Environments for clinical data, and worldwide, the Global Alliance for Global Health is establishing standards and protocols to enable swifter progress. For this to be successful, multi-disciplinary teams will be needed, involving clinicians, domain experts and machine learning experts, to develop the tools to exploit the data.

It has taken many years to establish the biological databases that are so widely used today—and the challenge for clinical data is even larger. This calls for immediate investment in creating a new health data infrastructure so that patients will be proud to contribute their data to improve human health and the world can face new pandemics with confidence. ❐

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J.M.T. wrote the first draft of the article, and R.A.L. and N.B. edited and improved it. R.A.L. performed the analyses and created the figures.

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J.M.T. sits on the board of Health Data Research UK.

Check for updates

Psychedelic therapy: a roadmap for wider acceptance and utilization

Psychedelics have shown great promise in treating mental-health conditions, but their use is severely limited by legal obstacles, which could be overcome.

Mason Marks and I. Glenn Cohen

The COVID-19 pandemic has exacerbated a national mental-health crisis in the United States. For two decades, drug-overdose deaths have risen exponentially, and suicide rates have steadily increased. These trends reflect deep-seated problems with the healthcare system, including low investment in preventative mental healthcare and a lack of innovation in psychiatry. In search of more effective treatments, clinicians are exploring the therapeutic use of psychedelic compounds, a promising avenue for addressing the mental-health crisis. However, there are social and legal obstacles to making psychedelics a viable treatment option[1].

Schedule I controlled substances

Psychedelics are a class of natural and synthetic compounds that includes psilocybin, MDMA (3,4-methylenedioxymethamphetamine), ibogaine and DMT (dimethyltryptamine). Some psychedelics have been used by Indigenous communities for hundreds or thousands of years. Others were first synthesized in the early 20th century. By the middle of the 20th century, clinicians used psychedelics as adjuncts to psychotherapy, reporting a variety of benefits. However, in the 1970s they were categorized as schedule I controlled substances, which are said to have "no currently accepted medical use and a high potential for abuse"; this blocked mainstream research on these compounds for decades.

In the late 1990s, the US Drug Enforcement Administration (DEA) permitted some researchers to study limited amounts of psychedelics, which allowed research to resume. Clinical trials have now been conducted at leading universities, and a growing body of evidence supports the use of psychedelics, such as psilocybin and MDMA, in the treatment of depression[2], post-traumatic stress disorder[3] and anxiety toward the end of life[4].

The schedule I status of most psychedelics imposes a ceiling on many policy recommendations. The evidence in support of rescheduling is strong, particularly for psilocybin, which is derived from fungi[5]. Unlike other schedule I substances such as heroin, and schedule II compounds, including cocaine and fentanyl, psilocybin exhibits a low risk of toxicity and a very low potential for dependence or addiction[6]. Psilocybin use is not criminalized in several countries, including Portugal and the Netherlands, and a study commissioned by the Dutch Ministry of Health found that over-the-counter sales posed minimal risk to individual people and the public[7].

Acknowledging its therapeutic benefits, the Canadian government made psilocybin available to people with life-threatening illness through compassionate-use regulation. On the basis of clinical-trial data, the US Food and Drug Administration (FDA) designated psilocybin a breakthrough therapy for major depressive disorder and treatment-resistant depression[8].

Rescheduling can occur through several means. The US Congress can amend the Controlled Substances Act, changing the categorization of any controlled substance[9]. Alternatively, the president or the federal

Psilocybin mushrooms. Credit: gre jak / Alamy Stock Photo

attorney general could command the DEA to reschedule a substance. Finally, any person from within or outside the government can petition the DEA to reschedule substances, which may trigger FDA review of available evidence.

The FDA is obligated to protect the public and ensure the dissemination of accurate medical information, and it has spontaneously opined on potential scheduling of unregulated substances, such as the dietary supplement kratom. Similarly, it could recommend the rescheduling of psilocybin because the available evidence no longer supports its current classification.

Limits on federal funding and research

Due to the schedule I status of most psychedelics, federal funding for research is nearly non-existent.

More directly, a federal appropriations rider — a provision inserted into a funding bill that may effectuate public policy by limiting how funds are spent — creates a considerable obstacle to such research. First enacted in 1996, the rider prohibits federal funds from supporting "any activity that promotes the legalization of any drug or other substance included in schedule I."[10] This rider has been renewed in every appropriations process since then. Because research on psychedelics could advance scientific knowledge and provide evidence that supports rescheduling, a form of legalization, the rider arguably prohibits the use of federal funds to support research on psychedelics, so long as they remain in schedule I.

Bills to eliminate the rider, in 2019 and 2021, both failed. However, as this Comment was going to print, the National Institute on Drug Abuse funded a trial to investigate the use of psilocybin for smoking cessation, possibly reflecting an encouraging policy shift.

Under existing regulation, well-capitalized private companies fund most research and, to a large extent, they control the agenda and shape federal drug policies. Instead, the goal should be a psychedelics industry in which patients and marginalized communities have seats at the table. Achieving this goal will require more-inclusive clinical trials and unbiased regulatory review of psychedelics by the FDA.

The FDA currently oversees phase 3 trials of MDMA for the treatment of post-traumatic stress disorder and phase 2 trials of psilocybin for the treatment of drug-resistant depression[11]. In addition to being funded by private donors, existing trials often lack diversity and exclude populations who may benefit from psychedelics, such as people with histories of severe trauma and self-harm[12]. An infusion of federal funds could be used to make psychedelics research more equitable and inclusive.

Patents may limit access

Given promising clinical-trial results, many stakeholders are attempting to patent psychedelic compounds and methods of producing and administering them.

Patents entitle their holders to exclude others from making, using or selling patented inventions for approximately 20 years[13]. The public-policy justification for patents rests on the theory that the right to exclude incentivizes drug development, an expensive endeavor, made riskier when other companies can copy an invention. Accordingly, companies such as the British pharmaceutical firm Compass Pathways have sought patents on psilocybin compounds and methods of treating a variety of mental-health conditions with psychedelics[14]. They argue that patents are necessary to protect their investments not only in drug discovery but also in commercialization, which may involve expensive clinical trials and other requirements to obtain approval from the FDA and other regulators and buy-in from the medical community[15].

At the same time, the sudden interest in patenting psychedelics has prompted criticism from stakeholders, including patient advocates, scientists, journalists, lawyers and Indigenous communities[16]. Some claim patenting psychedelics exploits the traditional knowledge of Indigenous communities without acknowledgment or compensation, a practice called 'biopiracy'.

Others argue that patents make a small number of companies gatekeepers for the emerging psychedelics industry, which could inhibit research, stifle innovation and restrict access to needed therapies.

These concerns are not unique to psychedelics. Patents on genetic technologies, cancer therapies and other innovations have engendered similar debates[17]. However, some features of psychedelics, including their long and complicated history, raise unique concerns that could exacerbate pre-existing problems with patenting medical products.

Novelty and non-obviousness are two conditions for patentability. However, because psychedelics are often derived from natural products that have been used in traditional practices for centuries, psychedelic inventions may lack novelty or would have been obvious to people experienced in the field. Nevertheless, the US Patent and Trademark Office (PTO) has issued psychedelic patents of questionable validity[18].

Weak psychedelic patents could potentially be invalidated in court, but that does not make them harmless, because patent holders can still wield them offensively. Defending against patent-infringement claims is expensive, and the prospect discourages action by smaller startups and non-profit research organizations, even when they are in the right.

One explanation for the issuance of problematic patents for psychedelics may be a lack of expertise at the PTO. Because psychedelics were criminalized for decades, the agency lacks personnel adept at evaluating novelty and non-obviousness in this field. To address this concern, a group called 'Porta Sophia' created a library of existing psychedelic technologies to help

patent applicants and PTO examiners assess the novelty of inventions[19].

Other potential solutions include encouraging inventors to sign patent pledges — promises not to enforce patent rights under certain conditions. During the COVID-19 pandemic, some companies took the Open COVID Pledge, promising not to enforce their rights against competitors using their technologies to address the pandemic. Impressive advancements have been seen in the psychedelics space without patents. Two leading non-profits, the Multidisciplinary Association for Psychedelic Studies and the Usona Institute, conduct clinical trials with psychedelics while eschewing patent rights.

Restricting patents on psychedelics may be necessary to promote their role in the meaningful advancement of mental healthcare. US law prohibits patents on products of nature, including human genes; abstract ideas, such as those expressed by mathematical formulas; and natural phenomena, including the laws of nature. Some might also think of psychedelics as tools of discovery that should be free to all and reserved exclusively to none. Psychiatrist Stanislav Grof once said that when psychedelics are used responsibly, they may do for psychiatry what the microscope achieved for biology and the telescope accomplished for astronomy[20].

Improving access and acceptance

As the evidence base for psychedelic therapies grows, it is essential that payers expand coverage.

Many who might benefit from psychedelics may be on Medicaid, and even if private insurers begin coverage, many patients will be unable to access these therapies. Coverage should therefore be central to policy-reform efforts in federal and state governments, or the liberalization of psychedelics may leave those most in need without access.

Many physicians who wish to incorporate psychedelics into their practices need training, and it will be essential to create evidence-based clinical-practice guidelines. Standards may help reduce fear among some healthcare professionals about medical malpractice liability if patients have bad outcomes while using these therapies. But litigation may be necessary to shape the boundaries here.

A final looming issue is the question of which healthcare or para-medical professionals will be empowered to help patients. It is not only licensed physicians who are interested in psychedelics practice, and it remains unclear who else may play leading roles and what licensure regimes might look like.

One approach would center psychedelics within a prescription model that requires licensed prescribers, typically physicians. This model has benefits, but it may raise challenges in a setting in which many patients already use psychedelics, either alone or with the assistance of healthcare professionals or spiritual healers. A prescription model may not be the best approach for everyone.

The Oregon model

The state of Oregon is pursuing an alternative model in which trained facilitators licensed by the Oregon Health Authority will administer psilocybin[21]. Clients seeking access to 'psilocybin services', as they are called in Oregon, need not have a medical diagnosis to participate. Because clinical-trial participants often report sustained feelings of wellbeing[22], some believe psilocybin services could help fill the current gap in preventative mental healthcare.

The Oregon model of psilocybin services envisions the facilitator as new type of professional trained in Western scientific knowledge as well as Indigenous uses of plant medicines. The Oregon Psilocybin Advisory Board, appointed by Governor Kate Brown in March, is advising the Oregon Health Authority on rules for this emerging industry[23].

Given the worsening mental-health crisis, and a lack of innovation in psychopharmacology, it is urgent that the US Congress make funds available for psychedelics research, which is currently sustained mainly by corporate and private donors. As with cannabis regulation, there will be challenges and opportunities when a medical model is introduced over a preexisting less-regulated model. This, however, is a good problem for the medico-legal community to face, compared with the status quo, in which the answer is firmly 'just say no'. ❐

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