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Feature

Is it now time to prepare psychiatry for a psychedelic future?

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Australia has just rescheduled two drugs controlled under the United Nations Psychotropic Drug Conventions, psilocybin and MDMA, as treatments for treatment-resistant depression and post-traumatic stress disorder respectively. This feature explores the reasons for these developments, the opportunities and challenges they provide to psychiatry communities and how along with health systems these communities might respond to these developments.

Keywords
Psychedelics; psilocybin; PTSD; depression; MDMA.

The last few decades have seen a resurgence in research on psychedelics such as psilocybin, lysergic acid diethylamide (LSD), NN-dimethyltryptamine (DMT) and the entactogen 3,4-Methyl enedioxy methamphetamine (MDMA, commonly known as ecstasy [tablet form] and molly or mandy [crystal form], both in terms of neuroscience and their potential as clinical treatments. For example, there are more than ten modern studies of psychedelics, particularly psilocybin, in depressive disorders and addictions, and a similar number for MDMA in post-traumatic stress disorder (PTSD). These trials are uniformly positive in terms of clinical benefits and drug tolerability, findings which have undermined the historic assertion that these drugs have no clinical value and are very harmful. Thus, control at the most stringent level under the United Nations Conventions has been shown to be unwarranted. This, coupled with the paucity of new drug treatment innovations in psychiatry, has led to significant changes in attitude by regulators and policymakers in some countries.

In Australia, the Therapeutic Goods Administration (TGA), the equivalent of the UK Medicines and Healthcare Regulatory Authority (MHRA) or the USA Food and Drugs Administration (FDA), decided in February 2023 that psilocybin and MDMA will be moved to schedule 8 to allow approved psychiatrists to use them for individuals who have failed two or more previous therapies.[1] So, from 1 July 2023, psilocybin has been prescribable for treatment-resistant depression, and MDMA for treatment-resistant PTSD. Of particular relevance to psychiatry is that under the new Australian regulations, treatment can only be given under the supervision of an authorised psychiatrist who will take responsibility for prescribing and overseeing the therapy. This presents both a huge opportunity as well as a significant challenge to psychiatry in Australia.

In the USA, President Biden has stated that both MDMA and psilocybin will be psychiatric treatments in the near future, and some US states (Oregon and Colorado) have recently legalised psilocybin for personal use and are making it available for therapy. Several Latin American countries now allow DMT in the form of ayahuasca for therapeutic use, which has been taken up by war veterans with mental illnesses with good patient-reported outcomes.[2] In the UK, there have been calls for a rescheduling of these drugs (equivalent to reclassification in Australia), including a letter from leading members of the Royal College of Psychiatry,[3] and the situation is currently under examination by the UK Advisory Council on the Misuse of Drugs (ACMD). In the Netherlands, a committee has just been set up[4] to explore accelerated access for MDMA therapy.

Why this has happened

First, medicine development for mental health has been in a period of stagnation. There have been very few major conceptual advances in the pharmaceutical treatment of mental illness for nearly 50 years. The treatments we currently use for schizophrenia, depression, anxiety and ADHD are all derivatives of drugs discovered in the 1950s. Though newer, safer versions of these are now the mainstay of psychiatric psychopharmacology, there has been little, if any, improvement in efficacy, and many people do not respond adequately. The one exception is ketamine, the 1970s anaesthetic with psychedelic-like properties, that has recently been shown to have rapid antidepressant effects in treatment-resistant depression, for which the enantiomer esketamine has now been approved as a treatment.[5]

Second, over the past 20 years, there has been a resurrection of interest in classic psychedelics (particularly psilocybin and LSD), including MDMA. There are many drivers for this. One is the much better understanding of the uniqueness of these compounds revealed by neuroimaging and molecular pharmacology studies.[6] Another is the recognition that the extreme severity of the controls that these drugs are subject to (i.e. Schedule 1 in the UK) is disproportionate to their harms.[7,8] To justify this toughest level of scheduling in the late 1960s, the harms and dependence potential of these drugs were exaggerated and their clinical value actively denied, despite much literature from the 1950s and 1960s showing their utility in clinical practice.[9] Small modern studies have confirmed remarkable efficacy of just one or two administrations of these drugs, with psychological support in treatment-resistant conditions such as depression and addictions (psilocybin[10–13]) and PTSD (MDMA[14]). All practising psychiatrists are aware that these are areas of severe mental illness where current treatments fail a significant proportion of patients. There are other potential benefits of psychedelic therapy, with growing evidence of value in a range of internalising disorders – for example, psilocybin for anorexia nervosa, PTSD, obsessive–compulsive disorder and body dysmorphic disorder, and MDMA for social anxiety in autism.

Why not wait until a marketing authorisation (licence) has been awarded?

At first sight, this is a reasonable question because most prescription medicines in use in Western psychiatry have been developed

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through this conventional regulatory route. Usually, private sector pharmaceutical companies conduct a series of double-blind randomised clinical trials, and if these reach the required size of effect, then the medicine is eligible for a marketing authorisation (a 'licence') in a given country. This then means they can be prescribed by psychiatrists if patients or the healthcare system can afford them.

However, for a number of reasons described below, there is no guarantee that this will happen with psychedelics and MDMA, and even if it does, many people will suffer and some will die by suicide in the intervening years. Providing data for the usual regulatory approval pathway that requires at least two randomised controlled trials (RCTs) usually costs many hundreds of millions of pounds per medicine, so few are conducted. Moreover, the decision on what indication should be tested is a commercial one made by companies and investors, rather than being based on medical needs; cancer treatments are seen as more profitable than psychiatric ones. This and the lack of novel therapeutic targets are major factors in the decline of psychiatric medicines research.

The decision about which country a company will make a marketing application to is usually determined by the population size and income, so low- and middle-income countries are at the end of the queue and may wait for decades to gain access, if they ever do. Incidents like the recent Turkish/Syrian earthquake and the wars in Ukraine and Sudan have left many hundreds of thousands of people with PTSD and/or depression, that could benefit from new treatments that they are unlikely to access under the current system.

For these reasons, many patient and doctor groups are seeking alternatives to this pharmaceutical company-centric model. Already psychiatrists in many countries are using ketamine 'off licence' to treat people with resistant depression. There is now comparable evidence of safety and efficacy for psilocybin and MDMA to allow, with the patients' informed consent, competent clinicians to try them out 'off licence'as well as in severe illnesses when other treatments have failed. One of the main arguments from patients and their carers is the distress that they cannot access treatments of proven efficacy until a company chooses to market them; these people are totally disempowered. In Australia, the issue of drug supply outside the usual drug company medicine marketing model was solved by a charity sourcing the medicines from accredited manufacturers (see Box 1). This model could be used elsewhere.

What does psychiatry need to do?

Given the rapidly emerging body of evidence of efficacy for psilocybin and MDMA, people's great need for innovative treatments and the move towards approval in some countries before licences are awarded, it seems likely that these two drugs will become a part of psychiatric practice for many in the foreseeable future. The psychiatry profession and practising psychiatrists need to prepare for this.

The profession needs to support patient access according to the challenges in each country. We cannot deal with each in detail, so we will use the UK as an example as it has conducted some of the most important studies in the neuroscience and clinical effects of these compounds. But despite all this, the UK lags behind Australia and the USA in regulatory reform, even though many professional groups including leading figures in UK psychiatry[3] and patient charities are arguing for it. The Advisory Council on the Misuse of Drugs (ACMD) was asked several years ago to review and make recommendations to improve this situation, but they appear to be acting under the misperception that a marketing authorisation generated by a pharmaceutical company is necessary to change the Schedule 1 status of these compounds in the Misuse of Drugs Regulations.[16] This is incorrect. For example, with medical cannabis in 2018, the then UK Chief Medical Officer decided there was enough real-world evidence to move cannabis to Schedule 2 without waiting for the ACMD.[17] There is now indubitably better evidence for psilocybin and MDMA in their respective Australian-approved indications than there was then for medical cannabis.

Of course, there would have to be appropriate regulatory controls, such as a register of practitioners and supervised data collection for efficacy and adverse effects, as are being set up in Australia (see Box 1). This could be conducted by the Royal College of Psychiatrists in a similar manner to how it oversees electroconvulsive therapy (ECT) treatment centres.

Box 1 Current plan for the provision and output assessments of psychedelic treatment in Australia

This provides a model for how psychedelic medicines might be rolled out in the UK and other jurisdictions without pharmaceutical company marketing authorisation.

Step 1 – medicine supply

As psilocybin and MDMA will be used as unregistered medicines, good manufacturing practice (GMP) quality drug substance will be provided to licensed pharmacies by a third party. The treating psychiatrist will prescribe the medicine on a named patient basis from a licensed pharmacist, though the medicine could also be provided by pharmaceutical companies.

Step 2 – patient selection and approvals

Only people with treatment-resistant depression or treatment-resistant PTSD will be eligible after assessment by a treating psychiatrist who is an authorised prescriber for these medicines under the Australian Therapeutic Good Administration's authorised prescriber scheme. Treatment resistance will be defined by documented failure to respond to at least two previous treatments, one of which must be an adequate course of a registered medicine.

The psychiatrist will take clinical responsibility for patient diagnosis, screening, writing the prescription, overseeing other therapists, drug administration and follow-up.

Step 3 – treatment procedures

People will be given the medicines according to standard procedures derived from the MAPS (MDMA) and Imperial College (psilocybin) trials, which include a preparation session prior to the treatment day, the treatment day itself, and on the next day a psychotherapeutic session to help the individual make sense of the treatment day (often called an integration session). This treatment regime will be repeated up to once more for psilocybin and up to twice more for MDMA at no less than monthly intervals. Subsequent medical or psychology follow-ups will be according to clinical need.

Step 4 – data collection and analysis

An independent data management and oversight group will be set up. Patients' data on prior treatment and the outcomes of the psychedelic therapy will be entered into a central database with appropriate safeguards against identification. Clinical ratings by the patient and the psychiatrist will be conducted before and then at regular intervals after treatment. Measures of quality of life and sleep will also be taken weekly. This is modelled on the UK Drug Science database of over 4000 people using medical cannabis, available at https://www.drugscience.org.uk/t21data/. The database will be made available for other research on receipt of scientifically legitimate expressions of interest, and available also to the TGA. Statistical analysis will include Bayesian methodology that has been used to demonstrate the power of psilocybin therapy (see Szigeti and Nutt).[15]

Step 5 – reporting of results

Data will be reported on a regular basis, ideally at least every 3 months, in the public domain through a dedicated website and through peer-reviewed papers.

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Implications of psychiatry training and professional development

We suggest that implementation of these novel treatments is likely to invigorate the profession with a fresh approach and to provide hope for individuals with intractable conditions. Many young psychiatrists in training are disillusioned by the lack of progress in psychiatric treatments over the past decades and see psychedelics as giving them, as well as their patients, new therapeutic tools. Brain imaging evidence reveals that psychedelics work through very different brain pathways than conventional antidepressant medicines and thus may work where these have failed.

The fact that psychedelic therapy involves psychological as well as pharmacological intervention for severe mental illness means that psychiatrists are the best trained and equipped group to deliver this new therapy. This modern model of psychiatric treatment has the potential to help recruitment to our profession by enhancing these two key therapeutic elements of our profession. We should seize the opportunity and prepare for these treatments being made legal soon. How are we going to do this?

Psychiatrists need to be supported in the implementation of this treatment by boosting capacity and enriching capability. Better systematic training and education directly relevant to these contemporary practices need to be integrated into ongoing training as soon as possible, so that practitioners feel confident to deliver treatment. This will help to allay practitioner anxieties about its methodology, safety and scientific credibility, and will change attitudes. It is largely the lack of confidence by practitioners who feel unsupported that has resulted in National Health Service (NHS) practitioners choosing not to prescribe medicinal cannabis.

Collaboration and communication between clinical specialists, educators and managers is a necessity to fulfil our moral duty of care to severely ill people. By utilising innovative technologies, many of the educational and administrative tasks can be undertaken remotely, and we can learn from other countries, such as Australia (see Box 1), as to how to coordinate the delivery of excellent treatment.

It is up to the gamut of professionals and organisations – for example, Royal College of Psychiatrists, the Chief Medical Officer, ACMD and other groups, to take the initiative early. We believe our UK College should convene a working group comprising, for example, adult general, old age and addiction psychiatrists, to begin considering ways we could implement this therapy. We need to be ready for a change in the law which would signal a turning point in the provision of better treatment for some of the most incapacitating illnesses in medicine.

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