. These attributes differ from those of established antidepressant strategies such as selective serotonin reuptake inhibitors (SSRIs) and psychotherapies.

The modest efficacy and tolerability of conventional treatments for depression have contributed to the emergence of a polarised debate about the efficacy and safety of psilocybin, fuelled by considerable interest among clinical researchers, the pharmaceutical industry, and the media.[6-9] Whether psychedelics should be widely used for the treatment of depression remains contentious, and polarised views between hard line supporters and critics are unlikely to be helpful for clinical decision making. Instead, an informed, rigorous, and healthy discourse between the scientific community and the public is required if lessons from past successes and mishaps in the history of psychedelics and antidepressants are to be learnt.

Against this complex background, the linked meta-analysis by Metaxa and Clarke (doi:10.1136/bmj-2023-078084)[10] provides updated evidence on the efficacy of psilocybin for the treatment of depression. Across seven short term randomised controlled trials including a total of 436 people with depressive disorders, psilocybin use led to a sizeable decrease in symptoms of depression compared with placebo (Hedges' g 1.64, measured as change in depression scores from baseline, which corresponds to a large effect size in terms of a decrease in symptoms of depression). Confidence intervals were wide but statistically significant (95% confidence interval 0.55 to 2.73), whereas prediction intervals, which reflect the dispersion of the true effect sizes and can better account for between study variation, were wider and not statistically significant (95% prediction interval −1.72 to 5.03).

Variability between studies was considerable (I^2=89.7%) and not meaningfully lower in any of the subgroup analyses. Despite a lenient assessment of the risk of bias and quality of evidence, the certainty supporting a strong antidepressant effect of psilocybin was judged to be low.

Many (but not all) problems known to affect the validity of psychedelics research[11] were acknowledged, including lack of participant diversity, the onerous presence of sponsorship bias, undeclared previous use of psychedelics, and the impossibility of adequate blinding. Furthermore, the authors rightly acknowledged that the current applicability of psilocybin for routine treatment of depression must consider the importance of an appropriate setting and its related high cost.[10] Adverse experiences, such as the proliferation of unregulated ketamine clinics, and, more recently, the use of psilocybin by unlicensed practitioners in the wellbeing industry, are a stark reminder of the potential misuse of these interventions.

This meta-analysis could not answer several questions. Firstly, it could not provide evidence for the effectiveness of psilocybin in depression (performance under real world conditions) until more information about potential effect modifiers is gathered. Pragmatic clinical trials and real world data could help to deliver that.[12] Secondly, there is still ongoing debate about whether psychedelics can express antidepressant activity on their own rather than by assisting specific forms of psychotherapy.[13] Thirdly, little information existed about the long term (>8 weeks) benefits of psilocybin in people with depression, as suggested by a preliminary investigation.[14]

Finally, and perhaps most importantly, this meta-analysis could not differentiate between those individuals most likely to benefit from psilocybin and those who might experience adverse events; as is the case for all analyses of aggregate data.[15] This knowledge gap poorly serves the former group of people, likely labelled as "treatment resistant" after completing several courses of ineffective and unnecessary antidepressant treatments[16] before psilocybin can be offered.

The observed heterogeneity in treatment responses to psilocybin may well be explained by the even more heterogeneous nature of depression related illnesses,[17] clustered together somewhat crudely at present—more research investment might be aimed first at resolving this predicament.

Conversely, suggestions by some stakeholders that psychedelics such as psilocybin cause only negligible side effects contrast with concerning reports of confusional states, substance misuse, intentional self-harm, suicidal behaviour, and psychotic symptoms, especially in people with pre-existing vulnerability.[18] Owing to inconsistent reporting

across clinical trials, this review did not quantitatively assess the safety of psilocybin use in people with depression.[10] The lack of reliable adverse event reporting in trials of psychedelics[19] does not mean that these drugs are safe—and, because of the high visibility of these agents in the media, particular caution is required to avoid unhelpful setbacks in the development of interventions for clinical use.[20]

Metaxa and Clarke's promising findings[10] therefore support a prudent approach in both scholarly and public settings, because more and better evidence is needed before any clinical recommendation can be made about therapeutic use of psilocybin.

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