News in focus

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Psilocybin, the active ingredient in hallucinogenic mushrooms, has been cleared for regulated use in therapeutic settings in Australia.

AUSTRALIA WILL BE FIRST TO PRESCRIBE PSYCHEDELIC DRUGS FOR PTSD AND DEPRESSION

Decision to make the previously illicit drugs MDMA and psilocybin available is dogged by suggestions that it was rushed.

By Rich Haridy

In a controversial move, Australia will become the world's first country to allow the drugs psilocybin and MDMA to be prescribed by doctors to treat psychiatric conditions, including depression and post-traumatic stress disorder (PTSD). But many scientists are concerned that research has not yet conclusively shown that these drugs are safe or effective. And some clinicians fear that the regulation that will govern access to the drugs is insufficient.

Australia's drug regulator, the Therapeutic Goods Administration (TGA), which approved the move, says that the decision followed a nearly three-year process and included extensive consultation with experts.

Research over the past few decades[1] has shown that some drugs that are illicit, but are often used recreationally, are effective in treating certain mental-health disorders when combined with psychotherapy. MDMA is widely known as the 'party drug' ecstasy, and psilocybin is the active ingredient in hallucinogenic mushrooms. A phase II trial, published late last year[2], showed that a 25-milligram dose of psilocybin was twice as effective as a 1-mg dose in combating treatment-resistant depression, although significant side effects were noted. And a report on a phase III trial of MDMA described it as a "potential breakthrough treatment" for PTSD[3]. The drugs have also shown potential for treating anxiety, anorexia and substance addiction.

Nations including the United States, Canada and Israel allow individual use of these drugs on compassionate grounds or in clinical trials, but on 1 July Australia became the first to regulate the drugs as medications, to be prescribed by approved psychiatrists.

Risks of a bad experience

Among researchers' concerns is that science has yet to show which patients are best suited to the treatments. "It's not for everybody. We need to work out who these people are that are going to have bad experiences, and not recommend it," says Susan Rossell, a psychiatrist at Swinburne University of Technology, Melbourne, who is working on Australia's only active clinical trial testing psilocybin-assisted psychotherapy for treatment-resistant depression. Rossell fears that, administered improperly, the drugs could give people bad trips and leave them with increased psychological issues. "That's the worst-case scenario," she says. Her own unpublished research suggests that 10–20% of trial participants have a "really terrible time" with these drugs.

The TGA approval follows an application in March 2022 by Mind Medicine Australia, a non-profit group in Melbourne that advocates psychedelic therapy, for MDMA and psilocybin to be made available in therapeutic settings. In December 2021, the TGA had denied a 2020 application by the organization after a long consultation process involving an independent expert panel.

Steve Kisely, a psychiatrist at the University of Queensland in Brisbane, was one of three researchers who worked on the 2021 report to the TGA. He says that the drugs show promise in some people when administered in clinical settings with professional support, but that researchers are still working out who is most suited to psychedelic medicines and what kind of psychotherapy leads to the best results.

Lack of guidance

He is concerned that the approval comes with no guidance or stipulation that the drugs should be administered in a clinical setting with intensive psychotherapy support. "It's really unclear about how it's going to be enforced."

John Skerritt, who until April was head of the TGA, said in an webinar about the decision that month that the clinical setting in which the prescription was written and administered was outside the TGA's purview. Like the US Food and Drug Administration (FDA) or the European Medicines Agency, the TGA is mainly responsible for regulating medicines and medical devices. It plays no part in stipulating broader clinical protocols.

"We were quite deliberate in not saying, 'Here's the clinical protocol.' We're not the regulators of clinical practice," Skerritt said during the webinar. "It is quite likely that other groups, whether they be clinical professional groups or others, will release guidance around it."

Rossell and her colleagues co-authored a May report[4] questioning why the TGA hadn't consulted them, given their experience – rare in Australia – of administering psilocybin to treat depression. "Instead, it seems the TGA has yielded to pressure from the public and lobby groups to increase access to these experimental treatments, outside of clinical trials," they wrote. "Sufficient levels of evidence have not yet been generated for broad-scale implementation to be justified."

Alan Davis, director of the Center for Psychedelic Drug Research and Education at the Ohio State University in Columbus, agrees: "It was too soon to make these changes before the research could fully determine clinical efficacy and safety."

The TGA rejected suggestions that the decision was rushed, or influenced by lobby groups.

Last week, in contrast to Australia's regulatory shift, the FDA published its first draft guidance for designing clinical trials of psychedelic compounds. The guidance suggests that clinical trials are yet to answer several questions regarding efficacy, the safety of long-term repeat dosing and optimal psychotherapy protocols.

"These are still investigational products," says Tiffany Farchione, director of psychiatry at the FDA.

How the drugs will be prescribed

Psychiatrists will prescribe the drugs using the TGA's Authorised Prescriber Scheme, which allows registered psychiatrists to prescribe medicines that have yet to be formally included on Australia's register of therapeutic goods. To sign up for the scheme, a psychiatrist must first seek approval from a panel that evaluates applications for human clinical-trial work, known in Australia as a human research ethics committee (HREC); most research organizations have one. Once approved by an HREC and the TGA, a clinician needs to provide the TGA with reports on patient numbers and serious adverse effects every six months.

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The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has produced protocols and standards for both psilocybin and MDMA therapy to guide HRECs and psychiatrists. But these protocols carry no regulatory weight, which Rossell and Kisely see as a problem. "There is no standardization in terms of HRECs," Kisely says. He also wonders how clinical practice will be supervised. "Once something's been approved, how does an HREC monitor whether they're actually sticking to what they said they would do? They just don't have the resources to do it. So there's no regulatory oversight."

The TGA says that doctors who prescribe MDMA and psilocybin must follow a code of conduct published by the Medical Board of Australia.

Richard Harvey, a psychiatrist in Geelong, Australia, who chairs the RANZCP's Psychedelic-Assisted Therapy Steering Group, has confidence in the protocols that the group has developed. And he says that Australian state and territory governments are likely to regulate licences for premises that offer psychedelic therapies, or require permits for each patient.

When slow is good

Harvey predicts that the roll-out of the therapy in Australia will be slow, given the cost and the complexity of delivering one-to-one psychedelic therapy. And he says that is a good thing. There must be "careful data collection, and a real laser focus on safety", he says.

But for Paul Liknaitzky, head of clinical psychedelic research at Monash University in Melbourne, the change is still too fast. Liknaitzky is joining forces with the Australian heath-care company Incannex, and working furiously to open one of the country's first psychedelic clinics, in Melbourne, this year. The suddenness of the TGA decision has left him scrambling to get the clinic ready before clients begin requesting the therapy.

He would like the TGA's reporting requirements to be more stringent, describing six-monthly reports as "obscenely minimal".

The RANZCP has strongly recommended data-collection protocols, but there are no mandated requirements and no centralized patient-data registry will exist. Liknaitzky says this is a missed opportunity for researchers to learn more about these drugs. "It's a shame for accountability, and also a shame for us being able to learn collaboratively on the ground."

Still, Liknaitzky is excited at the prospect of tailoring psychedelic therapies to the needs of individuals, which is something that he hasn't been able to do in formal clinical trials. "I want to do a better job in the real world. So the opportunity to get [the drugs] into the real world sooner rather than later is great."

1. Hadar, A. *et al. J. Psychoactive Drugs* https://doi.org/10.1080/02791072.2021.2022254 (2022).
2. Goodwin, G. M. *et al. N. Engl. J. Med.* **87**, 1637–1648 (2022).
3. Mitchell, J. M. *et al. Nature Med.* **27**, 1025–1033 (2021).
4. Rossell, S. L., Meikle, S. E., Williams, M. L. & Castle, D. J. *Aust. NZ J. Psychiatry* **57**, 935–936 (2023).