



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA multi-stakeholder workshop on psychedelics

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Introduction

Mental health conditions are a significant public health concern that have far-reaching implications for individuals, society, and the economy. The COVID-19 pandemic has had a detrimental effect, particularly among vulnerable groups such as those with pre-existing mental health conditions. With more than one in six in the European Union (EU) now affected by mental health conditions, there is a need for novel therapeutic treatments in the field of psychiatry. However, despite significant advances in understanding the underlying causes of mental health conditions in recent years, there has been limited innovation in the development of novel treatments.

In parallel, there has been a resurgence of interest in the research of psychedelics for the treatment of mental health conditions. Psychedelics are a diverse group of substances that can produce altered states of consciousness, often characterised by changes in perception, mood and thought. While there is no definitive classification of psychedelics, they can be categorised into different classes based on their pharmacological effects (how they work in the body) and chemical structure. In the 1950s and 60s, the therapeutic potential of psychedelics in treating a range of mental health conditions was extensively researched. However, this research was abruptly curtailed in the early 1970s when psychedelics were classified as Schedule I drugs under the United Nations Convention on Psychotropic Substances, a category reserved for substances defined as having no accepted medical use and significant potential for harm and dependence. This classification made it difficult to conduct further research into their therapeutic potential, leading to a long hiatus in the development of psychedelic medicines. Over the past decade, there has been a renewed focus on exploring the therapeutic potential of psychedelics for treating mental health conditions. As a result, there is a growing body of evidence, from both clinical studies and the scientific literature, suggesting that psychedelics may be effective in treating mental health conditions such as treatment-resistant depression (TRD), substance use disorders, post-traumatic stress disorder (PTSD) and psychological and existential distress associated with end-of-life conditions.

While regulators acknowledge the therapeutic potential of psychedelics, their development programmes must uphold the same requirements and evidentiary standards that apply to all medicines. A comprehensive evidence-based assessment is necessary to evaluate their therapeutic benefits and risks. However, the characteristics of psychedelics pose specific challenges that warrant careful reflection on how to generate reliable data to support such an assessment. Furthermore, for psychedelic medicines to safely achieve their intended effects in clinical practice, appropriate settings that integrate suitable frameworks of support for patients are essential. Restrictions on the production and supply of psychedelics due to their classification as controlled drugs and generation of a valid evidence base to determine their cost-effectiveness for reimbursement, add additional layers of complexity to their implementation within the therapeutic armamentarium.

This workshop created a platform for a diverse range of expert stakeholders to engage in open, multidisciplinary, evidence-based discussions on how to address these challenges to accelerate the development of psychedelic medicines. Participants included healthcare professionals, patient advocates, academic researchers, members of learned societies and industry, as well as representatives from different European and international regulatory bodies. By fostering collaboration and knowledge-sharing, the workshop aimed to improve public health outcomes by advancing safe and effective treatments for mental health conditions.

Regulatory perspectives and developments

Key messages

- Development programmes for psychedelic medicines must adhere to existing regulatory frameworks.
- Early dialogue with medicines regulators is critical to ensure development programmes align with regulatory requirements.
- While medicines regulators are responsible for the oversight and approval of medicines, they do not regulate the practice of medicine itself.

Adherence to the EU regulatory framework

The development of psychedelic medicines must adhere to the current EU regulatory framework. As is the case for all medicines, obtaining marketing authorisation for a psychedelic medicine in the EU requires applicants to submit an initial marketing authorisation application (MAA) containing relevant quality, non-clinical, and clinical data. This MAA is then evaluated by regulatory agencies to determine the benefit-risk profile of the medicine before recommending it for approval.

EMA recognises that the characteristics of psychedelics present several challenges for the design, conduct and interpretation of clinical trials, particularly regarding the choice of placebo and/or comparator, expectancy and unblinding, determining optimal therapeutic doses and the maintenance of effect. The Agency provided provisional guidance on these aspects in the updated draft guideline on clinical investigation of medicinal products for depression¹, which now includes a section on psychedelics. This reflects the initial thoughts of EU regulators on psychedelic development programmes, based on their deliberations in the context of scientific advice. This guidance outlines that short-term randomised, double-blind, placebo-controlled phase III trials, and trials to determine the maintenance of effect, are required to establish a positive benefit-risk balance for psychedelics. However, as noted during the workshop, adequate comparators may be considered given the challenges of mitigating functional unblinding with a traditional placebo control.

Recommendations included in EU guidelines reflect the current state of knowledge in the field, gathered through procedures such as scientific advice or stakeholder engagement. It is important to note that these recommendations may evolve as new data emerges. Further EU guidance in this area will be considered once a sufficient evidence base has been established to identify the optimal approach to support drug development and characterise the benefit-risk profile of psychedelics in their proposed indications.

Developers of psychedelic medicines should engage with EU regulators early in the development process so that regulatory challenges can be addressed in a way that considers the specific features of individual development programmes. Those who are uncertain about the best approach or want to deviate from existing EU guidelines can request feedback through the Agency's scientific advice procedure. During this process, the applicant presents their proposed

¹ European Medicines Agency, Clinical investigation of medicinal products in the treatment of depression—scientific guideline. <https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-depression-scientific-guideline> (accessed 27 April 2024).

plan for developing the medicine and identifies any questions or potential solutions. EMA then responds by offering guidance on the developer's proposals. Scientific advice may relate to quality, non-clinical and clinical aspects, methodological issues, and the overall development strategy. However, it should be noted that scientific advice provided by EMA is prospective and does not evaluate completed studies or determine whether a medicine's benefits outweigh its risks.

Medicines that address unmet medical needs may be eligible for [conditional marketing authorisation](#) (CMA). This type of authorisation allows patients to access innovative therapies earlier while ensuring that the necessary safeguards are in place to assure their quality, safety and efficacy. For applicants seeking CMA, the Agency may accept less comprehensive clinical data than would normally be required, if it is deemed that the benefits of immediate availability of the medicine outweigh the risk associated with the fact that additional data is still needed. This type of authorisation is granted under the condition that the marketing authorisation holder fulfils specific obligations within defined timelines. These obligations could include completing ongoing or new studies or collecting additional data to confirm the medicine's benefit-risk balance remains positive.

Evaluating a MAA under the centralised procedure may take up to 210 days; this excludes clock stops to enable the applicant to provide additional information. The CHMP may reduce this period to 150 days on request and upon receipt of sufficient justification for an [accelerated assessment](#).

Developers of psychedelic medicines can avail of support from the Agency through other scientific and regulatory platforms and tools such as the Agency's scientific advice working party [qualification procedure](#), [innovation task force](#), [scheme for priority medicines \(PRIME\)](#), support via EMA's small and [medium-sized enterprises \(SME\) office](#) and avail of [consultations in parallel with health technology assessment boards](#).

Common themes across regulatory jurisdictions

In addition to perspectives from EMA, representatives from international regulatory agencies including the Australian Therapeutic Goods Administration (TGA), the US Food and Drug Administration (FDA) and Health Canada, shared insights into their respective approaches to the development and therapeutic application of safe and effective psychedelic medicines. Despite having different mandates, key messages emerged from regulators across all territories.

- Although a psychedelic medicine has not been approved to date, regulators have noted a growing interest in their therapeutic potential as exemplified by a sharp increase in the number of clinical trials investigating their use for the treatment of mental health conditions across all jurisdictions.
- When determining appropriate frameworks of support for psychedelic medicines, it is important to bear in mind the distinction between medicines regulators and other bodies that oversee medical practice, particularly if the treatment involves psychotherapy. While medicines regulators are responsible for approving new medicines, they do not regulate the practice of medicine itself.
- To obtain a marketing authorisation for psychedelic therapies, it is crucial to adhere to the existing regulatory frameworks that apply to all medicines within respective jurisdictions. A positive benefit-risk balance must be established.

- Medicines regulators recognise that the characteristics of psychedelics pose specific challenges in designing robust clinical trials to support marketing authorisation applications. Developers are encouraged to engage in early dialogue with regulators to ensure that development programmes align with regulatory requirements.

International developments

The regulatory landscape surrounding psychedelics is rapidly evolving. An overview of recent developments in the field was provided by international medicines regulators that participated in the workshop. These include initiatives such as the Authorised Prescriber pathway by TGA, adaptation of legislation in the US and recent initiatives undertaken by the US FDA such as dissemination of draft guidance, and Health Canada's Special Access Program (SAP).

Australia

Although psilocybin and MDMA are not currently registered medicines in Australia, as of July 2023, experienced psychiatrists have been able to prescribe them for psychotherapy-assisted treatment of TRD and PTSD, respectively, through the Authorised Prescriber pathway. This was made possible through their reclassification, for these specific indications, from Schedule 9 (prohibited substances) to Schedule 8 (controlled drugs in a medical setting). This evidence-based process took approximately two years, and the decision was facilitated by measures to ensure their safe use.

The Authorised Prescriber pathway allows practitioners who are fellows of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) to prescribe restricted substances that have not yet received regulatory approval. To become an authorised prescriber, a psychiatrist must first receive approval from a panel that evaluates applications for human clinical trials, known in Australia as a Human Research Ethics Committee (HREC). This involves obtaining approval to prescribe MDMA and/or psilocybin under a clinical protocol that incorporates a full consenting process. The clinical protocol includes robust inclusion and exclusion criteria as well as established processes to manage patient safety. The final step in the process concerns authorisation of the prescriber by TGA. Psychiatrists must demonstrate a therapeutic relationship with their patient. There are restrictions regarding the make-up of the clinical team, namely that at least one of the therapists present during active treatment is subject to professional oversight by the national clinical regulatory body.

Authorised prescribers are required to report the number of patients they have treated with MDMA or psilocybin to TGA every six months. Adverse events or defects must also be reported within fifteen days of the prescriber becoming aware of them. As of 16 April 2024, there was nine authorised prescribers in Australia.

The United States

There is a growing interest in the therapeutic potential of psychedelics in the US, as exemplified by various indicators. These include legislative actions at both federal and state levels and a significant increase in the number of psychedelic investigational new drug applications submitted to the US FDA for psychiatric-related indications.

At the federal level, the US House of Representatives included a provision in the National Defence Authorisation Act (NDAA) related to psychedelic research. This mandates that the US Department of Defence conduct studies on specific conditions like PTSD and traumatic brain injury using certain psychedelics. Moreover, several US states have recently enacted or proposed legislation related to psychedelics, which generally falls into three categories:

1. Legalisation statutes that permit the use of certain psychedelics for medical or therapeutic purposes, such as Colorado;
2. Statutes that decriminalise the possession and personal, facilitated, or supported use of certain psychedelics, such as New Jersey;
3. Laws establishing working groups to study the medical use of psychedelics, such as Texas.

Recent regulatory developments in the US include both the granting of breakthrough therapy designations by the FDA for certain psychedelics to treat mental health conditions and the acceptance of a new drug application (NDA) for MDMA-assisted psychotherapy for PTSD. Breakthrough therapy designation expedites the drug development and review process when preliminary clinical evidence suggests that a drug may provide a substantial improvement over available therapies for serious conditions. While individual breakthrough therapy designations are not disclosed publicly by the FDA, at the time of the workshop, four of these designations have been reported publicly.

Month	Drug	Sponsor	Indication
August 2017	MDMA	MAPS (now Lykos)	Post-traumatic stress disorder
October 2018	Psilocybin	Compass Pathways	Treatment-resistant depression
November 2019	Psilocybin	Usona Institute	Major depressive disorder
March 2024	LSD	Mind Medicine	Generalized anxiety disorder
March 2024	Psilocybin	Cybin	Major depressive disorder

Source: Food and Drug Administration²

In line with other regulatory jurisdictions, the FDA emphasised that psychedelics must follow the same requirements and evidentiary standards that apply to all medicines. However, given the challenges imposed by their characteristics, the FDA published a draft guidance in June 2023 summarising advice provided to sponsors regarding the development of psychedelics³. The guidance includes information regarding requirements for chemistry, manufacturing and controls, non-clinical, clinical pharmacology and clinical data, as well as information concerning the assessment of abuse potential.

MDMA-assisted psychotherapy for PTSD, which was submitted to the FDA by Lykos Therapeutics, was granted breakthrough therapy designation in 2017; the corresponding NDA is receiving priority review by the FDA. On 4 June 2024, the FDA's Psychopharmacologic Drugs Advisory Committee discussed the overall benefit-risk profile of the NDA including the potential public health impact. The advisory committee provides independent expert advice to the FDA on human drug products for use in the practice of psychiatry and related fields to help the agency make sound decisions based on the available science. Advisory committees make non-binding recommendations to the FDA⁴. While the Psychopharmacologic Drugs Advisory Committee voted

² Food and Drug Administration. Psychedelic Drugs in Psychiatry: An American Regulatory/FDA Perspective. https://www.ema.europa.eu/en/documents/presentation/presentation-american-regulatory-perspective-psychedelic-drugs-psychiatry-m-sokolowska_en.pdf (accessed 21 April 2024).

³ Food & Drug Administration. Psychiatric Disorders Program. Psychedelic Drugs: Considerations for Clinical Investigations–Guidance for Industry. <https://www.fda.gov/media/169694/download> (accessed 28 April 2024).

⁴ US Food & Drug Administration. UPDATED MEETING TIME AND PUBLIC PARTICIPATION INFORMATION: June 4, 2024: Meeting of the Psychopharmacologic Drugs Advisory Committee Meeting Announcement. <https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-time-and-public-participation-information-june-4-2024-meeting-psychopharmacologic> (accessed 14 June 2024).

against recommending FDA approval, the NDA for MDMA-assisted psychotherapy is still under evaluation by the FDA, with a final decision anticipated in August 2024.

Canada

In December 2022, Health Canada published a notice outlining their expectations for risk management measures to be implemented by sponsors of clinical trials for psychedelic-assisted psychotherapy based on best practices identified in the scientific literature⁵. These measures relate to therapists, clinical settings, informed consent and compliance with good manufacturing practices.

In January 2022, the scope of Health Canada's Special Access Program (SAP) was expanded to include restricted substances such as psilocybin and MDMA⁶. The SAP was established by Health Canada to provide healthcare professionals with access to drugs that are not approved for sale in Canada but may be required to treat patients who have serious or life-threatening conditions. The SAP allows healthcare professionals to request access to these drugs, on behalf of their patients, when all other treatment options have failed, are unsuitable or unavailable. To request access through the SAP, healthcare professionals must complete an application form and provide detailed information about the patient's medical condition, previous treatment history and the expected benefits of the requested treatment. Once approved, the healthcare professional receives a letter of authorisation allowing them to import the drug. Healthcare professionals are obliged to report on the use of the drug and any adverse events that may occur.

Since January 2022, approximately 200 patients have received psilocybin and around 40 patients MDMA through the SAP. Around two-thirds of the requests for psilocybin were for major depressive disorder and the remaining third was for end-of-life psychological distress. The requests for MDMA concerned PTSD.

It was also noted that Health Canada is establishing a scientific committee on mental health disorders comprising experts who will examine the Canadian clinical context for treating different mental health conditions.

⁵ Health Canada. Notice to stakeholders: Health Canada's expectations regarding risk-management measures for clinical trials involving psychedelic-assisted psychotherapy. <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/expectations-risk-management-measures-clinical-trials-psychedelic-assisted-psychotherapy.html> (accessed 29 April 2024).

⁶ Health Canada. Notice to stakeholders: Requests to the Special Access Program (SAP) involving psychedelic-assisted psychotherapy. <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/requests-special-access-program-psychedelic-assisted-psychotherapy.html> (accessed 30 April 2024).

Methodological challenges

Key messages

- Mitigating the impact of functional unblinding and expectancy effects in clinical trials involving psychedelics is challenging, but measures can be taken to manage these issues.
- To address uncertainties in psychedelic research, such as those related to dosing, maintenance of effects and the requirements for “set and setting”, it is essential to generate reliable and valid data to support an MAA that adheres to regulatory standards and requirements.
- Incorporating either psychotherapy or psychological support into psychedelic treatment has implications for the design of pivotal clinical trials to evaluate efficacy which would potentially impact the wording of the approved indication in the MAA.

Overview

Clinical trials are an essential component of the drug development process, providing objective data on the safety and efficacy of new medicines. All clinical trials that support an EU MAA must adhere to requirements such as ICH guidelines for safety and efficacy. These include the generally accepted principles of sound trial planning noted in regulatory guidance documents such as ICH E6⁷, E8⁸, E9⁹, E10¹⁰, E17¹¹ and comprises, for example, the definition of primary and secondary endpoints, a justification of the sample size and its planning assumptions, and a predefined, clearly outlined, and detailed statistical analysis plan. Designing robust clinical trials to support MAAs for safe and effective psychedelic medicines is complex due to the characteristics of these substances. There are still many uncertainties surrounding how to optimally design such trials¹². Addressing these uncertainties will be key to ensuring that clinical trials generate valid and reliable data on the safety and efficacy of psychedelic medicines.

⁷ Guideline for good clinical practice E6(R2)

⁸ ICH guideline E8 (R1) on general considerations for clinical studies

⁹ ICH E9: Statistical principles for clinical trials

¹⁰ ICH E10: Choice of control group in clinical trials

¹¹ ICH guideline E17 on general principles for planning and design of multi-regional clinical trials

¹² McCulloch DE-W. et al. Knowledge gaps in psychedelic medicalisation: Clinical studies and regulatory aspects, Neuroscience Applied. 2024; 3.

Blinding and expectancy effects

Blinding is an important aspect of clinical trials which ensures that the reporting of outcomes is unbiased with respect to the treatment group allocation, thereby ensuring the validity and reliability of results. While EMA recognises that minimising the impact of functional unblinding in clinical trials of psychedelics is challenging, the Agency considers that adequate measures can be used to manage this. These include the use of:

- remote, blinded independent raters. This concept is illustrated by the [Spravato \(esketamine\)](#) development programme, which provides a useful example of how the separation between those who assess outcomes and those who administer treatment can be achieved;
- a blinding questionnaire to determine the impact of functional blinding. This entails asking participants in both treatment and control groups to guess their allocation and explain their reasoning;
- controlled trials administering different dose levels, such as low or comparative doses, which allows for some uncertainty in the treatment allocation.

The Agency noted that as a general principle, blinding is particularly important in clinical trials that measure treatment outcomes with subjective scales. If there is significant variability in the scale, more rigorous blinding procedures may be necessary to ensure reliable results. Furthermore, blinding is increasingly important when the treatment effect is small but may be less critical when it is substantial.

Representatives from the European College of Neuropsychopharmacology (ECNP) noted that several of these strategies had been used in psychedelic trials. The European Federation of Pharmaceutical Industries and Associations (EFPIA) specified that matching psychedelics with an inert comparator medicine is difficult, particularly for participants with prior experience with psychedelics. This functional unblinding may bias efficacy interpretation. However, in line with EMA, they considered that this could be mitigated by different strategies, such as including several dose levels in trials, to establish dose-response relationships and minimum effective dose levels, along with a placebo group to evaluate the effects of the active substance compared to an inert control.

Representatives from academia noted that there may be suitable active comparators available for use in psychedelic clinical trials. For example, an ongoing academic trial is evaluating a combination of ketamine and midazolam as a comparator to psilocybin.

Some representatives from academia and industry questioned whether regulatory agencies place too much emphasis on blinding in psychedelic trials. They noted that the challenge of blinding in clinical trials is not unique to psychedelic medicines, citing anti-psychotic placebo-controlled trials as examples where blinding can be compromised due to adverse events, or trials entailing surgical interventions. It was also mentioned that although placebo effects occur with psychedelics, they are typically short-lived. Therefore, long-term effects may be one of the best ways to differentiate between treatment and placebo effects.

Participants from academia, the Psychedelic Access and Research European Alliance (PAREA) and the European Brain Council (EBC), highlighted that current medicines regulatory frameworks are designed primarily for conventional medicines and may need to adapt to the challenges posed by emerging novel treatments such as psychedelics. In this regard, they noted that the gold standard of randomised controlled trials may not fit psychedelics.

The concept of expectancy (both positive and negative) and the nocebo effect were also discussed. Nocebo effects can negatively impact the treatment outcome, in a similar way that

placebo effects positively impact it. Participants outlined that the nocebo effect is not limited to the exacerbation of symptoms due to experiencing disappointment after receiving a placebo instead of the treatment within a trial; it also occurs when patients receive the treatment but do not have the expected therapeutic response. Several participants noted that comprehensive informed consent procedures and appropriately trained facilitators who manage the expectations of participants and provide support before, during and after treatment could be used to mitigate nocebo-related risks. It was also outlined that clinical trials using either low or comparative doses, may reduce the risk of bias and unfavourable outcomes due to nocebo effects, as these effects are more likely to be detected across all treatment groups. A point was raised regarding the possibility of bias due to expectancy effects emerging in trials where open-label delivery of active treatment is provided to all arms by the end of the trial. However, it was emphasised that if efficacy is demonstrated within the blinded timeframe, this is unlikely to be a concern.

Selection bias

ECNP noted the potential for selection bias in clinical trials investigating the use of psychedelics to treat mental health conditions. These disorders can impact motivation and treatment adherence among potential study participants. Recent media coverage that sensationalises the use of psychedelics may influence the selection of participants. For instance, if only enthusiasts are recruited, expectancy effects may arise which may bias the trial results.

Selection bias in clinical trials of psychedelics also raises important questions about their efficacy and safety in patient populations that may be less likely to enroll. For example, patients who have difficulty verbalising complex emotions or who have comorbidities may be under-represented in clinical trials.

Dose-response studies and maintenance of effect

Characterising the dose-response relationship in terms of safety and efficacy is a crucial aspect of any MAA. For psychedelics, this requires dose-finding studies to characterise the relationship between dose and effect, as well as the relationship between the subjective experience (unique psychological experiences and perceptions induced by psychedelics during active treatment) and therapeutic response. Other critical aspects that need to be determined include the requirement for individualised dosing strategies due to variability in pharmacokinetic parameters, but also based on the individual needs of participants.

There is limited information on the durability of response and the long-term effects of psychedelics. It is therefore imperative that the maintenance of response is also characterised. This includes assessing the durability of response during the dosing session and, most importantly, during the disease episode itself to inform on the need for repeat dosing. The latter should be done in a long-term study. To accurately determine the onset of response, it's crucial to distinguish between therapeutic response and continued subjective effects as potential reasons for early symptom improvement following active treatment.

A clear theme that emerged from the workshop was that further characterisation of the relationship between dose, subjective experience and therapeutic response is necessary. EFPIA highlighted that data from psychedelic studies indicate that the subjective effects may predict treatment outcomes, with emotional quality or valence potentially playing a role in determining efficacy. While this appears supportive of both a drug and dose-related effect, additional research is needed to fully understand this correlation.

ECNP reinforced this point, noting that the subjective experience and how it evolves, namely in terms of the speed of onset, duration, and intensity, appears to also play a role in predicting treatment efficacy. They also outlined that there is some evidence suggesting that the intensity of the subjective experience with psychedelics may be linked to plasma concentration levels and receptor occupancy¹³. Molecular neuroimaging data suggest that for psilocybin, a minimum receptor occupancy threshold of 40-50% is necessary for a discernible psychedelic experience, while a full subjective experience requires a threshold above 60%. However, further research is needed to fully understand the relationship between plasma concentration, receptor occupancy, and the subjective effects of different psychedelics. In the absence of molecular neuroimaging data, it can be questioned whether the variability between dose and subjective experience could be attributed to differential brain penetration (i.e., pharmacokinetic parameters). ECNP stated that available evidence from psilocybin studies indicates that blood-brain barrier penetration and target engagement appear to be relatively stable across individuals. As such, it remains uncertain whether these correlations can inform dosing strategies for treatment with psychedelics.

PAREA noted two important aspects to consider regarding the duration of effect; pharmacokinetic parameters, specifically the rate of excretion, and characterising the duration of effects based on proposed underlying neuroplasticity mechanisms.

Another aspect that requires further consideration is whether individual differences in drug metabolism, age, sex, and personality traits impact the dose-response relationship. Several participants from academia outlined that developing individualised treatment plans tailored to each patient's unique needs and preferences is essential to ensure the safe and effective use of psychedelic medicines. They suggested that initiating treatment at a low dose and gradually increasing it to achieve the optimal therapeutic dose level may be a more effective approach. The importance of involving patients in the decision-making process was also emphasised as not all patients require a complete dissolution of ego; a shift in perspective may be sufficient. Similarly, while some patients may benefit from profound subjective experiences, others may find them overwhelming.

A representative from academia noted that it has been suggested that so-called "sub-psychedelic doses" (i.e. a dose not considered to elicit a subjective experience), may have therapeutically relevant psychoactive and neurobiological effects, though they do not necessarily produce full-blown subjective experiences. As such, there is a need to clarify how such doses are conceptualised and studied, particularly regarding their potential impact on neuroplasticity. Further research is needed to characterise and determine the efficacy and safety of such doses.

¹³ Madsen MK et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology*. 2019;44:1328–1334. doi: 10.1038/s41386-019-0324-9.

Patient populations

To obtain marketing authorisation for any medicine, EMA emphasised the need for valid and reliable evidence demonstrating a positive benefit-risk balance in the intended patient population. Regulatory approval for new treatments requires clinical trial data that demonstrates a positive balance between the potential benefits and risks in the target population.

EMA outlined that the trial population, as described by the inclusion and exclusion criteria of the protocol, should represent the intended patient population that will be reflected in the MAA. It is therefore critical that inclusion and exclusion criteria are very clearly defined with respect to disease severity, response to previous treatments (particularly when defining a population of patients who are treatment-resistant), age, concomitant medicines and comorbidities.

Due to the potential for significant alterations of perception and behaviour with psychedelics, EMA recommends that the development of psychedelic medicines should be started in a patient population with a high unmet medical need, such as those with TRD. During the discussion, it was noted that gathering data for an MAA in a population with a high unmet medical need may be more feasible given the challenges associated with defining the benefit-risk profile. While identifying an unmet medical need for psychedelics among a broad patient population is possible, generating data to support a positive benefit-risk profile in this cohort may be more challenging.

The Agency noted that starting with the most severe indications that have a high unmet medical need, such as TRD, could enable further characterisation of the safety profile of psychedelics through the generation of real-world data. This data could then be applied to support their use in a broader patient population with less severe disease. The Agency also outlined that while there are some data regarding the use of psychedelics for therapeutic purposes, much about the optimal treatment paradigm remains unknown. Learned societies must also consider where to place psychedelics in overall treatment recommendations. This includes determining when it is appropriate to consider such treatments for specific cohorts of patients and how to effectively integrate them into existing treatment guidelines. FDA highlighted that it is not the role of medicines regulators, but rather medical societies, to determine treatment guidelines and, in this regard, they underscored the importance of collaboration between both parties.

Conversely, a representative from industry noted that many psychiatric diseases such as depression have a higher risk of further episodes with each new occurrence. They specified that as a general principle, early intervention is key. They outlined that this underscores the importance of treating individuals in the early stages of their disease rather than waiting until they become treatment-resistant or significantly advanced in their illness before offering the same treatment that may have changed the course of their condition. A clinician reinforced this point, noting that depressive episodes can be neurotoxic to the brain. Specifically, prolonged, or repeated episodes of depression may lead to a reduction in the size of the hippocampus¹⁴. However, studies with esketamine and ketamine have shown that these substances can elicit rapid improvement^{15,16}, indicating that neuroplasticity may play an important role in reversing

¹⁴ Schmaal L. et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry*. 2016;21:806–12. doi: 10.1038/mp.2015.69.

¹⁵ Moda-Sava RN. et al. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*. 2019;364, 147. doi: 10.1126/science.aat8078.

¹⁶ Höflich A, et al. Translating the immediate effects of S-Ketamine using hippocampal subfield analysis in healthy subjects-results of a randomized controlled trial. *Transl Psychiatry*. 2021;11:200. doi: 10.1038/s41398-021-01318-6.

the negative effects of depression on the brain, a mechanism also postulated for other psychedelics.

Representatives from academia also noted that treatments such as selective serotonin reuptake inhibitors (SSRIs) often take up to 6 to 8 weeks at full therapeutic dose to have an effect. In contrast, psychedelics may have a more immediate effect. This specificity may make them useful as a first-line treatment to immediately reduce the burden of disease on patients and provide space for clinicians to adjust other therapies. Lack of compliance with conventional antidepressants such as SSRIs, due to their slow onset of action and immediate onset of side effects was also raised. As psychedelics are administered in a controlled setting under supervision, this could potentially mitigate these issues, leading to greater adherence and ultimately improving treatment outcomes.

While acknowledging the potential of these treatments to address root causes of suffering, the Psychedelic Participant Advocacy Network (PsyPAN) cautioned that they may not be appropriate as a first-line treatment for all patients. PAREA emphasised that decisions about these treatments should take into account the burden of disease and associated mortality risk of mental health conditions. From their perspective, there is a need for a phased approach that prioritises meaningful regulation that ensures patient safety. They noted the importance of striking a balance between adapting a cautious regulatory approach whilst also taking action to improve outcomes for affected patient populations.

The discussion also touched on whether psychedelics should be considered for disease-specific or syndrome-specific indications. EURORDIS questioned whether a trans-diagnostic drug development approach could be applied. They suggested the need for a platform technology development programme to explore whether psychedelics could be effective in treating syndromes, when they are symptoms of other conditions. They also queried whether artificial intelligence (AI) could be used to determine which conditions could benefit from such treatments.

A clinician noted that participants in qualitative studies often describe similar growth experiences with psychedelics, regardless of the specific substance administered, their diagnosis, or the method of treatment. They outlined that this observation raises important questions regarding whether the effects of psychedelics are non-specific and if they target common psychological mechanisms that are essential for psychopathology. In other words, it is possible that the benefits of psychedelics are not specific to any one particular disorder or treatment approach, but rather reflect more general therapeutic mechanisms.

Several clinicians and academic representatives highlighted that there is a requirement for more diversity in clinical trials, particularly regarding sex and ethnicity.

“Set and setting”

“Set and setting” is the term used to refer to the mindset (i.e. “set”) and physical environment (i.e. “setting”) in which psychedelics are administered, which is believed to play a role in the therapeutic effects of these substances. However, elements of “set and setting” remain to be empirically defined with respect to the safety and efficacy of psychedelics.

Protocols for psychedelic development programmes generally include some form of psychological support or psychotherapy. Both are distinct; psychological support in the context of psychedelic treatments typically defines a framework to ensure the safety of patients, such as chaperoning them during active treatment, while psychotherapy involves an additional psychotherapeutic intervention. Both psychological support and psychotherapy are generally delivered within a standardised framework consisting of three stages:

1. so-called preparatory session(s) prior to administration;
2. administration session(s) (i.e. when the patient is experiencing subjective effects);
3. subsequent session(s) in which patients construct a narrative of their experience and are encouraged to derive their own insights, typically referred to as integration sessions.

Throughout the workshop, there was an ongoing debate regarding the value of the therapeutic element of psychotherapy compared to psychological support with psychedelics. Some participants considered that the therapeutic effects of psychedelics are inherently dependent on psychotherapy while others considered that a framework of support which focuses on ensuring the safety of the patient is the optimal approach.

From the perspective of the Agency, the use of either approach has implications in terms of the design of appropriate clinical trials to support an MAA and the therapeutic indication that will be reflected in the product information (i.e. summary of product characteristics and package leaflet). If a psychedelic is administered with psychological support that is implemented with the sole purpose of ensuring patient safety, this can be described and standardised in the protocol of a clinical trial. This can also be applied in a standardised method in clinical settings to ensure the safety of patients.

However, if psychotherapy is an integral part of the treatment, a clinical trial with a factorial design would likely be required to mitigate bias and enable evaluation of the contribution of both interventions (i.e. the psychedelic and psychotherapy) to relevant efficacy endpoints. ECNP also underscored the importance of clinical trials with factorial designs for accurate interpretation of respective treatment outcomes, although an industry representative emphasised the high cost of conducting such a trial. Industry representatives also noted that the use of psychedelics with psychotherapy or psychological support could be empirically tackled in the drug development programme and pointed to the use of AI to help demonstrate uniform behaviour by facilitators in a standardised environment across clinical studies. For example, AI can provide simultaneous translation and text creation while collecting analytics on the data. It was also noted that adherence instruments could potentially be used to verify that facilitators are following standardised procedures. EFPIA outlined that most drug development programmes for psychedelics do not involve psychotherapy, with the exception of MDMA-assisted psychotherapy for PTSD. EFPIA also highlighted the importance of following up on subjective experiences to ensure good treatment outcomes, but advised against including psychotherapy in this context as it may bias the assessment of efficacy.

Regarding the frameworks of support provided to patients, patient advocates from PsyPAN noted that based on their experience, most trial participants want or need additional therapeutic

sessions around the treatment to help them achieve lasting change and prolong response and remission. While they acknowledged that implementing such treatments in the therapeutic armamentarium will require standardisation, they also emphasised that flexibility is necessary to accommodate specific health conditions, individual needs, and the different ways in which various agents work. PAREA noted that the level of support required by patients will be dependent not only on the particular psychedelic but also on its proposed therapeutic indication. They also outlined the importance of determining appropriate levels of support for individual patients, which could be achieved with the use of digital tools including AI.

It is important to highlight that the regulation of medical practice in clinical settings falls outside the remit of medicines regulators. There are various types of psychotherapy; determining the optimal approach to be used with psychedelics is beyond the mandate of medicines regulators. Furthermore, the regulation of medical practice that applies such treatments is the responsibility of other professional bodies that regulate clinicians.

The FDA noted that although they can control the moderation of treatments during clinical trials, once they are in the public domain, they don't regulate the medical practice that would be applying such treatments. They noted that they have engaged with state medical boards to ensure that they are giving due consideration on how they will regulate these aspects in clinical practice. TGA also noted that it is the remit of RANCZP and the medical board of Australia to ensure that authorised prescribers who deliver psychedelic-assisted psychotherapy are subject to relevant regulations and codes of practice. Representatives from the European Psychiatric Association (EPA) emphasised the need for guidelines and protocols that are transposable into real-life situations pertaining to appropriate screening of patients, preparation, drug administration, and integration sessions.

Several clinicians and representatives from academia noted that determining appropriate standards and criteria for psychological support could be achieved by further collaboration in the field. To achieve this, one suggestion was to first identify what aspects of treatment can be standardised, such as psychological support and monitoring, delivery methods, qualification of clinicians and collection of adverse events (refer to section 3), as well as environmental factors (such as music and the set-up of the room). Regarding the latter, ECNP noted that existing evidence suggests that the environment plays an important role in determining therapeutic outcomes, although further research is needed to determine the most appropriate environment and its impact on therapeutic outcomes.

Standardisation of these factors could then form evidence-based recommendations to facilitate safe and effective treatment practices. Another point raised was the requirement to define a minimum amount of psychological support and integration that all practitioners could agree on to optimise patient care and therapeutic outcomes. This could be considered as an initial starting point. Given the variability associated with different disease states and substances, it was noted that it is important that these factors are considered when developing such recommendations. EMA stressed that input from key opinion leaders would be essential to agree on standardised recommendations for treatments.

PAREA suggested that a pan-European multidisciplinary advisory body should be established to offer a comprehensive framework for addressing mental health in the EU. This body could recommend care models for psychedelics, training and licensing standards, ethical guidelines, and safety standards. They noted that promoting a synergistic approach could unify the efforts of EU Member States, rather than addressing similar issues individually. PsyPAN supported this proposal, highlighting that an advisory body would facilitate strategic planning and create a collaborative approach for frameworks of support.

Concomitant medicines

As is the case for all drug development programmes, the potential for drug-drug interactions should be assessed in order to translate the results of these evaluations to appropriate treatment recommendations in the medicine's product information¹⁷. Such studies are typically undertaken in the context of pharmacokinetic and pharmacodynamic studies. In general, the programme to address the interaction potential of an individual medicine needs to be tailored to the specific medicine. Alternative approaches are acceptable if adequately justified and driven by science and the expected clinical consequence of the interaction. Trial protocols should also clearly define inclusion and exclusion criteria with regards to concomitant medicines¹⁵. This is a particularly important consideration for development programmes for psychedelics, given that in the field of psychiatry, polypharmacy tends to be more frequent, particularly in patients whose condition is severe¹⁸.

There are many uncertainties regarding the impact of psychedelics on concomitant psychiatric medicines that require further characterisation^{19, 20}. For instance, it is necessary to determine whether the concomitant administration of psychedelics affects the safety and efficacy of other medicines and vice versa.

While there is some data in the scientific literature suggesting that SSRIs may dampen the therapeutic effects of psychedelics, ECNP outlined that it does not appear that other medicines have a negative impact on psilocybin²¹. They noted that it is not clear whether SSRIs should be discontinued before initiating treatment with psychedelics other than psilocybin.

During the discussion, participants also addressed practical and therapeutic considerations related to discontinuing concomitant medicines. Clinicians noted that many clinical trials for psychedelics involve tapering existing treatments and require participants to discontinue the use of their psychiatric medicines, such as antidepressants, during the blinded period which introduces ethical concerns. Furthermore, these treatments are also frequently used as sleep aids for patients which is challenging as clinicians may need to prescribe hypnotics or sedatives as an alternative, particularly if patients do not respond to treatment with psychedelics. However, these agents have potential for abuse and addiction. They also noted that these elements could limit patient compliance with the trial protocol, as participants may require treatment with other medicines during the trial.

EPA highlighted the need to clarify whether psychedelics can be used in combination with other psychiatric medicines, to facilitate their application in clinical practice.

¹⁷ European Medicines Agency. Guideline on the investigation of drug interactions. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf (accessed 03 May 2024).

¹⁸ Wolff J. et al. Polypharmacy and the risk of drug-drug interactions and potentially inappropriate medications in hospital psychiatry. *Pharmacoepidemiol Drug Saf.* 2021 Sep;30(9):1258-1268. doi: 10.1002/pds.5310.

¹⁹ Becker AM et al. Acute Effects of Psilocybin After Escitalopram or Placebo Pretreatment in a Randomized, Double-Blind, Placebo-Controlled, Crossover Study in Healthy Subjects. *Clin Pharmacol Ther.* 2022 Apr;111(4):886-895. doi: 10.1002/cpt.2487

²⁰ Halman A et al. Drug-drug interactions involving classic psychedelics: A systematic review. *J Psychopharmacol.* 2024 Jan;38(1):3-18. doi: 10.1177/02698811231211219

²¹ Goodwin GM et al. Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication. *Neuropsychopharmacology.* 2023;48(10):1492-1499. <https://doi.org/10.1038/s41386-023-01648-7>.

Safety considerations

Key messages

- Larger and longer trials are necessary to characterise the safety profile of psychedelics, particularly in specific patient populations.
- There is a need for consensus on a standardised approach to systematically collect, evaluate and document adverse events during subjective experiences.
- To ensure participants are adequately prepared for treatment, they must be fully informed of all associated risks. Consideration must be given to the requirements for facilitators due to the potential for abuse.

Overview

There is limited data regarding the safety profile of psychedelics; available evidence originates primarily from trials with small sample sizes or in the context of illicit use. Furthermore, older clinical trials often failed to systematically collect and document adverse events. Trials with larger sample sizes and of longer duration are necessary to characterise the safety profile of psychedelics, especially in terms of their use in specific patient populations and long-term safety. The precise requirements for safety data can vary depending on the development programme and proposed treatment regimen (e.g. single- or repeat-dosing). Guidance regarding the safety evaluation of new medicines developed for long-term treatment of non-life-threatening diseases recommends a total patient exposure of about 1,500 and that a minimum of 300 and 100 patients use the medicine for six and twelve months, respectively, before approval²².

Comprehensive and systematic collection and evaluation of safety data in these trials is necessary to elucidate the frequency, severity, seriousness, and dose-response of adverse events²³, including potential differences across subsets of patients such as demographic, comorbidities, and/or concomitant therapy. As outlined in the EU Clinical Trial Regulation²⁴, investigators are required to document and report all adverse events, unless otherwise specified in the protocol, according to dedicated timelines. Serious, unexpected adverse reports (SUSARs) are subject to expedited reporting. Protocols should pre-specify the evaluation of safety and adverse events to be reported.

22 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E1 population exposure: the extent of population exposure to assess clinical safety. https://database.ich.org/sites/default/files/E1_Guideline.pdf (accessed 03 May 2024).

23 An adverse event is defined in ICH-E2D as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

24 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536> (accessed 04 May 2024).

As with any medicine, developers of psychedelic medicines must submit a comprehensive risk management plan (RMP) as part of the dossier for their MAA. The RMP documents the risk management system considered necessary to identify, characterise and minimise a medicines' important risks throughout its life cycle. The RMP, which is developed by the applicant and evaluated by the Agency, includes the:

- safety specification, which outlines the important identified and potential risks and areas where relevant data are missing;
- pharmacovigilance plan, which is a structured plan to enable characterisation and quantification of safety concerns within the safety specification and to identify new adverse reactions;
- planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

Routine and additional risk minimisation measures can be used to manage and minimise the risks identified in the safety specification. Routine measures, such as the summary of product characteristics, package leaflet, pack size, labelling and legal status, apply to all medicines. For prescription-only medicines, their legal status may be subject to additional conditions by classifying them into those available only with either a restricted medical prescription or a special medical prescription.

Additional risk minimisation measures are imposed as a condition of the marketing authorisation. Clear descriptions of each proposed additional risk minimisation measure should be provided in an RMP, including an explanation of which specific safety concern(s) it is intended to address and how it will achieve this objective. A variety of tools are currently available for additional risk minimisation if deemed necessary for psychedelics. These include:

- educational programmes: aim to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk;
- controlled access programmes: patient access is contingent on fulfilling one or more requirements prior to the medicine being prescribed or dispensed;
- controlled distribution systems: the stages of the distribution chain are tracked up to prescription and/or dispensing.

The pharmacovigilance plan can be used to facilitate further characterisation of concerns within the safety specification, post-approval. This consists of both routine pharmacovigilance activities that apply to all medicines, such as signal detection and adverse event reporting, as well as additional pharmacovigilance activities. The latter includes post-authorisation safety studies (PASS) such as non-clinical studies, clinical trials or non-interventional studies. Examples include long-term follow-up of patients from the clinical trial population or a cohort study to provide additional characterisation of the long-term safety of the medicine.

Current Understanding of Psychedelic Safety Profile

Several participants commented on the main safety findings from clinical trials noting the acute, subacute and serious adverse events that have been observed with psychedelics.

Although there may be some similarities in safety profiles, adverse events can differ depending on the pharmacological profile of individual agents. Available information indicates that safety and tolerability appear to depend on the dose²⁵. ECNP noted that this is particularly apparent for acute events observed during active treatment such as nausea, vomiting and anxiety, sometimes with derealisation. Developers must carefully consider what risk minimisation measures can be implemented to mitigate any particular safety concern identified in development programmes. Furthermore, consideration should also be given to how further data can be generated for specific safety concerns in the context of the pharmacovigilance plan (e.g. via PASS) in the RMP.

Cardiovascular effects

Classic psychedelics such as mescaline, lysergic acid diethylamide (LSD), psilocybin and dimethyltryptamine are agonists of 5-HT_{2A} receptors. Participants noted that existing data from trials has shown that these substances can result in short-lived and non-clinically significant sympathomimetic effects, such as hypertension (high blood pressure) and tachycardia (rapid heartbeat), during active treatment. However, as noted previously, larger and longer trials are necessary to obtain a clearer understanding of their impact on the cardiovascular system, particularly on the serotonergic system in the heart and vasculature and their sympathomimetic effects²⁶. It is also important to understand how these effects impact specific patient populations.

Challenging experiences

During the workshop, it was noted that the effects of psychedelics can sometimes be distressing and dysphoric, resulting in negative experiences or so-called “bad trips”²⁷. While there is no precise definition of such experiences, participants have reported experiencing fear, paranoia, dysphoria and/or anxiety, sometimes with derealisation. ECNP noted that based on available data, anxiety sometimes with derealisation, generally seem to occur at higher doses. They underscored the importance of ensuring that adequately trained facilitators are present with the participant during active treatment to help them manage these adverse effects. ECNP also outlined that patients may occasionally experience flashbacks or reoccurring experiences following active treatment. While these are not always necessarily negative, they can sometimes result in persistent and distressing experiences which according to DSM-5²⁸ are known as hallucinogen-persisting perception disorder (HPPD)²⁹. Further data is required to elucidate whether specific cohorts of patients are susceptible to such experiences. and what may cause these events.

²⁵ Holze F, Singh N, Liechti ME, D'Souza DC. Serotonergic Psychedelics: A Comparative Review of Efficacy, Safety, Pharmacokinetics, and Binding Profile. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2024; 9(5):472-489. doi: 10.1016/j.bpsc.2024.01.007

²⁶ Wsól A. Cardiovascular safety of psychedelic medicine: current status and future directions. *Pharmacol Rep*. 2023; 75(6):1362-1380. doi: 10.1007/s43440-023-00539-4.

²⁷ Schlag AK, Aday J, Salam I, Neill JC, Nutt DJ. Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. *Journal of Psychopharmacology*. 2022; 36(3):258-272. doi:10.1177/02698811211069100

²⁸ American Psychiatry Association, *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, May 2013.

²⁹ Müller F. et al. Flashback phenomena after administration of LSD and psilocybin in controlled studies with healthy participants. *Psychopharmacology (Berl)*. 2022; 239(6):1933-1943. doi: 10.1007/s00213-022-06066-z.

As stated by industry representatives, it is also vital to ensure that appropriate support is provided beyond treatment protocols to those who experience these so-called “bad trips” or negative experiences.

Abuse potential

During the workshop, several participants noted that available data does not indicate that classical serotonergic psychedelics show potential for addiction³⁰.

As outlined by EMA in the draft guideline for depression, it is nevertheless essential to carefully evaluate the potential for physical and psychological dependence in development programmes of psychedelics, depending on each substance's mechanism of action.

Psychosis and suicidality

EMA outlined that both psychosis and suicidality should be considered as adverse events of special interest (AESIs) for psychedelics. Although no direct causal relationship has been established between these particular safety concerns and psychedelics, it is critical that they are evaluated thoroughly and systematically in development programmes, particularly given the therapeutic context of use. As discussed during the workshop, these events could be elicited by a deterioration of a patient's condition due to a lack of efficacy. However, additional data is required to enable further characterisation of such events. As outlined by the Agency, it is imperative that data regarding events of psychosis and suicidality are recorded, documented and evaluated systematically in trials.

Representatives from industry noted that the risk of suicidality has been measured using specific scales in clinical trials. They emphasised the importance of carefully examining the pattern of change in suicidality over the course of treatment in all patients. While there were no completed suicides in the Compass trial³¹, the 10mg treatment group exhibited a slightly greater tendency towards change (i.e. deterioration) in suicidality, albeit not statistically significant, while the 1mg group had relatively low changes. However, interpreting these changes can be challenging, as they may indicate destabilisation of mood rather than suicidality. They noted that it is essential to recognise that treating a depressed patient population, especially one resistant to treatment, increases the risk of such mood instability translating into suicidality. They outlined that larger and longer trials are required to enable further characterisation and interpretation of these changes.

PAREA considered that even when the substance has been cleared from the body, the subjective experience may disarm the participants' inherent defense mechanism, which can be psychologically unsettling. They noted the importance of ensuring patients are adequately informed and well-prepared for treatment sessions to manage this.

³⁰ Rucker JJH et al. Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharmacology*. 2018 Nov;142:200-218. doi: 10.1016/j.neuropharm.2017.12.040

³¹ Goodwin GM et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N Engl J Med*. 2022 Nov 3;387(18):1637-1648. doi: 10.1056/NEJMoa2206443

Follow-up after trials

EFPIA emphasised that most trials observe patients for around 3 to 12 weeks, which provides a reasonable timeframe to detect potential adverse effects resulting from the subjective experience. They noted that if negative experiences (e.g. "bad trips") occur, they should be documented as adverse events. There is an obligation to follow up on these events and ensure that appropriate care is provided, regardless of whether the participant remains in the trial or not. They also outlined that there is only a limited timeframe in which treatment arms can be compared while maintaining the trial's integrity; after this, patients must transition back to their treating physician for further care if required.

Another industry representative added that clinicians in trials aim to maintain continuity of care and establish a "warm handoff" of participants to their treating physician(s). They outlined that this issue is not exclusive to psychedelics; it affects all clinical trials.

PsyPAN outlined that there is a need for support for a meaningful proportion of participants following clinical trials. Even if the participant's condition has improved, they may feel isolated in their social groups. For many, the end of the trial marks the beginning of their therapeutic journey; participants often seek spaces where people understand their lived experiences. In some cases, participants do not even have a support network. To address this, PsyPAN has established peer support systems for post-trial participants.

Systematic collection and documentation of adverse events

Interpreting the psychological or emotional adverse events that clinical trial participants may experience during active treatment with psychedelics can be ambiguous, subjective, context-dependent and open to interpretation³². A key theme that emerged during the workshop was the requirement for further consensus and guidance on the systematic recording and reporting of adverse events from psychedelic clinical trials, particularly those related to the subjective experience.

EFPIA considered that adverse events should be collected and documented using a validated, subjective scale that assesses the characteristics of the acute subjective experience. If these effects are negative or unfavourable, they should be reported as adverse events. However, since there is currently no consensus regarding the scale that should be used, they emphasised that further guidance is required. They considered that guidance is needed to determine whether this approach represents a new method for recording safety data in trials and whether scales should be used. EFPIA also noted that specific safety concerns considered critical to evaluating the safety of psychedelics may be pre-defined as AESIs in the study protocol. While EFPIA considered that events that form part of the subjective experience could potentially be classified and reflected as psychedelic effects in the product information, separate from adverse events, this warrants careful reflection.

²⁰ Schlag AK, Aday J, Salam I, Neill JC, Nutt DJ. Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. *Journal of Psychopharmacology*. 2022;36(3):258-272. doi:10.1177/02698811211069100.

Another representative from industry noted that the acute subjective experience should be characterised as this information is necessary to inform prescribers of what to expect during treatment so they can counsel patients accordingly. They noted that in a separate working group, a three-pronged approach was implemented to ensure the systematic collection and documentation of adverse events in clinical trials for psychedelics.

1. Investigators should collect information on the acute experience, regardless of whether they consider it on-target or not;
2. Adverse events should be defined as per the ICH-E2D definition. If the effects of the acute psychedelic experience persist beyond the duration of the acute phase or if they require any form of intervention for the safety of the patient, then they must be considered an adverse event;
3. AESIs should also be considered when addressing specific safety concerns such as potential abuse liability. In this regard, they noted that investigators and sponsors are usually provided with specific MedDRA Preferred Terms to collect abuse-related data, regardless of whether they classify them as adverse events.

ECNP noted that while there are scales to assess and describe acute subjective experiences, further collaboration is required to reach a consensus on how they should be used systematically in trials. They intend to reflect on this matter and gather feedback from those conducting clinical trials to establish systematic criteria for documenting and reporting adverse events in psychedelic clinical trials.

Informed consent

During the workshop, several participants highlighted that trials involving psychedelics pose specific challenges for informed consent that require careful consideration³³. This is due to risks associated with heightened suggestibility and the unpredictability of subjective effects. The informed consent process should ensure that patients are adequately prepared for the subjective experience; they should feel empowered to change their minds and be aware that the treatment may elicit alterations in their mindset. Patients need to be provided with complete information about what they can expect from the treatment and must feel confident that they are well-informed before deciding to participate. Several clinicians and academics stressed that although comprehensive informed consent procedures are typically used in trials, translating these into clinical practice is essential if psychedelic medicines are approved in the future.

It is important to emphasise that in the EU, the approval of informed consent forms and the informed consent process to be used in clinical trials falls within the remit of national ethics committees. Consent requirements for clinical trials vary between EU countries due to national laws and regulations, and so in this respect, each Member State may have its own national requirements for the specificities of the informed consent form for clinical trials. The concept of informed consent in clinical practice is regulated at the national level by EU Member States or by codes of deontology³⁴ for healthcare professionals. Consequently, EMA has no remit regarding the enforcement of this obligation.

33 Seybert C., Cotovio, G., Madeira, L. et al. Psychedelic treatments for mental health conditions pose challenges for informed consent. *Nat Med*, 2023; 29, 2167–2170.

34 Codes of deontology in healthcare concern ethical guidelines that outline the professional responsibilities and conduct expected of healthcare professionals.

However, it is possible that educational materials could be used to ensure patients are fully informed of all the potential risks associated with treatment. This can be managed through the RMP.

Facilitators

Facilitators can assist patients in managing adverse events, such as anxiety, during treatment sessions and post-dosing. However, since patients are in a vulnerable state, there is also potential for abuse by those responsible for chaperoning them during active treatment.

It is also important to mitigate so-called contact transfer, as noted by a clinician during the workshop. Contact transfer refers to the possibility that a therapist could inadvertently transfer their own adverse experiences or emotions to the patient during treatment. For example, if a therapist were to become anxious or upset while administering a psychedelic, the patient may pick up on these emotions and experience them as well. This could potentially worsen the patient's experience or trigger negative emotions.

Several academic representatives stressed the importance of having facilitators who are not only well-trained but also subject to professional oversight by regulatory bodies. This would help ensure patient safety during active treatment. PAREA echoed this sentiment, emphasising that support should be provided by licensed groups with established safeguards. EFPIA emphasised that a clear definition of individual support is required to ensure patient safety and noted that this can be standardised across clinical trials. They also outlined that the background of those providing support should be compatible with core competencies, though they need not necessarily be at the level of a psychiatrist or psychotherapist.

ECNP recommended that two facilitators should chaperone patients during acute treatment given the potential for abuse due to the vulnerable state of patients. Similarly, the FDA highlighted that their draft guidance specifies that two monitors should be present during treatment sessions. One must act as the lead monitor; they must be a healthcare provider with graduate-level professional training and clinical experience in psychotherapy, who is licensed to act independently.

During the discussion, it was also stated that there is a need for educational programmes to ensure that such facilitators are adequately trained. This training could potentially be provided as supplemental training to those who have a relevant background, given that knowledge regarding the disease is also pertinent. It was also noted by some participants from academia that there should be enhanced transparency regarding the level of support provided in clinical trials. One participant proposed that manuals outlining the frameworks of support provided in trials should be published as supplementary information with relevant scientific publications. One example of such an initiative concerns the PsyPal study, a multi-site double-blind placebo-controlled clinical trial to investigate the use of psilocybin to treat psychological distress associated with progressive, incurable palliative diseases. The sponsors of the study will provide both the training manual and module used in the study to others in the field under certain circumstances.

Real-world data

During the workshop, participants discussed the potential role of real-world data (RWD) in marketing authorisation applications for psychedelic medicines. RWD refers to “*routinely collected data relating to a patient’s health status or the delivery of health care from a variety of sources other than traditional clinical trials*”, while real-world evidence (RWE) refers to “*the information derived from the analysis of RWD*”³⁵.

EMA underscored the foundational role of randomised clinical trials in generating reliable data for development programmes to support MAAs of psychedelic medicines. While RWD cannot replace clinical trial data, it can serve as a complementary source of evidence. For example, RWD could potentially facilitate further characterisation of the safety profile of psychedelic medicines and may provide supportive data for extending indications to special populations, if safety and efficacy have already been established in a broad population.

However, as outlined by the Agency, the quality of RWD is paramount to its relevance for regulatory decision-making. In contrast to clinical trials, RWD studies are non-interventional in nature, with data collected during routine clinical care and practice. As a result, there is significant variability in the reliability and validity of such data. Therefore, protocols are required for RWD studies to ensure the robustness of the data, particularly in terms of data collection and analysis.

Both the FDA and Health Canada noted that while RWD could be considered for the approval of psychedelic medicines, there is still a need to evaluate the full dossier, including data from clinical trial programmes.

³⁵ International conference on harmonisation. Reflection paper on proposed international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting studies using real-world data, with a focus on effectiveness of medicines.
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-proposed-international-harmonisation-real-world-evidence-terminology-and-convergence-general-principles-regarding-planning-and-reporting-studies-using-real-world-data-focus_en.pdf (accessed 07 May 2024).

Considerations and challenges for implementation

Key messages

- The UN classification of psychedelic substances as Schedule I drugs may need to be revised given the emerging evidence regarding their therapeutic potential.
- Developers can obtain scientific advice from EMA in parallel with health technology assessment (HTA) bodies regarding proposals for generating an evidence base to support decision-making on marketing authorisation and subsequent reimbursement of new medicines.
- Research on psychedelics may be eligible for funding through EU frameworks, such as Horizon Europe and the Innovative Health Initiative (IHI).

Overview

Other factors beyond the Agency's mandate need to be considered when creating a framework to enable patient access to safe and effective psychedelic medicines in the EU. For instance, determining their cost effectiveness via HTA to facilitate reimbursement by national health systems, funding for research and overcoming obstacles imposed due to their legal classification as controlled drugs. Other aspects include the use of a dedicated nomenclature to facilitate standardisation as well as patient and public involvement in psychedelic research.

Legal classification

It is important to note that the scheduling of medicines is not within the mandate of the Agency due to the wider societal implications. MAAs for medicines containing active substances classified as controlled drugs follow the same requirements as for any other medicine in the EEA.

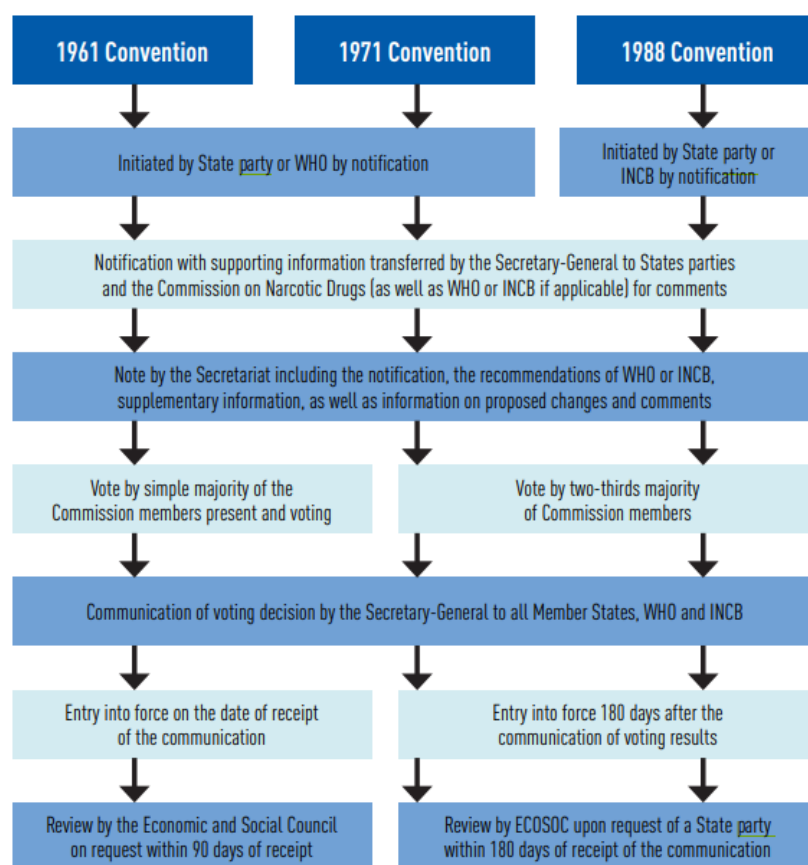
While the legal classification of psychedelics varies depending on the specific substance and the national legislation in each EU Member State, they are generally classified as controlled substances under legislation that aims to restrict their production, distribution and use for non-medical purposes. This is aligned with their classification as Schedule I drugs according to the United Nations Convention on Psychotropic Substances of 1971, which defines psychedelics as having little or no therapeutic value and carrying the highest potential for harm and dependence. PAREA highlighted that the provisions in the EU for psychedelics impose a level of regulatory control and supervision that is significantly more burdensome than for drugs classified as Schedules II-IV, making it challenging to conduct research.

During the discussion, participants highlighted that despite the scientific rigour of trials conducted during the 1950s and 60s not being on par with current standards, there was a growing body of promising evidence regarding the safety and efficacy of psychedelics, particularly LSD and psilocybin, before their Schedule I classification. However, after this classification, there was a sharp decline in research.

PAREA highlighted an asymmetry in the drug scheduling system, whereby a substance can be classified as Schedule I with minimal anecdotal evidence but extensive phase III clinical trial

data is required to reconsider its classification. Several participants emphasised that the classification of psychedelics as Schedule I drugs can hinder scientific research and collaboration. PAREA considered that the classification of psychedelics as Schedule I drugs can impede funding opportunities; public funds are typically not allocated to Schedule I drugs, meaning that large-scale trials depend on industry and private donors. If a psychedelic medicine is authorised in the future, bifurcated scheduling (when a specific medicinal product is placed in a different schedule from the active ingredient) may lead researchers to favor approved forms over those still classified as Schedule I drugs. Additionally, classifying substances as Schedule I drugs can limit the ability of clinicians to provide further treatment to patients who experience positive outcomes during clinical trials, which may lead them to seek these substances through illicit channels.

PAREA considered that there is enough evidence to initiate a discussion on the rescheduling of psychedelics, a process that falls under the purview of the UN Commission on Narcotic Drugs³⁶. The Commission on Narcotic Drugs is responsible for scheduling decisions under the three international drug control conventions³⁷. These decisions involve adding, removing, or transferring substances between schedules or tables, and are aimed at ensuring their adequate control and regulation. PAREA noted that such a discussion can be initiated by either the WHO or a country that was party to the original convention. The chart below presents a summary of the procedures²⁶.



Source: United Nations office on drugs and crime³⁶

³⁶ United Nations Office on Drugs and Crime. Scheduling procedures under the international drug control conventions. Vienna: United Nations, 2020.

³⁷ Single Convention on Narcotic Drugs (New York, 1961), Convention on Psychotropic Substances (Vienna, 1971), Convention Against Illicit Traffic in Narcotic and Psychotropic Substances (Vienna, 1988).

As noted previously, there have been recent developments in other regulatory jurisdictions regarding the legal classification of psychedelics. For instance, in Australia psilocybin and MDMA were reclassified for the treatment of TRD and PTSD, respectively, from Schedule 9 to Schedule 8, following an evidence-based evaluation. There have also been several legislative changes at both the federal and state levels in the US³⁸.

A representative from academia highlighted that the potential for abuse or addiction of any new central nervous system drug taken into development only becomes evident over time as it evolves through the process. They proposed a temporary rescheduling of psychedelics to facilitate research. This would allow the generation of data to inform on the potential for abuse and addiction with psychedelics.

Illicit use

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) provided an overview regarding the illicit use of psychedelics in the EU, particularly MDMA, ketamine and LSD. They noted that there are some concerns regarding the increased media attention surrounding the medical use of psychedelics as this may lead to an increase in experimentation and illicit use.

Meanwhile, EPA and several clinicians expressed concerns regarding potential delays in the development and approval of safe and effective psychedelic medicines, adding that this could prompt patients to seek access through illicit channels. The possibility of a registered psychedelic medicine being approved in the US but not in the EU was also discussed, with clinicians highlighting that this could further compound the issue.

Health technology assessment

HTA has a distinct function in determining the added value of new treatments compared to existing ones. By evaluating treatments from both clinical and economic perspectives, EU Member States are better equipped to make informed decisions about effective healthcare interventions for patients, ultimately contributing to the sustainability of national healthcare systems³⁹. Additionally, reimbursement systems have a significant role in terms of ensuring equitable access to care, as noted by EPA.

A representative from an EU HTA body noted that there is significant uncertainty regarding how psychedelics should be implemented in existing treatment paradigms. For instance, uncertainties remain around whether they should be given alongside other therapies and treatments (e.g. psychotherapy), the most appropriate clinical setting for their administration (e.g. inpatient versus outpatient), and which patient populations would benefit most from such treatments if they were authorised as medicines. This variability poses challenges for assessing their cost-effectiveness in the context of HTA frameworks. They considered that a new HTA framework that accounts for the specific properties of psychedelics may be required. They proposed that a regulatory sandbox or experimentation clause⁴⁰ could enable a structured approach to determine this framework.

³⁸ Psychedelic Alpha. Psychedelic Legalization & Decriminalization Tracker. <https://psychedelicalpha.com/data/psychedelic-laws> (accessed: 24 April 2024).

³⁹ European Commission. Mapping of HTA national organisations, programmes and processes in EU and Norway. https://health.ec.europa.eu/document/download/18a3dc1d-4876-4553-a292-84fc4a7f9e31_en (accessed 08 May 2024).

⁴⁰ European Council. Regulatory sandboxes and experimentation clauses as tools for better regulation: Council adopts conclusions. <https://www.consilium.europa.eu/en/press/press-releases/2020/11/16/regulatory-sandboxes-and-experimentation-clauses-as-tools-for-better-regulation-council-adopts-conclusions/> (accessed 11 June 2024).

To facilitate HTA assessment, it is important to adopt a clear and consistent strategy for incorporating psychedelic medicines into the therapeutic armamentarium across individual EU Member States. However, given the regional variations in national healthcare systems, creating such a strategy can be challenging. They also highlighted that consideration must be given to the use of RWE to support the evaluation of cost-effectiveness within HTA assessments.

Both EMA and representatives from EU HTA bodies emphasised the importance of generating an evidence base to support both marketing authorisation approval and HTA, early in the development process. Developers can obtain parallel EMA and HTA body scientific advice on a rolling basis until the new HTA regulation⁴¹ becomes applicable in January 2025. The HTA regulation will provide a new framework, under which EMA and HTA bodies will collaborate in the context of joint clinical assessments and scientific consultations, and the identification of emerging health technologies.

Funding opportunities

During the workshop, several participants noted the importance of research funding, particularly for larger clinical trials, for the investigation of the safety and efficacy of psychedelic medicines in the EU.

A representative from the European Commission's (EC) Directorate-General for Research and Innovation Unit on Health Innovations and Ecosystems shared information on potential EU frameworks for funding. Horizon Europe is the EU's key research and innovation funding programme for the 2021-2027 period. With a budget of €95.5 billion, it aims to foster collaboration, bolster the impact of research and innovation, and address global challenges through the facilitation of EU policies. The funding is open to any EU-established legal entity or associated country, including universities, research institutes, industry, SMEs, non-profit organisations and public bodies⁴². Horizon Europe recently awarded over €6.5 million in funding to a consortium of 19 European partners to study the potential benefits and risks of psilocybin in treating psychological distress in patients with a progressive, incurable illness that requires palliative care in the context of the PsyPal study. The study population consists of four patient groups including those with chronic obstructive pulmonary disease (COPD), amyotrophic lateral sclerosis (ALS), multiple sclerosis and atypical Parkinson's disease. The EC also pointed out that there could be other opportunities to support such research in Horizon Europe, for instance in further work programmes under Cluster 1 Health for which the topics are broadly defined⁴³.

The Innovative Health Initiative (IHI), an EU funding instrument that supports health research and innovation across sectors to deliver safe and effective health innovations, especially in areas of unmet medical need, was also discussed. IHI is a public-private partnership between the EU and industry associations representing various sectors involved in healthcare. Industry associations include COCIR (European Trade Association representing medical imaging, radiotherapy, health ICT and electromedical industries); EFPIA, including Vaccines Europe

⁴¹ Regulation (EU) 2021/2282 of the European Parliament and of the Council of 16 December 2021 on a framework for the development, production, supply, deployment and use of electronic health services and tools in the internal market, amending Regulations (EU) No 531/2012, (EU) No 1024/2012, (EU) 2016/679, (EU) 2016/1143, (EU) 2017/745, (EU) 2017/746 and (EU) 2019/787 and repealing Regulation (EU) No 910/2014 (accessed 21 May 2024).

⁴² European Commission. Horizon Europe. https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en (accessed 9 May 2024).

⁴³ European Commission. Cluster 1: Health. https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/cluster-1-health_en (accessed 9 May 2024).

(pharmaceutical industry and vaccine industry); EuropaBio (biotechnology industry); and MedTech Europe (medical technology industry)⁴⁴.

IHI is funded jointly by the EU (represented by the European Commission) and these associations. The partnership has a total budget of €2.4 billion for the 2021-2027 period, of which €1.2 billion comes from Horizon Europe and the rest from private partnerships, mostly as in-kind contributions. These contributions are vital for any topic in IHI, with at least 45% of each project's budget required to come from industry partners or contributing partner contributions⁴⁵. The EC representative noted that, in principle, psychedelic research is within the scope of IHI if it conforms to the pre-competitive and cross-sectoral nature of IHI and aligns with its research and innovation agenda.

Importantly, the IHI partnership features an 'ideas incubator' which provides a mechanism to facilitate the submission and assessment of ideas for potential new IHI topics from the wider research and health community following the concept of co-creation⁴⁶.

Compassionate use programmes

During the workshop, there was discussion regarding the use of compassionate use programmes to facilitate early access to psychedelic medicines, particularly for patients who have participated in clinical trials. Such programmes are used for individual patients based on a doctor's statement, or the company can make such medicines available to a group of patients. The cost may or may not be reimbursed, depending on the policies in the Member State⁴⁷.

Compassionate use programmes fall under national jurisdiction and, in most Member States, under the remit of national competent authorities. These programmes are coordinated and implemented by Member States. They decide independently how and when to open such programmes according to national rules and legislation. EMA's committee for human medicines, CHMP, provides a scientific opinion on these programmes in case a Member State requests the Agency for a recommendation on how to administer, distribute and use certain medicines for compassionate use or which patients may benefit from such programmes⁴⁸. CHMP can also do so when it becomes aware that compassionate use programmes with a given medicine are being set up in a number of Member States.

However, these recommendations are optional and are only implemented by Member States that wish to use them. They complement national legislation and do not replace it.

Nomenclature

Throughout the workshop, participants emphasised the importance of standardising the terminology and nomenclature used for psychedelic medicines. This is especially crucial given the historical stigma attached to these substances and the need for alignment and consistency across research and clinical practices. The use of terms like 'hallucinogenic' is considered pejorative and unhelpful, highlighting the necessity for a standardised lexicon that accurately

⁴⁴ IHI partners. <https://www.ih.europa.eu/about-ih/who-we-are/partners> (accessed 09 May 2024).

⁴⁵ IHI funding model. <https://www.ih.europa.eu/about-ih/ih-funding-model> (accessed 9 May 2024).

⁴⁶ IHI Propose ideas. <https://www.ih.europa.eu/shape-our-future-research/propose-ideas> (accessed 9 May 2024).

⁴⁷ European Commission. COMMISSION STAFF WORKING DOCUMENT –Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products – state of play 2015. https://health.ec.europa.eu/document/download/951139df-2a6c-4a5d-a298-9eabd65b1a46_en?filename=orphan_inv_cwd_20160126.pdf (accessed 9 May 2024).

⁴⁸ EMA. Compassionate use. <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compassionate-use> (accessed 9 May 2024).

reflects their mechanism of action and potential therapeutic benefits. Furthermore, there was discussion regarding the requirement for appropriate and standardised nomenclature regarding frameworks of psychological support that ensure patient safety and definitions for concepts such as sub-psychedelic doses.

Patient and public involvement (PPI)

PPI refers to the active participation of patients and members of the public in research studies, including clinical trials. This involvement is becoming increasingly recognised as an important element of the research process, as it helps ensure that research is conducted in a way that meets the needs and preferences of those who will be affected by its results. PPI begins at the level where at least some shared decision-making is involved.

During the workshop, it was noted that the benefits of PPI are numerous. For example, PPI can help researchers develop more patient-centered research questions, improve recruitment strategies and enhance the relevance and usability of study findings. Additionally, PPI can help build trust between patients and researchers, which is essential for effective collaboration and knowledge sharing. Although some psychedelic clinical trials, such as PsyPal, have incorporated PPI, it was outlined that, to date, it has not been widely adopted within psychedelic research. It was noted that PPI is considered particularly important for psychedelic research given the heterogeneity of the individual participant experience. Not taking patient perspectives into account may result in so-called “blue sky research”, leading to treatments that are not adopted into practice as they are not appropriate for naturalistic use.

Conclusion

The ecosystem surrounding the research and development of psychedelics is rapidly evolving, as exemplified by the notable increase in clinical trials in several regulatory jurisdictions. While the therapeutic potential of psychedelics is gaining recognition among clinicians and regulators alike, the development of safe and effective psychedelic medicines is a complex process.

Regulators recognise that the characteristics of psychedelics pose specific challenges for development programmes, including the design of associated clinical studies, to support marketing authorisation applications. However, as noted throughout the workshop, measures can be implemented to mitigate their impact. Developers can avail of advice and support from EMA through a variety of scientific and regulatory platforms. Early engagement with regulators is critical to ensure that regulatory challenges are addressed in a manner that takes the unique features of individual development programmes into consideration. This approach will enable developers to proactively address challenges and ensure alignment with existing regulatory frameworks.

During the workshop, there was consensus on the need to address knowledge gaps in the field. These include whether and how the subjective experience is associated with clinical outcomes and requirements for “set and setting”. Generating reliable and valid data is key to addressing these uncertainties. Additionally, participants agreed that further consensus is required on the optimal approach to systematically collect and document adverse events during active treatment.

Collaboration between academic and commercial researchers and developers was highlighted throughout the workshop as being critical. Cross-sector and multidisciplinary collaboration is required to not only accelerate the investigation and development of safe and effective psychedelic medicines but also to facilitate their implementation in the therapeutic armamentarium. Obstacles to implementation include restrictions on the production and supply of psychedelics due to their classification as controlled substances and the use of health technology assessment to determine their cost-effectiveness for reimbursement at national level. Learned societies must also consider where to place psychedelics in overall treatment guidelines and recommendations. Additionally, the capacity of national healthcare service providers to establish dedicated clinics for psychedelics is an important consideration. Bodies that regulate healthcare professionals must also reflect on regulatory standards for the field. While there was an ongoing debate on the role of psychotherapy versus psychological support throughout the workshop, there was general agreement amongst participants on the need for further collaboration to facilitate standardisation of appropriate frameworks of psychological support.

The workshop also underscored the importance of incorporating the lived experiences and perspectives of patients beyond their participation in clinical studies. Patient advocates contributed valuable insights, highlighting the need for shared decision-making with regard to shaping research design and frameworks of psychological support.

While there is much work to be done, the discussions and agreements reached during the workshop have laid the groundwork for continued collaboration in this emerging field of medicine.

Glossary

ADHD	Attention deficit hyperactivity disorder
AESI	Adverse event of special interest
AI	Artificial intelligence
ALS	Amyotrophic lateral sclerosis
CHMP	Committee for human medicines
CMA	Conditional marketing authorisation
COPD	Chronic obstructive pulmonary disease
COVID-19	Corona virus disease of 2019
EBC	European Brain Council
EC	European Commission
ECNP	European College of Neuropsychopharmacology
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EPA	European Psychiatric Association
ESOSOC	Economic and social council
EURORDIS	European Organisation for Rare Diseases
EU	European Union
FDA	Food and Drug Administration
HREC	Human Research Ethics Committee
HTA	Health technology assessment
HPPD	Hallucinogen-persisting perception disorder
ICH	International Conference on Harmonisation
IHI	Innovative health initiative
INCB	International narcotics control board
LSD	Lysergic acid diethylamide
MAA	Marketing authorisation application
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application

NDAA	National defense authorisation act
PAREA	Psychedelic Access and Research European Alliance
PASS	Post authorisation safety study
PPI	Patient and public involvement
PRIME	PRiority MEdicines
PsyPAN	Psychedelic Participant Advocacy Network
PTSD	Post-traumatic stress disorder
RANZCP	The Royal Australian and New Zealand College of Psychiatrists
RMP	Post authorisation safety study
RWD	Real-world data
RWE	Real-world evidence
SAP	Special access programme
SME	Small and medium-sized enterprises
SUSAR	Suspected unexpected serious adverse reaction
SSRI	Selective serotonin reuptake inhibitors
TGA	Therapeutic goods administration
TRD	Treatment resistant depression
US	United States
WHO	World health organisation

European Medicines Agency

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