Could the medicalization of psychedelics lead to the next generation of antidepressants?

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A major part of the counterculture that emerged in western societies in the 1960s centred around the use of mind-altering psychedelic drugs such as lysergic acid diethylamide (LSD). Humans had, however, been consuming hallucinogenic substances since prehistoric times and often incorporated them into their religious rituals. Concerns over the effects of potent psychedelics like LSD led to them being outlawed in many jurisdictions around the world via the UN Convention on Psychotropic Substances in 1971. During the intervening decades, the scientific investigation of psychedelics and their potential for legitimate therapeutic use has consequently been limited. In recent years, hints that psychedelics may be effective against certain treatment-resistant depressive states like post-traumatic stress disorder (PSTD) have led to more concerted efforts to obtain reliable clinical data that could convince drug regulators to approve them as legitimate medical treatments.

What are psychedelics?

'Psychedelic' is a term invented by British psychiatrist Humphry Osmond from a combination of the Greek '*psyche*', meaning mind or soul, and '*dēleín*' or '*deloun*' meaning to manifest or reveal. The common feature of psychedelic drugs is their ability to elicit in the user an altered state of consciousness, including a changed perception of their surroundings. Dream-like and mystical experiences are also often encountered. An intriguing side effect is an increased belief in the consciousness of a range of living and non-living things, and this can last for a considerable period after consuming the psychedelic substance. Psychedelics are often referred to as hallucinogens but it has been argued that this is an inaccurate label because people experiencing hallucinations are unable to distinguish their experiences from reality, whereas the altered sensory perceptions caused by psychedelics are usually recognized by the user to be unreal. The term 'pseudo-hallucinogen' might be a more suitable label.

'Classic psychedelics' fall into three main chemical classes: the tryptamines, such as the mushroom-derived psilocybin and plant-derived dimethyltryptamine (DMT), the phenethylamines such as mescaline which is found in certain American cacti and the ergolines, with the semi-synthetic LSD being the main protagonist (Figure 1). There are some fully synthetic compounds such as 3,4-methylenedioxymethamphetamine (MDMA) and ketamine that are also often referred to as psychedelics, but they are not actually true psychedelics, with MDMA belonging to a class of psychoactives known as entactogens or empathogens, whereas ketamine is a dose-dependent dissociative hallucinogen.

Trippin' like an ancient Egyptian

It is believed that humans have been partaking in hallucinogenic plants and fungi since prehistoric times, with one of the earliest examples thought to be the iconic fly agaric mushroom (*Amanita muscaria*, Figure 2). These mushrooms contain the hallucinogen muscimol, along with a range of other bioactives and toxins. Being a bioaccumulator of vanadium and other toxic metals, combined with the fungus' naturally produced toxins, the consumption of fly agaric mushrooms is associated with a variety of unpleasant effects. Nonetheless, their use was apparently incorporated into the shamanistic rituals of the Finno-Ugric people of northern Europe and Asia prior to the human migrations that led to the habitation of the Americas. During these expansions, people must have discovered other psychoactive organisms and it is probably in present-day Mesoamerica that indigenous Americans first encountered psilocybin-producing mushrooms like those of the *Psilocybe* genera. Both *Amanita* and *Psilocybe* mushrooms were also historically important to peoples of North Africa, including the ancient Egyptians.

There are a variety of plants native to the Americas that produce psychedelic substances, including several

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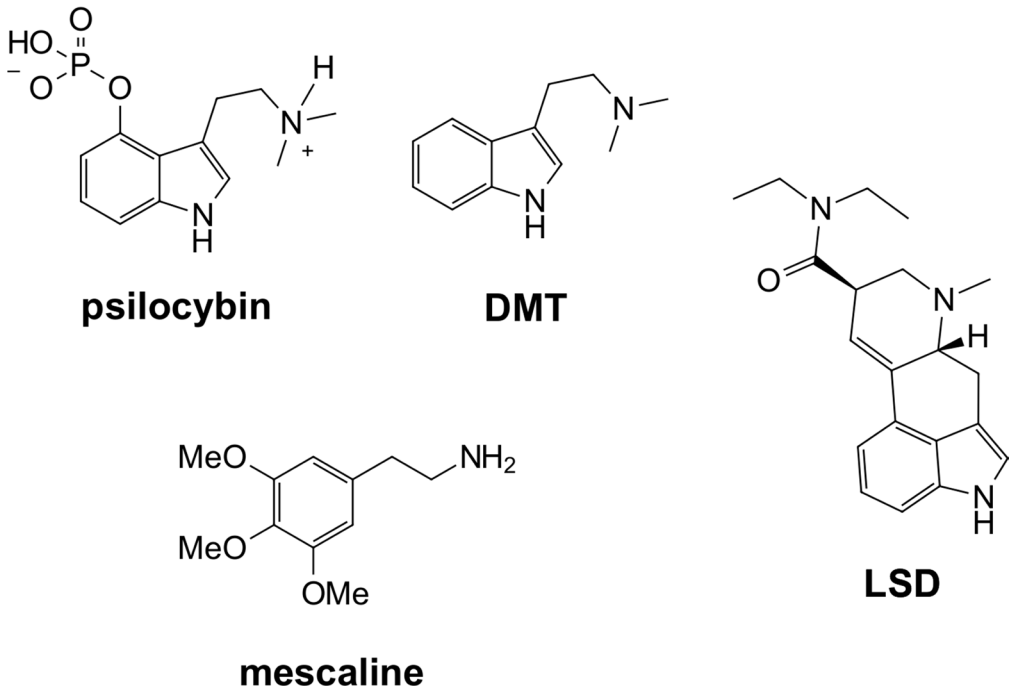

Figure 1. The common 'classic psychedelics'.

cacti that produce mescaline. People in the Amazon Basin developed a DMT-containing psychedelic decoction known as ayahuasca, which is still used in shamanic ceremonies today. A number of other traditional cultures from Africa and the Americas have also incorporated psychedelic and hallucinogenic natural substances into their religious practices. The psychedelic properties of LSD, which was first prepared in 1943, were discovered accidentally by the Swiss chemist Albert Hofmann when he was making synthetic modifications to the fungus-derived ergoline natural products. He subsequently became a leading pioneer in the field of psychedelic research.

Psychedelics are now being investigated as potential treatments for a range of mental health conditions including various forms of depression and anxiety, prolonged grief, anorexia nervosa, addictions, obsessive-compulsive disorder (OCD) and certain pain syndromes.

Figure 2. Left: psilocybin-producing mushroom *Psilocybe subaeruginosa;* Right: muscimol-producing mushroom *Amanita muscaria*.

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LSD and psilocybin were approved for limited clinical use in Switzerland in 2014 and, in 2023, psilocybin was approved in Australia for highly restricted use for treatment-resistant depression.

What's going on at the molecular level – serotonin interference?

While psychedelic compounds have been shown to bind to many different receptors in the body, the origin of the psychedelic effect is thought to result from interference with serotonin signalling in the brain through the binding of psychedelics to a particular serotonin receptor known as 5-HT_{2A}. For example, early studies revealed, for psychedelic compounds, a correlation between affinity for the 5-HT_{2A} receptor and the dose required for psychedelic effects in humans. Interestingly, however, not all compounds that bind strongly to the 5-HT_{2A} receptor are psychedelic, and even compounds with very similar chemical structures may have very different effects: The medication lisuride, which shares much of the chemical structure of LSD, also strongly binds to the 5-HT_{2A} receptor, yet is not psychedelic.

Recent advances in structural biology have allowed the determination of the structures of psychedelic-receptor complexes by X-ray crystallography and cryo-electron microscopy. These structures help to provide a molecular understanding of the behaviour of compounds discovered over the previous decades. An example is the binding of LSD to the 5-HT_{2A} receptor (Figure 3). LSD binds in a similar location to the natural signalling molecule serotonin, activating the 5-HT_{2A} receptor while blocking the binding of serotonin.

Separating the psychedelic effect from the antidepressant effect.

Psychedelic compounds produce both pseudo-hallucinogenic effects in humans and antidepressant effects. However, it is still unclear whether the psychedelic state is integral to the therapeutic effect, or a side effect. While the psychedelic symptoms are manageable, in practice they require long periods of medical supervision and present a risk of traumatic psychedelic experiences in already vulnerable patients.

This is an area of intense research and there are some signs that the therapeutic effect may be separable from the psychedelic effect. The non-psychedelic medication lisuride shows effects in mouse models of depression, which may indicate the psychedelic state is not essential for these compounds to act as anti-depressants. Psychedelics are thought to alter neuroplasticity in the brain by causing changes in the connections between neurons, and this may be the basis of the therapeutic effects. Recent research has shown that these changes in neuron connections can also be produced by non-psychedelic compounds, suggesting these latter compounds may also be useful therapeutics. Other recent work has suggested that these changes in neuron connections may instead be driven by binding at a different receptor, TrkB, separate from their pseudo-hallucinogenic effects that result from binding to the 5-HT_{2A} receptor. Further, pre-clinical research and human trials will be required before we know whether these compounds are improved therapeutics over psychedelics.

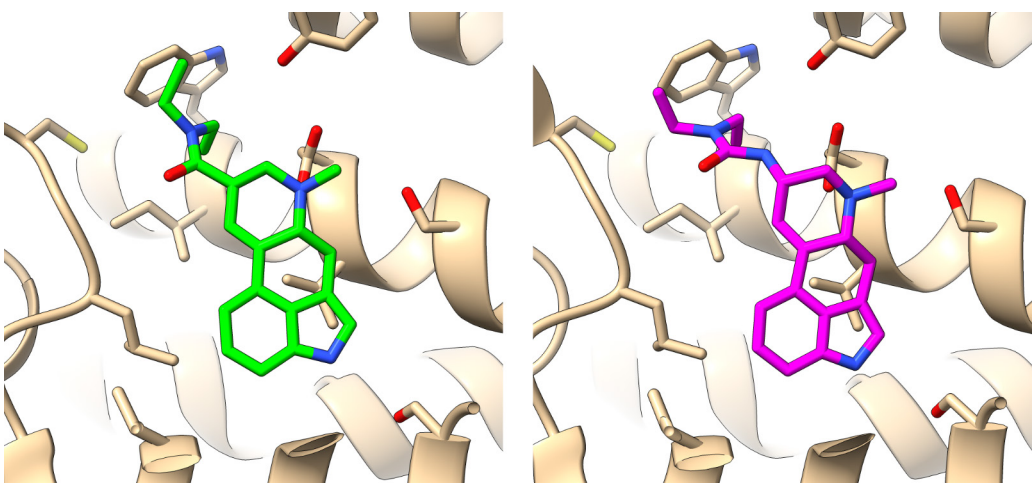

Figure 3. The binding of potent psychedelic LSD (green) and non-psychedelic lisuride (purple) in the 5-HT_{2A} receptor (tan) as revealed by X-ray crystallography (PDB ID: 7WC6, 7WC7). Both structures are presented in the same orientation, with neighbouring residue side-chains shown and the protein backbone in cartoon representation. Despite the large differences in biological effects of these substances, the overall similarity in binding the 5-HT_{2A} receptor is very clear.

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Why do psychedelics exist in nature – expanding the minds of insects?

Psychedelic compounds are found in nature across a variety of species. Some, such as psilocybin in fungi, are produced at high levels – greater than 1% of the dry weight of the fungus. This is an enormous metabolic cost to the fungus and must come with a strong benefit. Genomic studies indicate that the ability to biosynthesize psilocybin likely evolved at some point in the Paleogene era and spread via horizontal gene transfer between species, although it appears that at least one genus of fungi has evolved this ability independently much more recently. As primates were only beginning to emerge in the Paleogene era, it is possible that psilocybin originally evolved to modify insect behaviour, rather than that of primates.

Psilocybin-producing fungi are typically found in wood-decaying and dung-decaying ecological niches, both niches where insects are a significant competitor for resources and a potential predator. Psilocybin may be able to improve fungal survival by directly deterring insects and gastropods from feeding on fungal fruiting bodies. Experiments with the fruit fly *Drosophila* have found that synthetic compounds that interfere with the 5-HT_{2A} receptor reduce feeding behaviour, and this interference does not occur when the fly lacks an active 5-HT_{2A} receptor. Alternatively, the benefits of psilocybin to the host may not be due to the compound itself. Damage to psilocybin-containing fungi leads to the formation of a blue colouration, resulting from an enzyme-catalysed polymerization of psilocybin. This psilocybin polymer may deter insect feeding or be otherwise beneficial to the fungus.

Alternatively, psilocybin may be providing benefit by reducing competition for resources. In wood-decaying niches, fungi are in competition with highly organized social insects such as termites for wood to decay. Ingestion of psilocybin by these insects may block complex and coordinated behaviours by the insects and lead to increased wood resources for the fungi. Ants given LSD show decreased group formation and food-sharing behaviours, which suggest that it is possible to modulate insect behaviour in this way. Intriguingly, some fungal cicada parasites appear to manipulate their living host behaviour directly, producing psilocybin or the amphetamine cathinone.

Other psychedelics found in the plant kingdom such as mescaline and DMT may also act as antifeedants, protecting the plant from predators. Interestingly, animals (including humans) also make DMT endogenously, and DMT may not only interfere with neurotransmitters such as serotonin but may in fact be a neurotransmitter itself.

Are psychedelics leading to the next generation of antidepressants?

Clinical psychotherapists trialling naturally occurring psychedelics such as psilocybin have seen some impressive results for certain patients, with clinical improvement in depression resistant to other treatments and with the benefits in some cases lasting many months. Current treatment regimens are, however, time consuming and expensive. Despite the significant upfront costs of this approach, proponents argue that it could still be cost-effective in the long run and may provide treatment for patients where other approaches have failed. Psychedelics are by no means a panacea though, with some patients with difficult-to-treat depression not responding well to the treatment, having uncomfortable, confronting experiences and in the end not necessarily being better off. There are still many unanswered questions, such as what the long term effects of psychedelic treatments are and if repeated, long term dosing is required or safe. It is also unclear if the psychedelic experience is integral to the antidepressant effect or separate, with some researchers pursuing chemically-related but non-psychedelic small-molecule antidepressant drugs. It might be several years before we know if this is going to be a fruitful approach.

Psychedelics are an area of intense on-going research, and we certainly have much more to learn about these fascinating compounds. ■

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Further reading

- *Introductory Review*: Walker, S.W., Pullella, G.A., Piggott, M.J., and Duggan, P.J. (2023) Introduction to the chemistry and pharmacology of psychedelic drugs, *Aust. J. Chem.*, **76**, 236–257. DOI: 10.1071/CH23050
- *Traditional use of psychedelics*: McKenna, D. and Riba, J. (2016) *New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca*. In: Halberstadt, A.L., Vollenweider, F.X., Nichols, D.E. (eds) Behavioral Neurobiology of Psychedelic Drugs. Current Topics in Behavioral Neurosciences, vol 36. Springer, Berlin, Heidelberg. DOI: 10.1007/7854_2016_472
- *Relationship between psychedelic and antidepressant effects*: Pogorelov, V.M., Rodriguiz, R.M., Roth, B.L. and Wetsel, W.C.. (2023) The G protein biased serotonin 5-HT2A receptor agonist lisuride exerts anti-depressant drug-like activities in mice, *Front. Mol. Biosci*. **10**, 1233743 DOI: 10.3389/fmolb.2023.1233743; Moliner, R. et. al. (2023) Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nat. Neurosci.* **26**, 1032–1041. DOI: 10.1038/s41593-023-01316-5
- *Structural Biology:* Cao, D., Yu, J., Wang, H. et al. (2022) Structure-based discovery of nonhallucinogenic psychedelic analogs. *Science*, **375**, 403–411. DOI: 10.1126/science.abl8615; see also Kim, K., Che, T., Panova, O. et. al. (2020) Structure of a Hallucinogen-Activated Gq-Coupled 5-HT_{2A} Serotonin Receptor, *Cell*, **182**, 1574–1588, DOI: 10.1016 /j. cell.2020.08.024

Author information

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Scott Walker obtained his BSc (Hons) from Massey University and his PhD from the University of Canterbury. After post-doctoral work at the University of Adelaide, he moved to the Monash Institute of Pharmaceutical Sciences and worked on the development of new medicines for cancer. Scott is currently a Senior Research Scientist at CSIRO, working on the discovery of new medicines for a variety of diseases.

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