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Analysis

The Fragile Promise of “Psychedelics” in Psychiatry: A Critical Examination

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KEY MESSAGES

- . There has been renewed interest in the use of psychedelics, delivered alone or in combination with psychotherapy, for treating mental health problems.
- . Regulatory agencies have approved several psychedelics using accelerated procedures, with lower levels of evidence deemed sufficient to consider treatments as promising.
- . We identified problems in the treatment literature that include overstated benefits, small sample sizes, and short follow-ups, even for phase 3 trials, preventing assessment of long-term safety issues; additional problems include conflicts of interest, lack of standardization on safety outcomes, and functional unblinding.
- . More rigorous research and higher ethical standards are needed.

Contributors and sources

Relevant experience and expertise of each author: Our group is made up of senior experts with different clinical expertise -psychiatrists (FN, ET), psychologists (LC, IC, EIF), one addiction specialist (AB)- and three students (CLM, RC, MP) who compiled a large clinical studies database on psychedelic treatments in psychiatry. Some of us are part of the Lown List of Industry-Independent Health Experts (AB, LC, IC, FN, ET). No patients were involved in conceiving or writing this article. Sources of information used: Systematic searches of ClinicalTrials.gov were performed to describe all registered studies. A detailed protocol of these searches is available on the Open Science Framework (31). In short, we used the Center for Addiction and Mental Health (CAMH) definition of hallucinogens (32) to search all psychiatric studies on “psychedelics” (i.e. hallucinogens). CLM and FN (who serves as the guarantor) wrote the first draft. All the other authors contributed to revising it critically and have agreed on the final content.

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Conflicts of Interest

We have read and understood BMJ policy on declarations of interests and have the following interests to declare: FN received funding from the French National Research Agency (ANR-17-CE36-0010), the French ministry of health and the French ministry of research. He is a work-package leader in the OSIRIS project (Open Science to Increase Reproducibility in Science). The OSIRIS project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No. 101094725. He is a work-package leader for the doctoral network MSCA-DN SHARE-CTD (HORIZON-MSCA-2022-DN-01 101120360), funded by the EU. The other authors declare no competing interests.

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The Fragile Promise of “Psychedelics” in Psychiatry: A Critical Examination

This paper argues that psychedelic research lacks critical evaluation, and recommends that health authorities use standard regulatory pathways instead of expedited ones for assessing the efficacy and safety of hallucinogens.

Introduction

Estimated at USD 3.1 billion in 2022, and expected to expand at an annual rate of 10.6% until 2030, the US ketamine clinical market(1) is just one of many signs of a renewed interest in the use of “psychedelics” to treat psychiatric conditions(2). Various mind-altering drugs have already entered the market, such as esketamine nasal spray, for which Janssen Pharmaceuticals, Inc. was granted approval in 2019 by the US Food and Drug Administration (FDA). Following a 2022 application by Mind Medicine Australia, Australia’s Therapeutic Goods Administration (TGA) allowed the drugs psilocybin and 3,4-Methylenedioxymethamphetamine (MDMA) to be prescribed by authorized physicians for psychiatric conditions such as depression and post-traumatic stress disorder. This decision contrasted with the recommendation provided by the independent scientific report the TGA had commissioned, which advised against authorization based on the fact that the certainty of evidence for benefits was low or very low (3). “Psychedelics”, the lay term for substances classified as hallucinogens, have various targets and distinct purported mechanisms of action. For instance, psilocybin is a serotonergic agonist, while esketamine is a N-methyl-d-aspartate (NMDA) glutamate receptor antagonist, although its effect is also attributed to synaptic plasticity; mystical experiences have also been reported as a mechanism of action.

In this paper we review the clinical trial literature where hallucinogens are often understood as “a new paradigm of care for mental health”(4). While many countries, including the UK, Japan, Indonesia, Saudi Arabia, Singapore, Russia, and China, have maintained relatively strict regulatory standards for hallucinogens, we illustrate the stakes for health authorities with examples from USA, Australia and Europe, and show that the field continues to ignore repeated calls for a critical evaluation (2,4) of the evidence.

Regulatory challenges

The clinical use of hallucinogens began after the accidental discovery of LSD's psychotropic effects by Alfred Hofmann in 1943 at Sandoz(5). Initially hailed as a cure for mental health issues, enthusiasm waned (6) a few years later due to negative clinical outcomes, controversial experiments by Timothy Leary, and failed military research. Sandoz ceased LSD and psilocybin production in 1965(7). Furthermore, new standards for drug evaluation following the thalidomide scandal, the adoption of the Kefauver-Harris Drug Amendments Act in 1962(8) and the Comprehensive Drug Abuse Prevention and Control Act of 1970, barred research on hallucinogens in the USA. Fifty years later, the renewed interest in hallucinogens comes at a time when major pharmaceutical companies have reduced research into psychopharmacology, leaving patients and clinicians with psychotropic drugs of limited efficacy(9) and unmet medical needs that they hope hallucinogens will address. Simultaneously, regulatory agencies are deploying expedited pathways more frequently(10), resulting in a lowering of approval standards worldwide. However, the evaluation of hallucinogens comes with unique methodological and regulatory challenges. In the US, the FDA must assess efficacy through "adequate and well-controlled trials," but this is challenging with hallucinogens due to functional unblinding, where participants often know their group. While blinding isn't always essential, it's a crucial safeguard, especially for subjective outcomes (11) and when there are strong participant expectations or investigator conflicts of interest. The FDA(12) and the European Medicine Agency (EMA)(13) are therefore developing guidelines to address pitfalls such as unblinding, suitability of control groups, and safety issues (**Box 1**). Furthermore, because hallucinogens use is often combined

with a psychotherapy component, it is even more difficult to separate the effects of the drug from the therapeutic context, complicating comprehensive evaluations and product labelling (**Box 2**).

Characterization of clinical pharmacology

- . Assess potential drug-drug and drug-disease interactions.
- . Evaluate inter-individual variability in drug metabolism due to age, sex, diet, etc.
- . Define dose-response relationship.
- . Explore connections between acute experience and long-term effects for both efficacy and safety.

Study design

- . Address functional unblinding by using independent and blinded raters and questionnaires in order to minimize bias from perceptual disturbances.
- . Include psychedelic-naive patients to reduce expectancy bias and regularly assess patient expectations.
- . Use both active placebos, i.e. placebos that produces effects that may convince the person being treated that they are receiving the drug under study.
- . Triangulate evidence using dose-response data and evidence from studies with inactive controls that can help to contextualize safety findings.
- . Evaluate effects over at least 12 weeks and monitor long-term symptom recurrence over a year.

Safety

- . Identify and manage adverse events (e.g., anxiety, headaches, tachycardia).
- . Set monitoring requirements before, during and after the studies.
- . Exclude subjects with pre-existing conditions (valvopathy or pulmonary hypertension) and explore risks of 5-HT_{2B} agonists (assess valve structure and function and pulmonary artery pressure).
- . Evaluate the potential for abuse misuse.
- . Ensure the healthcare system can prevent overdose for both patients and non-patients.

Box 1: Key challenges for hallucinogen trials identified by the FDA(12) and the EMA(13), in relation to the pharmacological component

Definition of the psychotherapeutic component

- . Determine appropriate psychotherapeutic characteristics for treatment.
- . Characterize suitable clinical settings.
- . Identifying the type of psychological support or psychotherapy needed before, during, and after drug administration.

Study design

- . Avoid involvement of in-session therapists or monitors in post-session psychotherapy to prevent deducing treatment assignments and inducing performance bias.
- . Manage high expectancies by limiting the potential for psychotherapeutic interventions to increase expectations and performance biases.
- . Establish the added value of psychedelic drugs compared to psychotherapy or psychological support alone, potentially using factorial designs.
- . Explore the maintenance of effects and the need for repeated sessions and follow-up psychotherapy, with or without adjunctive pharmacological treatment.

Safety

- . Involve an appropriate information of participants about potential changes in perception, cognition, and judgment, and the increased vulnerability and suggestibility during the treatment session.
- . Recognize that patients remain vulnerable for up to 12 hours post-treatment.
- . Ensure safety monitoring by two professionals (health professional and assistant monitor) during sessions.
- . Have a licensed on-call physician available within 15 minutes in case of emergency.

Box 2: Key challenges for hallucinogen trials identified by the FDA(12) and the EMA(13), in relation to the psychotherapeutic components

Marketing Authorisation: Theory to Practice in the USA and Europe

To address the unmet need for severe and treatment-resistant mental illness, the FDA has encouraged research on hallucinogens by granting some of them the Breakthrough Therapy designation (BTD), an expedited review process for drugs “intended to treat a serious condition [where] preliminary clinical evidence indicates that the drug could demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)”(14). This means that even a low level of evidence suggestive of efficacy is deemed sufficient to consider the treatment as promising for an unmet medical need. Expedited development and regulatory review pathways are frequently used by companies to accelerate regulatory approval of expensive cancer drugs despite a lack of robust evidence for their efficacy and safety. However, BTD is often misinterpreted by physicians, with one quarter wrongly believing that drugs receiving this designation were safer than previously approved treatments(15). The FDA granted esketamine BTD for the indication “treatment-resistant depression” (TRD) although there was no consensual definition of TRD. In addition, the FDA lowered the regulatory limit by not enforcing its decades-old standard of at least two positive initiation trials(16). Of the three short-term (4-week) initiation trials, only one showed a significant benefit over placebo. For the first time, a maintenance trial was accepted in place of a second positive initiation trial, despite the such trials overestimate treatment effects(9). Esketamine is not an isolated example. The FDA also used the BTD pathway to approve bupropion + dextromethorphan for MDD, and MDMA (post-traumatic stress disorder), LSD (anxiety) and psilocybin (depression) were granted BTD. In Europe, the EMA followed the FDA’s lead regarding esketamine, but several European Health Technology Assessment Bodies such as the French National Authority for Health and National Institute for Health and Care Excellence (NICE) diverged because of significant gaps in the evidence base (e.g. questionable clinical added value and/or insufficient data concerning long terms efficacy and safety). Of note, NICE's decision not to recommend esketamine nasal spray for TRD (17) was based on both clinical efficacy and cost-effectiveness, highlighting that different agencies’ standards include considerations beyond clinical evidence.

A growing research agenda, many inconsistencies

Given the hopes it has raised, research into hallucinogens has been a hot topic, with many new players. Alongside prominent pharmaceutical companies such as Janssen (esketamine), many studies are sponsored by smaller biotechnology companies such as COMPASS pathways (psilocybin) or Axsome Therapeutics (dextromethorphan). A non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS) sponsored many trials on MDMA before a wholly owned subsidiary of MAPS announced that it had become a drug-development public benefit company renamed Lykos Therapeutics. The research agenda is rapidly growing. A search of interventional studies registered on ClinicalTrials.gov shows trends typical of products in the early phases of development with registered study information often poorly described and inconsistent, with small sample sizes and short follow-up durations (18). Inconsistencies are not limited to trial entries on registries but are also evident in published articles on hallucinogens. For instance, a *JAMA Psychiatry* publication published an open-label psilocybin study without a control group as a “non-randomized controlled trial”(19); a recent study published in *eclinical Medicine* used ‘double-blind’ in the title, while the text reported clear and strong evidence of unblinding(20); and a meta-analysis on psilocybin published in *the BMJ* received an expression of concern just three days after publication due to likely inconsistencies and errors(21).

Overstated benefits

In pivotal studies, there was little evidence that the adequacy of blinding was assessed. For esketamine, functional unblinding was not specifically assessed, even though esketamine has been shown to increase the risk of dissociation seven-fold (22). For MDMA-assisted psychotherapy, functional unblinding was not formally assessed in the first pivotal study used for FDA new drug application (23) but it can be estimated that 81/90 (90%) participants may have correctly guessed which treatment they received at the end of the intervention(24). For the second pivotal study used for

FDA approval, the article misleadingly stated that the trial was “double-blind” and that “not all participants correctly identified the treatment that they received.” However, the supplement (p 16) shows that 94% of the patients assigned to MDMA correctly guessed their treatment assignment, versus 20% who thought they received MDMA in the placebo group (25). In addition to the problem of functional unblinding, a report from the Institute for Clinical and Economic Review (ICER) concluded that it was “not able to assess the frequency of misreporting of benefits and/or harm and thus the overall net benefit balance with MDMA”. ICER also noted (p 2) that “concerns have been raised by some that therapists encourage favourable reports by patients and discourage negative reports including reports of substantial harm, potentially biasing the recording of benefits and harm”(26).

There is evidence that both the scientific literature and media reports have overstated the benefits of hallucinogens. Even the scientific literature could be compromised by industry influence. *Nature* published advertorials in 2022, with the biotechnological company Atai Life Science (with programs on psilocybin, DMT, ibogaine, MDMA and novel 5-HT_{2A} Receptor Agonists) sponsoring a “Nature Outlook” series of 12 news features, one editorial and a “sponsor feature”(27). Regarding media reports, *The Guardian* reported “a more successful treatment for depression than a typical antidepressant”(28), although the study presented no findings on its primary outcome(29). In Maryland there were misleading, possibly false, claims in online direct-to-consumer advertising for the off-label use of ketamine (30).

Unique Safety Concerns

In contrast to well-established drug classes, hallucinogens have various proposed mechanisms of action, and their long-term effects are not fully understood. The potential for harm and serious adverse events from long-term use of hallucinogens would not be evident in short-term trials.

Pharmacovigilance suggests that esketamine could be linked to suicidal behaviours(31). A similar signal is observed for psilocybin, suggesting that it could increase serious adverse events, especially suicidal ideation and behaviours(32). Cardiovascular issues are to be expected, especially in vulnerable populations, as esketamine increases the risk of hypertension. While some of these events were observed during the development program, evidence suggests that not all were reported in the journal publications because of suboptimal reporting of safety issues(33). Furthermore, 5-HT_{2B} agonists such as psilocybin increase the risk of valvular disease(12). Urinary disorders occur with increased probability among ketamine and its derivatives, and severe ulcerative cystitis has been documented(34). Potential for abuse/misuse must not be underestimated, e.g. ketamine recreational use, poisoning(35), and legal seizures(36) are on the rise in the USA.

Beyond the drug-related adverse events, the psychotherapeutic component of "psychedelic-assisted psychotherapy" introduces additional safety concerns. Mind-altering drugs place patients in a state of heightened vulnerability and potentially increased risk of harm. For example, legal proceedings are underway involving therapists accused of sexual assault in a clinical trial sponsored by the MAPS(37). The fact that such events occurred in closely monitored clinical trials, where best practices are theoretically ensured, is particularly concerning. This raises significant concerns about the potential risks when implemented in everyday clinical practice. Despite said risks, attention to safety has been lax following Australia’s legalization of psilocybin and MDMA for use in depression and PTSD treatment(38).

Moving forward

The marketing of treatments for so-called treatment-resistant disorders is gaining popularity. According to a 2023 narrative review by key opinion leaders in *World Psychiatry*(39), treatment resistance could now affect up to 55% of people receiving antidepressants. In the context of a global shortage of clinicians, ensuring widespread availability of treatment facilities with appropriately trained and licensed professionals to guarantee medical oversight and safety precautions is a challenge. In addition, these new treatments will likely involve multiple therapy sessions at considerable costs —

estimates for treatments in Australia range between A\$25,000 to A\$30,000(40) — likely limiting accessibility and exacerbating (mental) health inequalities.

Because the stakes are so high, it is imperative that the benefits of hallucinogens outweigh the risks associated with relying on low-quality evidence. To guarantee that hallucinogens are rigorously vetted before endorsing them as safe and effective treatments, medical journals must appraise the evidence more critically, fully account for limitations, and avoid spin and unsubstantiated claims.

This should be associated with correcting the records when needed, e.g. the journal *Psychopharmacology* just retracted three MDMA therapy papers because of data integrity concerns and lack of transparency regarding some of the authors' conflicts of interest(41). Health authorities must require standard regulatory pathways over accelerated ones. Otherwise, they set a concerning precedent and encourage research of degraded quality, whose numerous inconsistencies are not up to standards. Regarding MDMA-assisted therapy, the FDA declined to approve the application(41). It remains to be seen whether this decision will prompt the generation of higher quality evidence in the area of hallucinogen research.

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