Altered states: psilocybin for treatment-resistant depression

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"Alice remained looking thoughtfully at the mushroom for a minute, trying to make out which were the two sides of it; and as it was perfectly round, she found this a very difficult question". To resolve the issue, Alice ate the mushroom; in more recent times, however, experimentation with psilocybin-containing magic mushrooms has been strongly discouraged. In the UK, in 2005, magic mushrooms were classified as a Class A substance, with then Home Office Minister Paul Goggins commenting: "Magic mushrooms are a powerful hallucinogen and can cause real harm, especially to vulnerable people and those with mental health problems".[1]

In this context, Robin Carhart-Harris and colleagues[2] deserve much praise for effectively and safely completing an important clinical investigation into the effect of psilocybin on treatment-resistant depression, in the face of many regulatory and practical hurdles. Findings from their study—an uncontrolled trial in which 12 patients were given two doses of psilocybin 7 days apart, reported in *The Lancet Psychiatry*—support the feasibility and safety of this protocol, with preliminary efficacy data suggesting an antidepressant effect. Of course, great thanks are due to the participants; their description of the lived experience of the study and the aspects they found most beneficial will, when published, add substantially to assessment of the intervention.

New treatments for the substantial proportion (perhaps 20%) of patients with depression who do not recover well with either cognitive psychotherapy or medication are certainly needed.[3] Unfortunately, the development of new, more effective medicines through the usual industry-led process of drug discovery has stalled. Intriguingly, into this void have come some repurposed older drugs, for example ketamine,[4] scopolamine,[5] and nitrous oxide;[6] by contrast with conventional antidepressants, these drugs produce rapid and profound changes in mood and consciousness. Ketamine has been the most studied and, although rapid alleviation of mood is reported in a reasonable proportion of patients, the effects are relatively transient and disappear after a few days as the pharmacological effect wanes.[4] The concept underlying the use of psychedelic agents such as psilocybin seems quite different, namely that administration of one or two doses results in profound, spiritually meaningful experiences that produce enduring gains in wellbeing and personal adjustment.[7] Such effects have not been studied systematically in patients with depression previously, but benefits have been claimed following the use of psilocybin to treat anxiety and distress during end-of-life care, and in patients with alcohol and nicotine dependence.[7]

How typical were the patients studied of those seen more generally with resistant depression? They were perhaps better educated than the average sample, with ten of the 12 participants having obtained at least an undergraduate degree. Unlike patients in secondary care, they seemed to have received little in the way of more conventional treatment strategies for severe chronic depression, for example pharmacological augmentation with lithium, atypical antipsychotic drugs, or the use of electroconvulsive therapy. Thus, although the patients met current criteria for treatment resistance, they would not generally be considered as treatment refractory by specialists.[3]

Perhaps the most important feature of the patient group is that most self-selected for the investigation, with five of the 12 participants reporting previous use of psilocybin. Presumably, these participants had experienced a positive psychological response to psilocybin previously, and believed that the drug could help them. This is significant in an open-label study because, as acknowledged by the authors, it increases the likelihood of expectancy effects. Perhaps related to this factor was the substantial clinical response to the first low-dose treatment of 10 mg psilocybin. Detailed data are not provided, probably because the Carhart-Harris and colleagues regarded the two doses of psilocybin (given 1 week apart) as a treatment package. However, the reduction in score on the Hamilton Depression Scale of around 10 points at 1 week after the low dose suggests a powerful antidepressant effect of a moderate psychedelic experience. Might the patients have done as well on the low-dose treatment given alone? Although the present data make it difficult to answer this question, it does point to a possible way in which future studies might be controlled by comparing the effect of low and standard doses of psilocybin in patients with depression who have no previous exposure to psychedelic drugs.

The key observation that might eventually justify the use of a drug like psilocybin in treatment-resistant depression is demonstration of sustained benefit in patients who previously have experienced years of symptoms despite conventional treatments, which makes longer-term outcomes particularly important. The data at 3 month follow-up (a comparatively short time in patients with extensive illness duration) are promising but not completely compelling, with about half the group showing significant depressive symptoms. Further follow-ups using detailed qualitative interviews with patients and family could be very helpful in enriching the assessment.

Dramatic physical treatments in psychiatry come with a historical health warning, with insulin coma therapy as an oft-cited example. Relative to other misused substances, magic mushrooms have a low risk of harms such as dependence,[8] but there are unwanted effects, including acute anxiety and paranoia together with the possibility of longer-term adverse consequences on mental health in the psychologically vulnerable.[9] In this respect, Carhart-Harris and colleagues provide a good framework for the safe conduct of psilocybin studies that follow guidelines established by researchers at Johns Hopkins University.[9]

The possible therapeutic use of psilocybin in treatment-resistant depression comes at a time of intense debate about the harms of recreational drug use and the role of government and the criminal justice system in regulation. Most clinicians will be pragmatic and ask whether benefits substantially outweigh harms. This equation will include the difficulties of using a drug whose crucial positive psychological effects are likely to be exquisitely sensitive to individual disposition, environmental setting, and therapeutic relationship (the author Edna O'Brien describes a petrifying LSD psychotherapy session with RD Laing, during which the famous anti-psychiatrist metamorphosed into a rat).[10] Patients with treatment-resistant depression seeking psychological insight with a less exciting trajectory might consider the slow route offered by traditional dynamic psychotherapy.[11]

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In the past 3 years I have been a member of an advisory board for Lundbeck.

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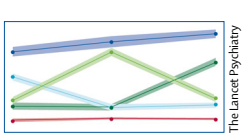
Depression in old age—the first step to dementia?

A better understanding of the link between depression and dementia is essential, given the rapid growth of the elderly population, with an anticipated doubling of global dementia prevalence every 20 years.[1] In the *Lancet Psychiatry*, the findings presented from the study by Saira Mirza and colleagues[2] have brought us one step closer to answering whether depression is a risk factor for dementia or vice versa. They assessed different trajectories of depressive symptoms and their association with subsequent dementia in a large community sample of older adults over the course of 10 years. The beauty of their study is the identification of five different depression trajectories: stable low, decreasing, remitting, increasing, or stable high depressive symptoms over ten years. With results analysed by a Cox proportional hazards model adjusted for age, sex, *APOEε4* carrier status, educational level, body-mass index, smoking, alcohol consumption,



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