The therapeutic potential of psychedelics: the European regulatory perspective

Published Online
February 10, 2023
https://doi.org/10.1016/
S0140-6736(23)00264-7

In the EU, mental health problems affect more than one in six people with considerable impacts for individuals and society and economic costs that exceed 4% of gross domestic product across the EU.[1,2] There is a need for effective, safe new treatments for mental disorders. In the past decade there has been a renewed interest worldwide in psychedelics as potential treatments for various mental health conditions,[3] such as treatment-resistant depression, addictive disorders, post-traumatic stress disorder, and end-of-life psychological distress.[4–7] These psychoactive compounds have overlapping effects via different mechanisms of actions which, in the context of therapeutic use, remain to be established.[8] Psychedelic substances induce alterations of consciousness, including visual effects, transient feelings of oneness with the universe, transcendence of time and space, and ego dissolution, but can also induce anxiety and psychological distress,[9] which can be alleviated through interpersonal support during administration.[10,11] Classic psychedelics act via 5-HT2A receptor agonism and include mescaline, N,N-dimethyltryptamine, lysergic acid diethylamide, and psilocybin. Atypical psychedelics (eg, 3,4-methylenedioxymethamphetamine and ketamine), have different pharmacological mechanisms of action and also differ in terms of legal status (eg, ketamine and esketamine are approved as medicines in the EU).

SDI Productions/Getty Images

We do not, therefore, include atypical psychedelics in this discussion of the European regulatory context for potential therapeutic uses of psychedelics in mental disorders. The issues we raise here are informed by our work for the European Medicines Agency (EMA), the EMA's Central Nervous System Working Party, and the European College of Neuropsychopharmacology (ECNP).

More research is needed to determine the therapeutic potential of psychedelics for mental disorders and there are multiple challenges that must be overcome for psychedelics to become safe and effective treatment options in Europe.[12] Challenges with research methodology need to be addressed to enable valid efficacy estimations in clinical trials. Maintaining double blinding in trials is challenging since placebo can be distinguished from the psychedelic experience by both patients and raters. Other study design strategies have been used, such as low-dose comparators or an active placebo.[13] However, the absence of a real placebo group might bias the effect estimate in either direction. Another important factor to consider is the role of positive expectancy[14] in the treatment effect and whether it leads to inflation bias. Similarly, consideration must be given to the role of disappointment or negative expectancy among research participants and its effect on symptom worsening or safety issues (nocebo effect).[15] The use of independent, blinded external raters, including psychedelic naive patients, and quantifying unblinding and expectancy should be considered in clinical trials.

Investigation is required to establish optimum doses of psychedelics, the relation between characteristics of the acute psychedelic experience and clinical improvement, and the need for individualised dosing due to inter-individual variability in drug metabolism and pharmacokinetics in relation to factors such as age, sex, or bodyweight.[16]

Trials also need to establish the added value of psychedelics compared with psychotherapy or psychological support alone. In clinical trials of psychedelics it is standard to include psychological support or psychotherapy,[4,17] and this approach is expected to be

reflected in future labelling. Trials should confirm that clinical improvements are not due to psychotherapy alone and characterise appropriate clinical settings, including pre-dose and post-dose psychological support or psychotherapy needed for optimal treatment. The need for and content of preparatory psychotherapy sessions should be investigated, because such therapy may lead to an increase in expectancy among patients and unblinding. The role of psychotherapy poses additional methodological challenges—eg, how to best evaluate the effects and compare different types of psychotherapy or psychological support.[18,19] Maintenance of effect, the need for repeated sessions, follow-up psychotherapy, or adjunctive pharmacological treatment must also be investigated.

The safety of psychedelics needs to be thoroughly assessed based on trial data and pharmacological properties, especially half-life. Further investigation of potential effects is warranted, including anxiety with derealisation, headaches, increased blood pressure, tachycardia, and suicidal ideations and behaviours.[20,21] Safety data on drug–drug interactions are also important, especially for regular co-administration with other medications.[22] Possible separation of acute versus long-term effects should be further elucidated: can the acute psychedelic effects be separated from the long-term effects? All conditions and restrictions related to safe and effective use of the psychedelic treatment would need to be defined at the time of approval, notably how and by whom the product should be administered, and what monitoring requirements should be in place before, during, and after the administration. Regulatory tools can be used to achieve this (eg, summary of product characteristics, risk management plan, and pharmacovigilance studies) together with additional risk minimisation measures, such as educational materials, appropriate training of staff, and controlled access programmes, which have been successfully implemented in the EU since 2019 after the authorisation of esketamine for treatment-resistant major depression in adults.[23] Additionally, the UN classification of psychedelic substances as schedule 1 drugs[24] might need to be revised given the emerging research on psychedelics. Classic psychedelics do not show potential for addiction[25] and the justification for the UN schedule 1 classification (ie, drugs with "no currently accepted medical use and a high potential for abuse"), as adopted in the 1971 Convention on Psychotropic Substances,[26] should be questioned by evidence of the therapeutic potential of psychedelics.

Depending on clinical facilities and training capacities, national health systems are likely to face practical and financial issues with the implementation of psychedelic therapies in comparison with approved treatments.

The EMA can support stakeholders to address some of these challenges. The EMA can offer consultations in parallel with the European Network for Health Technology Assessment (EUnetHTA)[27] to obtain feedback from regulators and HTA bodies. The EMA has also provided scientific advice to some developers on their development programmes.[28] Specific qualifications procedures on assessment instruments, methods, and study design can also be requested. Additionally, EMA guidelines are regularly updated—eg, the guideline on the clinical investigation of medicinal products in the treatment of depression is presently under revision.[29] Other EMA platforms to support engagement with regulatory processes and requirements for emerging psychedelic treatments include the Innovation Task Force, the small and medium-sized enterprises office, and specific approval paths that can allow earlier access to promising medicines through the priority medicines scheme or accelerated assessment. The new EMA Clinical Trials Regulation[30] could also facilitate the conduct of larger trials and help harmonise approaches for clinical investigation of psychedelics.

The therapeutic potential of psychedelics has triggered new hopes and high expectations, but larger clinical trials are needed to further evaluate efficacy and safety. A thorough scientific assessment of the benefit–risk balance will be required, as for any other medicines. Developers are encouraged to engage early with the EMA through all available scientific and regulatory platforms in their efforts to overcome the challenges associated with the development of psychedelic treatments.

ST reports consulting fees paid directly to his former employee from Cybin, a pharmaceutical company developing psychedelics (no personal payment). DE-WM reports a PhD stipend paid for by an unrestricted grant from COMPASS Pathways, a commercial company involved in trials of psychedelic substances for mental health conditions, that had no involvement in the writing of this Comment. GMK reports grants or contracts from Lundbeck Foundation, Novo Nordisk Foundation, Danish Research Council, the EU and other funding bodies; payment or honoraria from Sage Biogen, Onsero, Pangea, H Lundbeck, and

Angelini for consulting, lectures, presentations, or educational events; participation on data safety monitoring board or advisory board for the Human Brain Project, IMIM, Barcelona, and SGK Foundation; is a past President of the ECNP (not paid); and has Novo Nordisk stock options unrelated to the topic discussed (Novo Nordisk has no current therapies under investigation in this field). JL reports grants from the Swedish Research Council, lecture honorarium from Novartis, and financial support and in-kind work to provide investigational products (niacin and psilocybin) for researcher initiated phase 2b trial PSIPET (EudraCT-number: 2020-002790-94) from the non-profit Osmond Foundation. DSS reports grants from the Independent Research Fund Denmark, the Heath Foundation, and the Nordic Research Council; honoraria as speaker for the Lundbeck Foundation; and is a paid scientific adviser for Clerkenwell Health, a commercial company involved in trials of psychedelic substances for mental health conditions. The other authors declare no competing interests. This Comment comes from a collaboration between the EMA, the EMA's Central Nervous System Working Party, and the ECNP. The views expressed in this Comment are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the authors are employed or affiliated.

*Florence Butlen-Ducuing, Drummond E-Wen McCulloch, Marion Haberkamp, Taina Mattila, Ewa Bałkowiec-Iskra, Georgios Aislaitner, Pavel Balabanov, Johan Lundberg, Dea Siggaard Stenbæk, Andre Elferink, Gitte M Knudsen, Steffen Thirstrup

florence.butlen@ema.europa.eu

European Medicines Agency, 1083 HS Amsterdam, Netherlands (FB-D, PB, ST); Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark (DE-WM, DSS, GMK); Section Neurology, Psychiatry, Ophthalmology, Federal Institute of Drugs and Medical Devices, Bonn, Germany (MH, GA); Medicines Evaluation Board Utrecht, Netherlands (TM, AE); Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland (EB-I); Urząd Rejestracji Produktów Leczniczych, Wyrobow Medycznych i Produktów Biobójczych, Warsaw, Poland (EB-I); Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (JL); Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden (JL); European College of Neuropsychopharmacology (ECNP) Transnosological Working Group on Psychedelics, Utrecht, Netherlands (JL, DSS, GMK); Institute of Psychology (DSS) and Department of Clinical Medicine (GMK), University of Copenhagen, Copenhagen, Denmark

1 Organisation for Economic Co-operation and Development. A new benchmark for mental health systems: tackling the social and economic costs of mental ill-health. OECD Health Policy Studies. Paris: OECD Publishing, 2021.

2 Organisation for Economic Co-operation and Development, European Union. Health at a glance: Europe 2018: state of health in the EU cycle. Paris: OECD Publishing, 2018.

3 Tullis P. The rise of psychedelic psychiatry. *Nature* 2021; **589:** 506–09.

4 Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med* 2022; **387:** 1637–48.

5 Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse* 2017; **43:** 55–60.

6 Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J Psychopharmacol* 2020; **34:** 155–66.

7 Holze F, Gasser P, Müller F, et al. Lysergic acid diethylamide–assisted therapy in patients with anxiety with and without a life-threatening illness: a randomized, double-blind, placebo-controlled phase II study. *Biol Psychiatry* 2023; **93:** 215–23.

8 Grieco SF, Castrén E, Knudsen GM, et al. Psychedelics and neural plasticity: therapeutic implications. *J Neurosci* 2022; **42:** 8439–49.

9 Reiff CM, Richman EE, Nemeroff CB, et al; Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. Psychedelics and psychedelic-assisted psychotherapy. *Focus (Am Psychiatr Publ)* 2021; **19:** 95–115.

10 Barrett FS, Bradstreet MP, Leoutsakos JS, Johnson MW, Griffiths RR. The Challenging Experience Questionnaire: characterization of challenging experiences with psilocybin mushrooms. *J Psychopharmacol* 2016; **30:** 1279–95.

11 Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 2008; **22:** 603–20.

12 McClure-Begley TD, Roth BL. The promises and perils of psychedelic pharmacology for psychiatry. *Nat Rev Drug Discov* 2022; **21:** 463–73.

13 Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry* 2022; **79:** 953–62.

14 Butler M, Jelen L, Rucker J. Expectancy in placebo-controlled trials of psychedelics: if so, so what? *Psychopharmacol* 2022; **239:** 3047–55.

15 Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Rev Clin Pharmacol* 2021; **14:** 1133–52.

16 Vizeli P, Straumann I, Holze F, et al. Genetic influence of CYP2D6 on pharmacokinetics and acute subjective effects of LSD in a pooled analysis. *Sci Rep* 2021; **11:** 10851.

17 Carhart-Harris RL, Roseman L, Haijen E, et al. Psychedelics and the essential importance of context. *J Psychopharmacol* 2018; **32:** 725–31.

18 Nayak S, Johnson MW. Psychedelics and psychotherapy. *Pharmacopsychiatry* 2021; **54**: 167–75.

19 Horton DM, Morrison B, Schmidt J. Systematized review of psychotherapeutic components of psilocybin-assisted psychotherapy. *Am J Psychother* 2021; **74:** 140–49.

20 Madras BK. Psilocybin in treatment-resistant depression. *N Engl J Med* 2022; **387:** 1708–09.

21 Breeksema JJ, Kuin BW, Kamphuis J, van den Brink W, Vermetten E, Schoevers RA. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: a mixed-methods systematic review. *J Psychopharmacol* 2022; **36:** 1100–17.

22 Nayak SM, Gukasyan N, Barrett FS. Classic psychedelic coadministration with lithium, but not lamotrigine, is associated with seizures: an analysis of online psychedelic experience reports. *Pharmacopsychiatry* 2021; **54:** 240–45.

23 European Medicines Agency. Spravato (esketamine). https://www.ema.europa.eu/en/medicines/human/EPAR/spravato (accessed Feb 1, 2023).

24 International Narcotics Control Board. Green List—list of psychotropic substances under international control. 2022. https://www.incb.org/incb/en/psychotropics/green-list.html (accessed Feb 7, 2023).

25 Vollenweider FX, Vontobel P, Hell D, et al. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man—a PET study with [11C]raclopride. *Neuropsychopharmacol* 1999; **20:** 424–33.

26 Lambkin M. Prescription psychedelics: the road from FDA approval to clinical practice. *Am J Med* 2022; **135:** 15–16.

27 European Medicines Agency. Parallel joint scientific consultation with regulators and health technology assessment bodies. 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-joint-scientific-consultation-regulators-health-technology-assessment-bodies (accessed Feb 1, 2023).

28 European Medicines Agency. Scientific advice and protocol assistance. 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance (accessed Feb 1, 2023).

29 European Medicines Agency. Clinical investigation of medicinal products in the treatment of depression—scientific guideline. 2023. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-depression-scientific-guideline (accessed Feb 1, 2023).

30 European Medicines Agency. Clinical Trials Information System. 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system (accessed Feb 1, 2023).