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An initiative for living evidence synthesis in clinical psychedelic research

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Renewed interest in psychedelics as treatments for mental disorders has recently emerged, but substantial challenges remain in obtaining evidence from available data to inform clinical decision-making. This Comment explores the current landscape of clinical psychedelic research, highlighting the need for a systematic approach to evidence synthesis.

Psychedelics have a long and varied history in human culture. Many societies around the world have used naturally occurring psychedelic substances for cultural, religious and healing ceremonies. Although there is much debate on the formal definition of a psychedelic compound[1,2], here we refer to psychedelics as compounds that act as either direct or indirect agonists of the serotonin system and produce a significant alteration of conscious experience. As such, these agents include but are not limited to: psilocybin (the tryptamine found in 'magic' mushrooms), lysergic acid diethylamide (LSD; the synthetic ergoline first prepared by Sandoz laboratories in 1938), *N,N*-dimethyltryptamine (DMT; the tryptamine found in the South American ceremonial brew, ayahuasca), 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT; found in the Sonoran Desert toad), mescaline (the phenethylamine found in species of cacti) and 3,4-methylenedioxymethamphetamine (MDMA; the phenethylamine currently developed therapeutically as midomafetamine by Lykos Therapeutics).

Scientific exploration of the therapeutic potential of psychedelics began in the mid-twentieth century. However, these studies were not designed with the rigor expected of contemporary clinical trials. Systematic research was eventually halted by regulatory backlash and hurdles. Today, the field of psychedelic therapy is marked by renewed interest, driven by emerging evidence to suggest that psychedelics have the potential to treat mental health conditions such as depression, anxiety, post-traumatic stress disorder (PTSD) and addiction[3]. Substantial public and private investments are evidenced by funding and educational initiatives from the European Union (EU) and US National Institutes of Health (NIH), along with over 1,000 related patents filed by dozens of companies[4].

Although there has been increasing interest and investment in the potential of psychedelics for mental health treatment, there are substantial challenges in synthesizing evidence from the available data[5]. Most studies so far have been small, and there has been substantial variability in design and methods across trials. In addition, the mechanisms that underlie potential therapeutic effects — experiential and/or neuroplastic — are not fully understood. Advanced imaging techniques are beginning to shed light on some of these mechanisms[6,7] but more research is necessary[8]. The risks associated with psychedelic therapies also remain unclear, as study populations are often carefully selected and may be unrepresentative of post-approval treatment populations. Issues such as functional unblinding and expectancy effects also complicate interpretation. These issues are highlighted by the recent decision by the US Food and Drug Administration (FDA) to not approve the new drug application for MDMA as a treatment for PTSD, citing concerns about the durability of the drug's therapeutic effects, the potential for expectancy bias, the role of psychotherapy, and safety. This decision represented an apparent shift in the FDA's positive outlook towards the treatment after designating MDMA as a 'breakthrough therapy for PTSD' in 2017.

Anyone casually following the psychedelic field over the past decade may have been surprised by the FDA's decision. Researchers, companies and the media alike have at times been zealous in their enthusiasm for psychedelics — leading to great expectations and considerable hype[9]. Recent years have seen an increasing amount of popular coverage of results from small studies by prominent news organizations. Meanwhile, attempts to consolidate evidence via meta-analyses and systematic reviews are quickly rendered out of date by new research. Rigorous, up-to-date evidence syntheses are essential to address uncertainties in the field and provide accurate data for clinicians, policymakers and patients about the therapeutic potential of psychedelics and their risk/benefit ratio[10].

SYPRES: a public resource

Our overarching goal is to create a robust and dynamic resource to assess the rapidly evolving evidence base in clinical psychedelic research. To achieve this, we will leverage living systematic reviews (LSRs) as an essential tool to navigate fast-paced scientific fields[11]. LSRs are continuously updated reviews that incorporate new evidence as it becomes available, ensuring that the latest findings are always reflected in the synthesis of data.

In the context of psychedelic research, the field's rapid progression presents notable challenges in consolidating data. Traditional systematic reviews quickly become outdated, failing to capture the most recent developments. By using LSRs, we can maintain an up-to-date and comprehensive understanding of the therapeutic potential and safety of psychedelic therapies.

We will create a series of meta-analyses published in peer-reviewed journals that will be subsequently updated on a regular basis as LSRs. These reviews will be accessible to a broad audience through open-access platforms, ensuring that researchers, clinicians, policymakers and the public can benefit from the latest insights. Importantly, unlike traditional peer-reviewed papers, these reviews will not be static; they

Table 1 | Investigating the efficacy and safety of psychedelics

Phase	Review question	Pre-registration
1	What is the efficacy of MDMA or MDMA-assisted therapy for PTSD and comorbid depressive symptoms?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=584945
	What is the efficacy of psilocybin or psilocybin-assisted therapy for depressive symptoms?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=584938
2	What is the efficacy of psilocybin or psilocybin-assisted therapy for anxiety symptoms?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=584943
	What is the efficacy of LSD or LSD-assisted therapy for anxiety symptoms?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=585184
3	What are the adverse effects of MDMA or MDMA-assisted therapy in randomized controlled trials?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=585190
	What are the adverse effects of psilocybin or psilocybin-assisted therapy in randomized controlled trials?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=585186
	What are the adverse effects of LSD or LSD-assisted therapy in randomized controlled trials?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=585197
4+	Additional drugs and conditions	

will be living documents, regularly updated and integrated into an online public dashboard. This public dashboard, known as SYPRES (Synthesis of Psychedelic Research Studies), will adhere to the principles of open science, maximizing transparency and reproducibility. All eligible studies, regardless of the direction or magnitude of their results, will be included – harnessing the benefits of meta-analysis to integrate conflicting results and assess their confidence and variability. Notably, assessments of study quality and risk-of-bias judgements will be made using the Cochrane risk-of-bias tool[12]. These assessments will be presented alongside our results in an accessible format for non-researchers. In cases where there is enough data to support doing so, we will analyze how design parameters, inclusion/exclusion criteria, and study quality metrics influence results. By publishing the code, data and methods used in our reviews, we aim to foster a collaborative and open scientific environment that enables continuous scrutiny and improvement of the evidence base while promoting high standards of research integrity and rigor.

Our initiative will initially contain three phases that investigate the efficacy and safety of psychedelics in randomized controlled trials (RCTs). In phase 1, we will investigate the evidence base for the most developed psychedelic therapies: MDMA for PTSD symptoms and psilocybin for depressive symptoms. In phase 2, we will investigate the efficacy of psilocybin and LSD for symptoms of anxiety. In phase 3, we will assess the safety profile of each of these three drugs across all conditions (including studies in healthy volunteers). Beyond these first three phases, we will continue to pre-register and perform further analyses as the field matures and more evidence on other drugs and conditions is available (Table 1). In addition to synthesizing evidence on efficacy and safety, we will also seek to answer questions on design and mechanism. For example, are two drug doses more efficacious than one drug dose? How different are effect sizes in open-label versus double-blind RCTs? What MRI-based mechanisms are linked to outcomes? What psychological-based mechanisms (such as therapeutic alliance or emotional breakthrough) mediate response? Does patient expectancy or unblinding influence results? Importantly, we will perform robust sensitivity analyses to understand how methodological and patient population factors influence our results.

In addition to being available through open-access peer-reviewed journals, our results will be on an interactive dashboard that will be updated as the field evolves. By presenting results in a manner accessible to the public, while also providing the underlying data and code for clinical researchers, we aim to provide valuable tools for multiple stakeholders under one unified resource. Individuals will be able to reference SYPRES to retrieve the current evidence base for different research questions, and interactively observe the influence of analysis choices and inclusion criteria.

Concluding remarks

The research examining psychedelic therapy is at a pivotal juncture. Although the therapeutic potential of these compounds is promising, the need for robust evidence synthesis is equally crucial. LSRs offer a promising solution to keep pace with the rapidly evolving evidence base, ensuring that the latest and most reliable data are readily accessible.

Transparency, open-science and collaborative efforts are essential to advance our understanding of psychedelics[13]. By committing to these principles, we can foster a scientific environment that maximizes reproducibility and rigor. Our initiative to create a series of open-access LSRs, supported by our online dashboard SYPRES, aims to provide a valuable resource for researchers, clinicians, policymakers and the public.

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