EUDA
EUROPEAN UNION DRUGS AGENCY

Frequently asked questions (FAQ): therapeutic use of psychedelic substances

Context

Recent years have seen a growing public and clinical interest in the potential therapeutic use of a number of psychedelic substances, including some novel and little-known substances. A number of jurisdictions outside the EU have begun regulating the use of psychedelics for medical and therapeutic purposes, while significant commercial interest has arisen in this area, evidenced through the appearance of so-called 'psychedelic retreats' in a number of countries. An increasing number of clinical studies are exploring the potential of a range of psychedelic substances for different mental health conditions. Some research appears promising; however, generalising in this area is difficult, partly because of the large number of substances under review and partly because of the wide range of conditions that are being studied. Taken together, these developments have given rise to questions at the policy level relating to the risks associated with the increase in experimental use of these substances, their potential to cause harm, and appropriate policy responses.

In Europe, there are now indications of changes in patterns of use of psychedelics, including an increase in unregulated and/or illegal practices in which these substances are used as part of a wellness, therapeutic or spiritually oriented intervention (EMCDDA, 2023). Some of these psychedelic-related practices and interventions appear to market their services by referencing the latest developments in medical research, either directly in relation to the substances or indirectly by providing links to research and scientific papers.

Due to the limited information that currently exists in this area, the European Union Drugs Agency (EUDA, former EMCDDA) has launched a project to increase our understanding of key developments and respond to concerns raised by policymakers. These FAQs aim to respond to some of the key questions raised and provide a better understanding of ongoing developments in this field. While the focus of these FAQs is on the therapeutic use of psychedelic substances, additional questions have been added to provide important contextual information on related developments in this area, such as the prevalence and patterns of use of psychedelic substances in Europe, the presence of unlicensed and illegal psychedelic practices, and developments in clinical research.

What are psychedelic substances?

There are different ways in which psychedelic substances can be categorised, usually determined by their mechanisms of action (i.e. how they work in the brain). One common way of categorising these substances, particularly in clinical trials involving psychedelics for mental health conditions, is to divide them into typical (or classical) serotonergic psychedelics and atypical psychedelics (EMA, 2023). Other categorisations have also been proposed, such as separating psychedelic substances from dissociative drugs and 'other' substances that affect various brain functions and may cause psychedelic and/or dissociative effects (NIDA, 2023). As research is quickly progressing in this area, and understanding of the properties of these substances deepens, there may be future changes in their classifications.

Typical or classical serotonergic psychedelics generally include, but are not limited to:

- LSD (lysergic acid diethylamide)
- psilocybin (sometimes referred to as 'magic mushrooms')
- DMT (N,N-Dimethyltryptamine, a component of 'ayahuasca' and/or 'yagé')
- 5-MeO-DMT (5-Methoxy-DMT, a component of Bufo alvarius venom or 'yoppo')
- mescaline (sometimes referred to as 'peyote' or 'San Pedro').

Atypical psychedelics generally include, but are not limited to:

- dissociative anaesthetics, or simply dissociatives, such as ketamine, esketamine and phencyclidine (PCP, also known as 'angel dust') and their analogues, as well as dextromethorphan (DXM)
- entactogens (e.g. MDMA)
- ibogaine
- salvinorin (sometimes referred to as 'magic mint').

Classical psychedelics act on the serotonergic system in the brain, as agonists of the type 2A serotonin receptors (5HT-2A). They produce effects that impact perception, mood and cognition, and may cause visual distortions, altered sensory experiences, and a sense of expanded awareness, contributing to a complex and multifaceted effect often referred to as an 'altered state of consciousness'. The subjective effects, however, vary greatly depending on dose, but also between individuals and from one episode of use to the next within the same person.

Atypical psychedelics share some of the psychoactive effects of typical or classical psychedelics while having a distinct pharmacological mechanism of action. While atypical

psychedelics can also induce altered states of consciousness, the subjective experience may also be qualitatively distinct from what is induced by typical or classical psychedelics (Yaden and Griffiths, 2021). To date, the most commonly trialled psychedelics for mental health conditions have been (es)ketamine, psilocybin, MDMA, DMT (including 5-MeO-DMT) and LSD (see 'Why are psychedelics currently being researched in the medical field?').

There are also a number of new synthetic psychedelics, sometimes referred to as 'designer psychedelics', but there is currently little information on their risks to public health. In 2021, for example, 39 phenethylamines and 25 tryptamines, some of which could be classified as psychedelics (dependent on their mechanisms of action and subjective effects), were reported to the EU Early Warning System on new psychoactive substances (EMCDDA, 2023).

Are psychedelics controlled substances?

Currently, three UN conventions describe the basic framework for controlling the production, trade and possession of several hundred psychoactive substances (most of which have a recognised medical use). With some exceptions, most typical and atypical psychedelic substances are controlled under Schedule I of the United Nations Convention on Psychotropic Substances of 1971 (United Nations, 1971), which requires countries to enact national responses including penalties for unauthorised actions. These conventions have been signed by all EU Member States. Ketamine has not been scheduled in the UN conventions.

For more information on penalties, or rehabilitative responses, for the core offences of drug use, possession for personal use, and supply-related offences across countries in Europe, see the EUDA web page 'Penalties at a glance'. As laws differ across EU Member States and are subject to change, it is important to consult the relevant national competent authority for the most up-to-date information.

What information exists on the prevalence and patterns of use of psychedelics in Europe?

The data available suggest that, overall, the prevalence of use of most classical serotonergic psychedelics remains generally low in Europe. Among young adults (aged 15 to 34), recent national surveys show last year prevalence estimates for both LSD and hallucinogenic mushrooms (generally psilocybin) equal to or less than 1 %, although there are differences between countries (EMCDDA, 2024). Recent estimates of last year prevalence of ketamine use, an atypical dissociative psychedelic, among young adults range from 0.8 % in Romania (aged 15 to 34 in 2019) to 0.9 % in Denmark (aged 16 to 34 in 2023) (EMCDDA, 2024). An important caveat is that classical psychedelics and most atypical psychedelics are not well monitored by existing surveillance systems, meaning that it is difficult to comment with confidence on prevalence of use and recent trends. The information available does suggest, however, that in some countries, subgroups or settings, the use of some of these substances has become

more common (EMCDDA, 2024). For example, the Netherlands has reported that ketamine use has increased among young people in nightlife settings (EMCDDA, 2024).

There is more in-depth understanding of patterns of use and prevalence of MDMA, which is generally classified as an atypical psychedelic (EMA, 2023). MDMA use in Europe has generally been associated with episodic patterns of consumption in the context of nightlife and entertainment settings. General population surveys conducted by 26 EU Member States between 2015 and 2023 suggest that 2.2 million young adults (aged 15 to 34) used MDMA in the last year (2.2 % of this age group) (EMCDDA, 2024).

There are signals that patterns of use of psychedelics, both typical and atypical, are shifting in Europe. In particular, it appears that the use of psychedelics for wellness, therapeutic or spiritually oriented reasons is increasing. These uses appear to often take place in 'psychedelic retreats', although a solid understanding of these practices is currently lacking (see 'What are 'psychedelic retreats'?'). To better understand these evolving issues, the EUDA has an ongoing project on mapping the existence of psychedelic-related practices and interventions in Europe.

In addition, it has been reported that the 'microdosing' of psychedelics may be increasing in Europe, also for wellness, therapeutic or self-development reasons. There is no scientific consensus on what microdosing entails (Kuypers et al., 2019), and little is known about potential risks or health benefits. It appears that this pattern of use involves consuming a small dose of a psychedelic substance, such as LSD or psilocybin, on a periodic basis to achieve cognitive or mood-enhancing effects.

Why are psychedelics used?

Psychedelic substances are used in diverse contexts and for different reasons. This includes use in recreational settings among people who use drugs; for religious, spiritual and cultural reasons; and among certain indigenous and non-indigenous groups. Several classical psychedelic substances, such as DMT (in the form of ayahuasca) and mescaline, have a long history of ritualistic and/or religious use in collective practices across indigenous and non-indigenous groups around the world (particularly in Latin America) (NIDA, 2023). Psychedelic use in these contexts is well documented by researchers including anthropologists, where the consumption of psychedelics has been described as being a catalyst for social affiliation, cultural integration and belief (see e.g. Rodríguez Arce and Winkelman, 2021).

Clinical researchers are also investigating the therapeutic properties of a variety of psychedelics for specific mental health conditions (see 'Why are psychedelics currently being researched in the medical field?'). In conjunction, there appears to be a new wave of psychedelic use in Europe, where people are using psychedelics for wellness, therapeutic or spiritually oriented interventions (see 'What information exists on the prevalence and patterns of use of psychedelics in Europe?' and 'What are 'psychedelic retreats'?').

What are ‘psychedelic retreats’?

Psychedelic retreats appear to be part of a wide range of psychedelic-related practices and interventions that now exist in Europe. Such practices are reported to range from naturalistic/spiritual events (which appear to be commonplace for psychedelic retreats) to interventions that mimic the psychedelic-assisted therapy used in some clinical trials. Specifically, psychedelic retreats appear to be structured and guided experiences in which groups of individuals engage in the use of psychedelic substances, such as psilocybin (‘magic mushrooms’), LSD, DMT (ayahuasca), ketamine and MDMA. They are reported to take place in nature or specially designed facilities, led by facilitators or guides, and may take place over one or several days. The primary goals of psychedelic retreats appear to revolve around therapeutic, spiritual or self-development purposes. Some legal psychedelic retreats are reported to operate in the Netherlands, although in other EU Member States they generally seem to be unlicensed or illegal.

Psychedelic retreats and similar practices have a long-established tradition in Latin America and recently appear to have grown in number in Europe. As little is known about the range of psychedelic practices in Europe, the EUDA has an ongoing project to map these practices and the services they claim to offer.

What are the risks of using psychedelics?

The risks of using psychedelics depend on a number of factors, such as the substance (including dosage, potency/purity, and the presence of adulterants), patterns and settings of use, for example whether it relates to recreational patterns of use or for unregulated therapeutic purposes.

For example, there are well-documented risks related to recreational patterns of MDMA use, including acute poisonings and deaths, partly due to the presence of ecstasy tablets with a high MDMA content and partly due to adulteration of ecstasy tablets with other harmful substances (EMCDDA, 2023; Trimbos-instituut, 2023). Ketamine has been linked to various dose-dependent acute and chronic harms, including neurological and cardiovascular toxicity, mental health problems and urological complications, such as bladder damage from intensive use or the presence of adulterants.

For some psychedelics, particularly the new synthetic psychedelics, there is limited data on the risks stemming from long-term or intensive use. As with all synthetic drugs, there are inherent risks related to potency and purity when used in recreational settings, including the risks of consuming substances that have been mislabelled or mis-sold.

The specific risks of consuming psychedelics for unregulated therapeutic purposes remain poorly understood.

In the context of psychedelic-assisted psychotherapy, there appear to be unique risks related to the vulnerability of the consumer when experiencing an 'altered state of consciousness'. Specifically, research has highlighted increased vulnerability of patients, the potential for power imbalance between patients and clinicians, and subsequent risks of harm or abuse within treatment, due to the effects of the substances themselves combined with the psychotherapeutic modalities employed (McNamee et al., 2023; Meikle et al., 2024). These particular risks may be heightened in unlicensed or illegal settings (e.g. 'psychedelic retreats'), where such substances are consumed for wellness, therapeutic or spiritually oriented interventions, in the absence of trained or regulated medical professionals. The EUDA has an ongoing project with the aim of developing a better understanding of the risks related to such unregulated psychedelic practices.

In the context of clinical research with psychedelics, some mild to adverse events have been reported. Adverse events are any unwanted medical occurrences during a clinical study where pharmaceutical products were administered. Most adverse events from clinical trials with psychedelics are reported to occur during the acute effect of the substance and resolve spontaneously (such as related to acute anxiety). However, it is important to consider that there appear to be significant asymmetries in the quantity and quality of safety data that is available for different psychedelic substances (Breeksema et al., 2022). How such risks will be mitigated if these substances are used for medical treatment outside of clinical trials remains an important concern, particularly regarding reported occurrences of challenging experiences (sometimes referred to as 'bad trips') and the aforementioned issues around patient suggestibility and vulnerability to abuse.

Why are psychedelics currently being researched in the medical field?


credit: iStock

Since 2010 there has been a rapid expansion of clinical trials and other studies in the medical field involving both classical and atypical psychedelic substances for specific mental health conditions, particularly ones that are resistant to conventional treatment. Esketamine, psilocybin, MDMA, DMT and LSD have been the most frequently trialled substances. Psilocybin has, for example, been trialled in the treatment of depression (particularly treatment-resistant depression and major depressive disorder), obsessive compulsive disorder, eating disorders and nicotine and alcohol use disorders. Clinical trials conducted with MDMA have mainly focused on the treatment of post-traumatic stress disorder (PTSD), alcohol use disorder and symptoms of social anxiety in patients with autism spectrum disorder. Meanwhile, LSD has been trialled to treat end-of-life anxiety and substance-related disorders. This recent wave of clinical trials has also stimulated research with psychedelics in animal models and healthy individuals (see e.g. Carhart-Harris et al., 2012; De Gregorio et al., 2021; Odland et al., 2022) in a bid to understand the safety of psychedelic drugs as well as their underlying neurobiology and mechanisms.

According to the available data from these clinical trials, some psychedelics have shown promise in alleviating specific symptoms associated with difficult-to-treat neuropsychiatric disorders. The level of evidence appears relatively consistent when treating PTSD with MDMA-assisted therapy (see e.g. Mitchell et al., 2021). In addition, psilocybin-assisted therapy may reduce depressive symptoms in patients with treatment-resistant depression and major depressive disorder (see e.g. Goodwin et al., 2022; von Rotz et al., 2023). However, across many studies, a clear definition of the adjunct psychological intervention appears to have been limited, and as such, in some cases, it may be difficult to distinguish the interaction between the psychedelic itself and the associated therapy, and the degree to which each of these components influences results. There also appears to be limited data about potential benefits for other psychiatric indications, such as the treatment of substance-related disorders with DMT (ayahuasca) and ibogaine. A complicating factor is reported to be that a large number of studies still present methodological challenges (Butlen-Ducuing et al., 2023; EMA, 2023) and limitations, particularly related to blinding (a process designed to minimise bias by preventing participants and organisers, and sometimes those analysing the data, from knowing which treatment or intervention participants are receiving), which may compromise the interpretation of results.

What developments have taken place in relation to providing access to the medical use of psychedelic substances?

Formal regulation of the medical use of psychedelics has thus far mainly occurred outside Europe, such as in the United States and Australia. For example, the states of Colorado and Oregon have regulated some form of access to psychedelic-assisted therapies (Colorado General Assembly, 2023; Oregon Health Authority, n.d.). In Australia, the Therapeutic Goods Administration announced in February 2023 that psychiatrists will be able to prescribe MDMA for PTSD and psilocybin for treatment-resistant depression from 1 July 2023 (Therapeutic Goods Administration, n.d.).

No such legislative changes have been introduced in the EU Member States. However, there have been some developments in funding for psychedelic trials in the EU. In Czechia, for example, the Drug Action Plan 2023-2025 has earmarked funding for research with psychedelics in addiction treatment (Office of the Government of the Czech Republic, 2023). At EU level, in early 2024, the Horizon Europe programme awarded EUR 6.5 million in funding for psychedelic therapy research for treatment-resistant mental disorders in palliative care (Eccles, 2024).

Are psychedelics already available for treatment in Europe?

At the time of writing in 2024, no classical psychedelics have been approved by any regulatory mechanisms at the Member State or EU level for the medical treatment of neuropsychiatric disorders. However, one atypical psychedelic has been approved, namely esketamine, or Spravato, which has received marketing authorisation for adults with major treatment-resistant depression (EMA, 2024). Apart from this exception, the European Medicines Agency has not evaluated any marketing authorisation for a psychedelic medicine for use in patients in the EU. Separately, there appears to have been an increase in the off-label use of ketamine (Wilkinson et al., 2017) (approved for use as an anaesthetic in several EU Member States) in the treatment of depression and other diagnoses in some clinical settings across Europe. The 'off-label' use of a medicine is the application of a medicine for an indication that has not been approved, or in an age group, dosage, or route of administration different from what has been approved.

Several psychedelic substances are now reported to be at advanced stages of clinical trials and may be submitted for regulatory and medical review in future. This includes psilocybin, which has completed Phase 2 studies for treatment-resistant depression, and MDMA, which has completed Phase 3 studies for PTSD. A key issue in future, should psychedelics become available as medicines in Europe, will be funding reimbursement. As medication or treatment reimbursement procedures and costs are country-specific, this issue will have a significant impact on the availability of any authorised medicine.

References

Breeksema, J. J., Kuin, B. W., Kamphuis, J., Van Den Brink, W., Vermetten, E. and Schoevers, R. A. (2022), 'Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review', *Journal of Psychopharmacology* 36:10, pp. 1100-1117.

Butlen-Ducuing, F., McCulloch, D. E.-W., Haberkamp, M., Mattila, T., Bałkowiec-Iskra, E., Aislaitner, G., Balabanov, P., et al. (2023), 'The therapeutic potential of psychedelics: The European regulatory perspective', *The Lancet* 401:10378, pp. 714-716.

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., et al. (2012), 'Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin', *Proceedings of the National Academy of Sciences* 109:6, pp. 2138-2143.

Colorado General Assembly (2023), SB23-290 — *Natural medicine regulation and legalization*, https://leg.colorado.gov/bills/sb23-290 [last accessed 1 July 2024].

De Gregorio, D., Aguilar-Valles, A., Preller, K. H., Heifets, B. D., Hibicke, M., Mitchell, J. and Gobbi, G. (2021), 'Hallucinogens in mental health: Preclinical and clinical studies on LSD,

psilocybin, MDMA, and ketamine', *The Journal of Neuroscience* 41:5, pp. 891-900.

Eccles, M. (2024), 'EU funds first psychedelic study, in patients with incurable diseases: Magic mushrooms trial gets underway', *Politico*, 24 January 2024, [last accessed 21 February 2024].

EMA (European Medicines Agency) (2023), *Guideline on clinical investigation of medicinal products in the treatment of depression – Revision 3*, EMA/CHMP/185423/2010, Rev.3, September 2023.

EMA (2024), *Spravato*, [last accessed 21 February 2024].

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2023),*European drug report 2023: Trends and developments*, Publications Office of the European Union, Luxembourg, [last accessed 1 July 2024].

EMCDDA (2024), *European drug report 2024: Trends and developments*, Publications Office of the European Union, Luxembourg, [last accessed 1 July 2024].

Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., et al. (2022), 'Single-dose psilocybin for a treatment-resistant episode of major depression', *The New England Journal of Medicine* 387:18, pp. 1637–1648.

Kuypers, K. P., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A. and Nutt, D. (2019), 'Microdosing psychedelics: More questions than answers? An overview and suggestions for future research', *Journal of Psychopharmacology*, 33:9, pp. 1039-1057.

McNamee, S., Devenot, N. and Buisson, M. (2023), 'Studying harms is key to improving psychedelic-assisted therapy — Participants call for changes to research landscape', *JAMA Psychiatry* 1:80(5), pp. 411-412, doi:10.1001/jamapsychiatry.2023.0099.

Meikle, S., Carter, O. and Bedi, G. (2024), 'Psychedelic-assisted psychotherapy, patient vulnerability and abuses of power', *Australian & New Zealand Journal of Psychiatry* 58:2, pp. 104-106, doi:10.1177/00048674231200164.

Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G., M., et al. (2021), 'MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study', *Nature Medicine* 27:6, pp. 1025-1033.

NIDA (National Institute on Drug Abuse) (2023), *Psychedelic and dissociative drugs*, accessed 20 February 2024.

Odland, A. U., Kristensen, J. L. and Andreasen, J. T. (2022), 'Animal behavior in psychedelic research', *Pharmacological Reviews* 74:4, pp. 1176-1205.

Office of the Government of the Czech Republic (2023),*Ak?ní plan politiky v oblasti závislostí 2023-2025* [Action plan: Policies in the area of addiction 2023-2025], Prague.

Oregon Health Authority (n.d.), *Oregon psilocybin services*, Prevention and Wellness, Public Health Division, accessed on 22 January 2024.

Rodríguez Arce, J. M. and Winkelman, M. J. (2021), 'Psychedelics, sociality, and human evolution', *Frontiers in Psychology* 12:729425, doi:10.3389/fpsyg.2021.729425.

von Rotz, R., Schindowski, E. M., Jungwirth, J., Schuldt, A., Rieser, N. M., Zahoranszky, K., Seifritz, E., et al. (2023), 'Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial', *eClinicalMedicine* 56:101809.

Therapeutic Goods Administration (n.d.), *MDMA and psilocybin hub*, Australian Government, Department of Health and Aged Care, accessed on 22 January 2024.

Trimbos-instituut (2023), *Annual report 2022: Drugs information and monitoring system (DIMS)*, Trimbos-instituut, Utrecht.

United Nations (1971), *United Nations Convention on Psychotropic Substances of 1971*, United Nations, Vienna.

Wilkinson, S. T., Toprak, M., Turner, M. S., Levine, S. P., Katz, R. B. and Sanacora, G. (2017), 'A survey of the clinical, off-label use of ketamine as a treatment for psychiatric disorders', *The American Journal of Psychiatry* 174:7, pp. 695-696.

Yaden, D. B. and Griffiths, R. R. (2021), 'The subjective effects of psychedelics are necessary for their enduring therapeutic effects', *ACS Pharmacology and Translational Science* 4:2, pp. 568-572.

Acknowledgements

These Frequently Asked Questions (FAQs) were drafted with support from a technical background report written by Albino Jorge Oliveira-Maia and Carolina Seybert. The technical background report conducted a systematic review of clinical trials involving a broad range of psychedelic substances for mental health conditions, focusing on evidence of efficacy and risks.