RECENT DEVELOPMENTS INVOLVING PSYCHEDELICS
In recent years, there has been a renewed interest in the therapeutic use of some psychedelic substances, in psychedelics-related tourism and in self-therapy with psychedelics, linked with experiences of spiritual awakening and mindfulness.

There have also been policy developments in some jurisdictions allowing for the use of psychedelics for medical and non-medical (or quasi-medical) purposes.

In addition, there is a growing commercial interest in capitalizing on the psychedelics-related developments in the different spheres.

Overall, the pace of these developments is unprecedented in the area of drug policy and some developments may outpace the scientific evidence on therapeutic use of psychedelics.

It is in this context that the present section discusses recent developments surrounding the therapeutic, spiritual and non-medical use of a number of substances grouped under the term “psychedelics” as covered in the current debate and literature, although some of them may not be considered to be classic psychedelics.

The psychedelics being discussed in the current debate on their use include:

- Classic hallucinogens or psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT) and mescaline
- Entactogens, such as 3,4-methylenedioxymethamphetamine (MDMA)
- Dissociative anaesthetics, such as phencyclidine (PCP) and ketamine

While there are hundreds of more substances classified as hallucinogenic or psychedelic, including NPS with hallucinogenic effects, this section does not cover the issues around non-medical use of those substances.
establishments which are directly under the control of their Governments or specifically approved by them. There are psychedelics such as ketamine that are not under international control, but they have been subject to national control in some countries. The Convention grants exceptions to some of the control provisions for plants that contain psychedelics and that are “traditionally used by certain small, clearly determined groups in magical or religious rites”. To apply for this exception, a State must, at the time of signature, ratification or accession, make reservations concerning these plants and their traditional use. It is only the active compounds, such as mescaline and psilocybin, that are placed under international control, and not the traditional plants containing psychedelics themselves (e.g. ayahuasca, iboga and peyote).

FIG. 4 WHAT ARE PSYCHEDELICS?
Psychedelics are a diverse group of substances that induce distorted states of consciousness, perception, thinking and feeling, accompanied by different degrees of auditory or visual hallucinations.

In medical research, three broad groups of psychedelics are currently being investigated on the basis of their mechanism of action and effects: classic psychedelics, MDMA (entactogens) and dissociative anaesthetics. The classic psychedelics include LSD, psilocybin, dimethyltryptamine (DMT) and mescaline. While the mechanism of action of most classic psychedelics is complex and not fully understood, in general they act as agonists (full or partial) of the serotonin 5-HT receptors, increasing the availability of serotonin in the body. Many classic psychedelics are naturally occurring, but can also be synthesized from plant-derived materials. For instance, mescaline is derived from the peyote cactus and psilocybin from numerous species of mushrooms. DMT and many of its analogues can be synthesized, but DMT is found in numerous plants indigenous to South America. The plant-based psychedelic brew ayahuasca, for example, contains DMT, as well as monoamine oxidase inhibitors (MAOIs), which block the breakdown of DMT in the liver and thereby facilitate its hallucinogenic effect. LSD, on the other hand, is a synthetic compound that was first synthesized in 1938. Many of the plant- and fungi-based psychedelics have been used traditionally for millennia in spiritual or folk healing rituals in many regions, but they have been better documented in the Americas.

The second group of psychedelics, known as entactogens, includes MDMA, which, in addition to producing effects that are similar to those of amphetamines, also acts as a serotonin-releasing agent and has effects that may be similar in some ways but are substantially distinct in others, from the classic psychedelics. For example, unlike psychedelics, MDMA enhances the release of oxytocin, which is considered likely to be responsible for its subjective effects.

The third group of substances, which are not considered classic psychedelics and are known as dissociative anaesthetics, includes phencyclidine (PCP) and ketamine. Although currently there is no clinical use of PCP, it was introduced as an anaesthetic agent in 1950; it was, however, discontinued due to therapeutic safety concerns. Ketamine was introduced as a safer alternative to PCP and is widely used as an anaesthetic for medical procedures, particularly in paediatric and veterinary medicine. Both PCP and ketamine act as antagonists to the NMDA receptor complex and in part contribute to the cognitive or dissociative changes they produce.

Psychedelics, in general, rank lower in the degree of “abuse liability and dependence potential” than substances such as opioids, psychostimulants, cannabis or alcohol. However, a dependence syndrome has been identified in a small percentage of people who use psychedelics. Except for a few substances, such as DMT, tolerance to both the physical and psychological effects of psychedelics develops rapidly. The psychoactive effects do not occur after three to four days of repeated use and may recur only after several days of abstinence. Repeated use of PCP can lead to tolerance and the development of a substance use disorder that includes a withdrawal syndrome when use of the substance is stopped.
What does scientific research currently say about the effect of medical and non-medical use of psychedelics?

Medically supervised use

Given the increasing burden of disease attributed to mental health disorders globally, a relatively recent wave of clinical trials, mainly in high-income countries, is presenting early yet promising results on the potential use of psychedelics to treat a range of mental health disorders in combination with conventional psychotherapies. The selected psychedelics are being considered particularly for patients with severe mental health disorders, such as PTSD, or those who are resistant to, or cannot tolerate, the conventional treatment interventions involving pharmaceutical drugs such as selective serotonin reuptake inhibitors or other non-pharmaceutical interventions and psychotherapies. As at February 2023, there were 450 registered clinical studies on the use of psychedelics, conducted mainly in the United States, Canada and Europe, that are looking into the therapeutic effects of psychedelics. Many of these clinical trials involve multidisciplinary teams and different approaches.

Most of the major ongoing clinical trials are either in phase 2 or phase 3 and, therefore, have yet to determine the efficacy and safety of psychedelics, a requirement from regulatory authorities to approve and mainstream psychedelic-assisted therapy. So far, however, the results of early phases of those clinical trials have shown the potential of psychedelics to treat several complex mental health disorders, including substance use disorders, in controlled settings, often producing sustained therapeutic effects.

Moreover, a common element that is emerging from the clinical trials is that positive health outcomes are subject to the administration of the psychedelic substance under strict clinical guidelines in formal settings, including with the direct supervision of a trained professional following appropriate screening and controls, and coupled with conventional psychotherapy sessions.

The combined therapy, that is, psychedelic-assisted psychotherapy, encompasses meticulous preparation involving professionally trained psychiatrists, psychotherapists and other facilitators. The preparations include an intake and medical screening of the patient, one or multiple hours-long supervised psychedelic (administered) sessions that are guided and supervised by trained therapists, and then extensive integration sessions. These sessions are followed by conventional psychotherapies such as cognitive behavioural therapy or motivational enhancement therapy. In short, it is not the substances alone but their combination with the broader sequence of psychotherapy with trained psychiatrists and psychotherapists that ensures the therapeutic benefit. Therefore, while the ongoing research gives hope of new treatments for certain mental health disorders, it also suggests that such medical treatment will require demanding infrastructure and substantial resources, particularly in terms of psychotherapists' time.

Adverse effects arising from non-medically supervised use

The use of psychedelics is not free of risks and may cause a number of acute adverse health effects. Some people who use a psychedelic can experience an acute anxiety or panic reaction in response to the drug’s effects – commonly referred to as a “bad trip”. Other effects that people may experience after a “trip” with classic psychedelics include flashbacks, which are usually transient and innocuous experiences of the same visual distortions as those experienced during the “trip”. Severe adverse reactions to the non-medical and unsupervised use of psychedelics may involve psychiatric or somatic symptoms, especially after chronic use; such adverse reactions depend on the dose and psychedelic substance used, as well as the presence of a pre-existing risk of developing psychosis. Although their occurrence is low, two long-term effects associated with the use of classic hallucinogens include persistent psychosis and hallucinogen persisting perception disorder (HPPD). Furthermore, the unsupervised use of psychedelics in a non-conducive environment can sometimes lead to physical harm to the persons using these substances or those around them.
**TABLE 2**  Medical and therapeutic use and major clinical trials of psychedelic-assisted psychotherapy, as registered in the National Library of Medicine (United States)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Status of control or proposal for therapeutic use</th>
<th>Conditions for which clinical trials are proposed or ongoing</th>
<th>Clinical trials completed</th>
<th>Major clinical trials in 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psilocybin</td>
<td>Approved for prescription by psychiatrists in Australia in supervised settings for specific treatment-resistant mental health disorders (e.g. depression) More advanced clinical trials are ongoing for a range of disorders in North America and Europe Several states in the United States have begun approving psychedelic therapies for a range of conditions</td>
<td>• Depression • Bipolar disorder • Anxiety (especially in patients with terminal illness such as cancer) • PTSD • Obsessive-compulsive disorder (OCD) • Eating disorders • Cluster headaches • Migraines • Alzheimer’s disease • Parkinson’s disease • Post treatment Lyme disease • Treatment of alcohol, tobacco, methamphetamine and opioid use disorders</td>
<td>Multisite phase 2 trials have been completed in the United States and Ireland</td>
<td>Phase 3 clinical trials on treatment-resistant depression with psilocybin-assisted therapy in the United States Phase 2 clinical trials for binge eating disorders in the United States Phase 2 trial for PTSD among veterans in the United States and Canada</td>
</tr>
</tbody>
</table>

| DMT and 5-MeO-DMT | DMT research is less advanced and in early stage pre-clinical and clinical trials | • Depression (including major depressive disorder, and among terminally ill patients) • Depression and anxiety in Parkinson’s disease • Chronic pain • Substance use disorders (alcohol and cocaine) | Phase 2 clinical trials for treatment-resistant depression and major depressive disorder completed in the Kingdom of the Netherlands and phase 2 trial for major depressive disorder in the United Kingdom Phase 2 trial for major depressive disorder in cancer patients in the United States | Phase 2 trials for treating major depressive disorder with DMT-assisted therapy in the United States |

| LSD | Early-stage pre-clinical and clinical trials | • Depression • Illness-related anxiety • Cluster headaches • Attention deficit hyperactivity disorder (ADHD) | Phase 2 clinical trials for anxiety disorders and major depressive disorder completed in Switzerland | Phase 2 clinical trial for cluster headaches and phase 2 trial for ADHD in Switzerland |

| MDMA | Granted "Breakthrough Therapy" designation by the United States Food and Drug Administration (FDA) in 2017 for a development programme for MDMA for the treatment of PTSD | • PTSD • Autism spectrum disorder • Obesity • Mood disorder • Anxiety • PTSD and opioid use disorder, after childbirth • Substance (alcohol) use disorder • Eating disorder | Phase 3 clinical trials for PTSD completed in the United States and phase 2 trials completed in Canada, Israel and Switzerland | Second phase 3 clinical trial to treat PTSD with MDMA in the United States, Canada and Israel |

| Ketamine | The only substance among these psychedelics that is not under international control is being studied in the United States for a wide range of indications, other than its main use as an anaesthetic First approved ketamine-derived spray licensed for the treatment of treatment-resistant depression in the United States by FDA in 2019 Fast-track designation in the United Kingdom | • Depression (also major depressive disorder) • Bipolar disorder • PTSD • OCD • Obesity • Anxiety • Delirium • Chronic daily headaches • Suicidal ideation • Epilepsy • Substance use disorders (alcohol, cannabis, cocaine, tobacco, opioid) • Gulf war syndrome • Autism spectrum disorder • Acute and chronic pain • Parkinson’s disease | Phase 2 clinical trials for treatment-resistant depression completed in multiple sites in Canada and the United States Phase 2 trial for Rett syndrome in the United States Phase 2 trial for OCD in the United States Phase 2 trial for PTSD in the United Kingdom Phase 2 clinical trials for alcohol use disorders completed in the United States and the United Kingdom, and opioid and cocaine use disorders in the United States | Phase 3 clinical trial for treating alcohol use disorders with ketamine-assisted psychotherapy in the United Kingdom |


*Note:* The database is maintained by the National Library of Medicine of the National Institutes of Health (NIH). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study. Studies, not only limited to the United States, are generally submitted to the website (that is, registered) when they begin, and the information on the site is updated throughout the study. In some cases, the results of the study are submitted after the study ends.
Traditional Indigenous medicine is protected by law in a few countries (the constitutions of the Plurinational State of Bolivia and Ecuador, for example, include regulations specific to Indigenous traditional medicine) and is recognized under some multilateral frameworks. Given the various developments related to the therapeutic use of psychedelics, and the use of psychedelics outside the settings of traditional spiritual rites, there are increasing concerns among many Indigenous nations regarding “cultural appropriation of their traditional medicines, a lack of recognition of the sacred cultural positioning of psychedelics within their communities and cultures, the exclusionary practices in research and scale up endeavours and the threat to their intellectual property rights with patents of traditional Indigenous medicines”.

Apart from concerns regarding the appropriation of Indigenous traditions, there can be other unintended or adverse consequences arising from the use of psychedelics in touristic retreats. These retreats may not be regulated in terms of their practices, such as screening of the persons participating, in terms of the availability of trained facilitators to administer the psychedelic substance or in terms of the level of dosing. Some psychedelics may not be well tolerated or suited to some individuals, especially those with a pre-existing mental health disorder such as a psychotic disorder or a history of mania. There are also concerns regarding instances of abuse, including sexual abuse by providers or guides at psychedelic retreats, and different groups have called for greater awareness of such circumstances to reduce the risks, and for caution about referrals to retreat centres.

Unsupervised self-therapy

In addition, many studies have documented the experiences of people in the unsupervised use of full doses or microdoses of psychedelics as self-medication to treat mental health disorders such as anxiety, depression or PTSD, or even to manage chronic pain, highlighting varying frequency of use and a range of doses for such purposes. However, the precise dose and concentration of psychedelics required by patients to achieve the therapeutic benefit they are seeking are yet to be established through scientific evidence.
In recent years, social media and Internet discussions have played a vital role in the growing visibility of microdosing practices as a subculture of psychedelic use. Microdosing involves ingesting any of the psychedelics in amounts that are considered below the levels required to produce a hallucinogenic effect, typically less than one tenth of the full dose of a psychedelic substance.

The practice of using repeated minimal doses of psychedelic substances is still under-researched, and there is limited clinical evidence of its effectiveness or safety. However, there are concerns that such practices of self-therapy can result in a “bad trip” or physical harm to the user; furthermore, among vulnerable individuals who have not been screened for pre-existing conditions, the use of such substances may precipitate a mental illness such as psychosis.

Non-medical use of psychedelic substances

The non-medical use of psychedelic substances is not uncommon. “Ecstasy” or MDMA remains a common substance used in recreational and nightlife settings. In 2021, 20.2 million people, or 0.4 per cent of the global adult population, were estimated to have used it in the past year. There are no global estimates of the use of other psychedelic substances, but many countries report their (non-medical) use. The non-medical use of ketamine in recreational settings is also common and reported by many countries in Europe and North America, as well as a continuing concern in South-East Asia, where it is mostly sourced through illicit production.

The use of classic psychedelics, mainly LSD, is also not uncommon and has been reported by many countries in Europe and the Americas. However, it is difficult to ascertain whether the self-reported use of psychedelics in national surveys is part of self-therapy or a pattern of personal spiritual exploration, or purely for recreational purposes.
**Regulatory developments related to psychedelics**

The recent reports of clinical trials of therapies incorporating psychedelics have encouraged different advocacy and commercial interest groups and the public, mainly in high-income countries, to push for fewer restrictions on access to, and the use of, psychedelics, including for personal use as self-therapy or for recreational purposes. There is also a growing commercial interest in capitalizing on these developments, especially with the outcomes of clinical trials; forecasts for 2028 have estimated a market for ketamine-assisted therapy valued at over 1 billion dollars and a market for MDMA-assisted therapy valued at over 2 billion dollars in the United States alone.

**Speeding up medical use**

At the federal level in the United States the possession and distribution of many psychedelic substances, including those controlled by the 1971 Convention on Psychotropic Substances, are illegal except for research purposes. In the context of a high burden of mental health disorders and suicides including among veterans, and considering preliminary evidence supporting efficacy and safety in treating various conditions, research on medical use of psychedelics has been accelerated with the Food and Drug Administration in 2017 granting the “breakthrough therapy” designation for a development programme for MDMA for the treatment of PTSD as well as for psilocybin to treat depression, and approval of esketamine (the S enantiomer of racemic ketamine) nasal spray for...

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**MAP 1 Policy and regulatory developments related to psychedelics in the United States, 2023**

![Policy and regulatory developments related to psychedelics in the United States, 2023](image)

*The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the United Nations.*

*Source: Psychedelics Legalization and Decriminalization Tracker - Psychedelic Alpha.*

*Notes: The map shows regulatory developments as at 3 April 2023. At the federal level, the possession of psychedelics is illegal throughout the United States unless authorized to a properly licensed researcher, or for a purpose approved by the federal Food and Drug Administration, regardless of state-level programmes or initiatives purporting to authorize such use.*
Monitoring ongoing trends

The discussion surrounding access to and the use of psychedelics is advancing, sometimes beyond the realms of their therapeutic use and the outcomes of clinical research. Although research on the supervised clinical use of psychedelic substances has developed in the last 20 years, best practices, clinical guidelines and protocols for the medically supervised administration of psychedelics are yet to be developed. The risk is that the perception of psychedelics as good remedies for mental health disorders (strongly advocated for by a growing number of advocacy groups and commercial interests) will move faster than scientific evidence, opening up the market to unsupervised self-medication and recreational use before supervised therapeutic use is established. This may even undermine the further development of psychedelic-assisted psychotherapy. With a supervised medical treatment coupled with psychotherapy, which is likely to require substantial resources, including trained professionals and infrastructure, there is also the risk that the medical treatment may not be accessible to all. This may trigger the development of an underground and unsafe market for such therapies, with the inherent risks of misuse and abuse of an unregulated practice. Some of the policy developments taking place, for instance, in some jurisdictions in the United States, and even retreats catering to psychedelic tourism, or commercial interests, are outpacing the clinical evidence of the therapeutic benefits of psychedelics. All of these factors may allow the development or expansion of markets with little or no regulation or monitoring of the quality of substances and of the “therapies”, which may further facilitate the unsupervised self-therapeutic, non-medical and recreational use of psychedelic substances.
Notes and references


4 Ibid.


7 However, there are many other psychedelics, including NPS with psychedelic effects, that were identified at a later stage and may not be under international control.


10 Carhart-Harris and Goodwin, ‘The Therapeutic Potential of Psychedelic Drugs’.


12 Tupper et al., ‘Psychedelic Medicine’.


16 For information on ketamine, see the section on ketamine in the present report and for the non-medical use of MDMA, see the online segment of the *World Drug Report* 2023.


19 Article 32, para 4 ibid.

20 Article 32, para 2, 3 and 4 ibid.

46 In the first phase 3 clinical trial treating PTSD with MDMA-assisted therapy, 88 per cent of the patients with severe PTSD who received MDMA-assisted therapy had a 50 per cent or more reduction in their symptoms and 67 per cent of the patients no longer met the diagnostic criteria for PTSD. While clinical trials involving psilocybin have been less promising, the John Hopkins University clinical trial found that psilocybin was four times more effective than SSRIs for treating depression. Source: James Halifax, “5 Most Important Psychedelic Clinical Trials in 2022”, Psychedelic Spotlight, 30 March 2022.


48 Based on the database search of: psychedelics - List Results - ClinicalTrials.gov.


51 Efficacy refers to a drug’s ability to produce the desired results (treating the condition), while safety refers to the type and likelihood of adverse effects that a person may experience after administration of the drug.

52 Tupper et al., ‘Psychedelic Medicine’.

53 Brain Rush et al., ‘Psychedelic Medicine: A Rapid Review of Therapeutic Applications and Implications for Future Research: Key Findings’ (Homewood Research Institute, October 2022).

54 Carhart-Harris and Goodwin, ‘The Therapeutic Potential of Psychedelic Drugs’.

55 Fuentes et al., ‘Therapeutic Use of LSD in Psychiatry’.


61 Tupper et al., ‘Psychedelic Medicine’.


64 Felix Müller et al., ‘Flashback Phenomena after Administration of LSD and Psilocybin in Controlled Studies with Healthy Participants’, Psychopharmacology 239, no. 6 (June 2022): 1933–43.


67 Meyer and Quenzer, Psychopharmacology.

68 World Health Organization, Neuroscience of Psychoactive Substance Use and Dependence.

69 HPSS includes experiencing hallucinations, other visual disturbances (such as seeing halos or trails attached to moving objects) and symptoms mistaken for neurological disorders.

70 NIDA, ‘What Are the Effects of Common Dissociative Drugs on the Brain and Body?’

71 Ibid.


74 Schultes, Hofmann, and Rätsch, Plants of the Gods.


77 These substances include datura, atropa belladonna and cannabis resin.


88  Regulation to law 459 of ‘Constitución Política del Estado (CPE) - República de Bolivia’, December 2007.
90  These include, for instance, ILO Convention No. 169; the United Nations Declaration on the Rights of Indigenous Peoples; the American Declaration on the Rights of Indigenous Peoples; the Convention on Biological Diversity; the Nagoya Protocol; and the Sharm El Sheikh Declaration: Investing in Biodiversity for People and Planet (2018).
93  These concerns led representatives of Indigenous communities to come together between October 2021 and March 2022 to review the different developments related to the use of psychedelics beyond their traditional use and the effects of the “psychedelic industry” on Indigenous communities, and to develop a consensus for an approach to address “traditional indigenous medicine ethically in the West”.
94  Celidwen et al., ‘Ethical Principles of Traditional Indigenous Medicine to Guide Western Psychedelic Research and Practice’.
97  Breeksema et al., ‘Psychedelic Treatments for Psychiatric Disorders’.
100  Rush et al., ‘Psychedelic Medicine: A Rapid Review of Therapeutic Applications and Implications for Future Research: Key Findings’. 
105  Anderson et al., ‘Psychedelic Microdosing Benefits and Challenges’.
107  Grinspoon, MD, ‘The Popularity of Microdosing of Psychedelics’.
108  Ibid.
109  See the online segment of the World Drug Report 2023.
110  See section on Ketamine in the present booklet.
114  SAMHSA, ‘Results from the 2021 National Survey on Drug Use and Health: Detailed Tables:’ (Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration,., 2022). 
117  Office of Mental Health and Suicide Prevention, ‘2022 National Veteran Suicide Prevention Annual Report’ (United States Department of Veterans Affairs, September 2022).
118  Food and Drug Administration “breakthrough therapy” designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint.
121  Food and Drug Administration, ‘FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at
a Certified Doctor’s Office or Clinic’, Office of the Commissioner, FDA (FDA, 24 March 2020).


124 In Oregon, the supervised use of psilocybin allows anyone aged over 21 to access the drug, with or without a mental health diagnosis, as long as trained facilitators are present during the session. The consumption of psilocybin must take place at a licensed service centre. The certification programmes for facilitators are open to anyone who has a high school diploma and has passed a background check.


126 In Colorado, proposition 122 was voted for in the November 2022 elections, which decriminalizes the personal possession, growing, sharing and use, but not the sale, of five natural psychedelic substances by individuals aged 21 and over. By late 2024, the state will allow the supervised use of psychedelics at licensed facilities, the regulatory structure for which is being developed.

127 Pardo et al., ‘Psychedelics and Veterans’ Mental Health’.