

An initiative for living evidence synthesis in clinical psychedelic research

S. Parker Singleton^{1,2*}, Brooke L. Sevchik^{1,2}, Simon N. Vandekar³, Eric C. Strain⁴, Sandeep M. Nayak⁴, Robert H. Dworkin⁵, J. Cobb Scott^{6,7†}, Theodore D. Satterthwaite^{1,2,8†}

¹Penn Lifespan Informatics and Neuroimaging Center, University of Pennsylvania, PA, USA

²Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, PA, USA

³Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

⁴Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

⁵Departments of Anesthesiology and Perioperative Medicine and Neurology, University of Rochester School of Medicine and Dentistry, New York, Rochester, USA

⁶Department of Psychiatry, Brain Behavior Laboratory, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

⁷VISN4 Mental Illness Research, Education, and Clinical Center at the Philadelphia VA Medical Center, Philadelphia, PA, USA

⁸Penn-CHOP Lifespan Brain Institute, Perelman School of Medicine, Children's Hospital of Philadelphia Research Institute, Philadelphia, PA, United States

* *Corresponding author*

† *These authors contributed equally*

Abstract:

Renewed interest in psychedelics as treatments for mental disorders and symptoms has produced a rapidly growing body of research across public and private spheres over the last decade. However, there are substantial challenges in synthesizing evidence from available data to inform both clinical decision-making and policy. This Comment explores the current landscape of clinical psychedelic research, highlighting the need for a systematic, evolving approach to evidence synthesis. We propose the establishment of living systematic reviews (LSRs) as a means to navigate the dynamic and rapidly burgeoning evidence base. Additionally, we outline our vision for creating a publicly available online resource, *SYPRES (Synthesis of Psychedelic Research Studies)*, that adheres to the principles of open science, transparency, and data accessibility. By providing a comprehensive and continuously updated repository of meta-analyses, we aim to support researchers, clinicians, policymakers, and patients in making informed decisions about the therapeutic potential of psychedelics.

Why psychedelics and why now?

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. While 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-20th 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 suggesting that psychedelics have potential to treat mental health conditions such as depression, anxiety, PTSD, and addiction³. Substantial public and private investment is evidenced by funding and educational initiatives from the EU and NIH, along with over 1,000 related patents filed by dozens of companies⁴.

While 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 data⁵. Most studies to date have been small, and there has been substantial variability in design and methods across trials. Additionally, the mechanisms underlying 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 necessary⁸. 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 FDA's recent decision to not approve the new drug application for MDMA as a treatment for PTSD, citing concerns regarding 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 last 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 significant hype⁹. 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 regarding the therapeutic potential of psychedelics and their risk-benefit ratio¹⁰.

SYPRES - a public resource

Our overarching goal is to create a robust and dynamic resource for assessing the rapidly evolving evidence base in clinical psychedelic research. To achieve this, we will leverage living systematic reviews (LSRs) as an essential tool for navigating fast-paced scientific fields¹¹. 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 significant challenges in consolidating data. Traditional systematic reviews quickly become outdated, failing to capture the most recent developments. By employing 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 will be living documents, regularly updated and integrated into an online public dashboard. This public dashboard, *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 tool¹². 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, allowing for continuous scrutiny and improvement of the evidence base while promoting high standards of research integrity and rigor.

Our initiative will initially contain three phases investigating 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 psilocybin and LSD's efficacy 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 additional analyses as the field matures and more evidence on other drugs and conditions is available. 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 (e.g. therapeutic alliance, emotional breakthrough, etc.) 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.

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	

Table 1. Investigating the efficacy and safety of psychedelics.

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. While the therapeutic potential of these compounds is promising, the need for robust evidence synthesis is equally critical. 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 advancing our understanding of psychedelics¹³. 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.

Acknowledgments

This effort is supported by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks and Pediatric Anesthesia Safety Initiative (ACTTION/PASI) public–private partnership with the US Food and Drug Administration (FDA). The views expressed in this article are those of the authors, and no endorsement by the FDA should be inferred. ACTTION has received research contracts, grants, or other revenue from the FDA, multiple pharmaceutical and device companies, philanthropy, royalties, and other sources. The authors would like to thank Michael Haichin, Manoj Doss, and Matthew Baggott for their insightful feedback on the original draft of this comment.

Competing interests statement

ECS has received in the past 2 years consulting fees from Pear Therapeutics and Fast Track Drugs & Biologics. SMN is a co-investigator on a Usona Institute sponsored trial of psilocybin for Major Depressive Disorder. RHD since January 1, 2021 has received research grants and contracts from the US Food and Drug Administration and the US National Institutes of Health, and compensation for serving on advisory boards or consulting on clinical trial methods from Acadia, Akigai, Allay, AM-Pharma, Analgesic Solutions, Beckley, Biogen, Biosplice, Bsense, Cardialen, Chiesi, Clexio, Collegium, CombiGene, Confo, Contineum, Eccogene, Editas, Eli Lilly, Emmes, Endo, Epizon, Ethismos (equity), Exicure, GlaxoSmithKline, Glenmark, Gloriana, JucaBio, Kriya, Mainstay, Merck, Mind Medicine (also equity), NeuroBo, Noema, OliPass, Orion, Oxford Cannabinoid Technologies, Pfizer, Q-State, Regenacy (also equity), Rho, Salvia, Sangamo, Semnur, SIMR Biotech, Sinfonia, SK Biopharmaceuticals, Sparian, SPM Therapeutics, SPRIM Health, Tiefenbacher, Validae, Vertex, Viscera, and WCG. All other authors (SPS, BLS, SNV, JCS, and TDS) have no conflicts to declare.

Author contributions

SPS, JCS, and TDS wrote the initial draft of the manuscript with critical feedback provided by RHD, ECS, SMN, BLS, and SNV.

References:

1. Nichols, D. E., Nichols, C. D. & Hendricks, P. S. Proposed Consensus Statement on Defining Psychedelic Drugs. *Psychedelic Med.* **1**, 12–13 (2023).
2. Nichols, D. E., Hendricks, P. S. & Nichols, C. D. If Everything Is Psychedelic, Then Nothing Is: A Response to O'Donnell et al. and Lepow et al. *Psychedelic Med.* **1**, 195–197 (2023).
3. Reiff, C. M. *et al.* Psychedelics and Psychedelic-Assisted Psychotherapy. *Am. J. Psychiatry* **177**, 391–410 (2020).
4. Siegel, J. S., Daily, J. E., Perry, D. A. & Nicol, G. E. Psychedelic Drug Legislative Reform and Legalization in the US. *JAMA Psychiatry* **80**, 77–83 (2023).
5. van Elk, M. & Fried, E. I. History repeating: guidelines to address common problems in psychedelic science. *Ther. Adv. Psychopharmacol.* **13**, 20451253231198466 (2023).
6. Siegel, J. S. *et al.* Psilocybin desynchronizes the human brain. *Nature* 1–8 (2024)
doi:10.1038/s41586-024-07624-5.
7. Erritzoe, D. *et al.* Exploring mechanisms of psychedelic action using neuroimaging. *Nat. Ment. Health* **2**, 141–153 (2024).
8. Linguiti, S. *et al.* Functional imaging studies of acute administration of classic psychedelics, ketamine, and MDMA: Methodological limitations and convergent results. *Neurosci. Biobehav. Rev.* **154**, 105421 (2023).
9. Yaden, D. B., Potash, J. B. & Griffiths, R. R. Preparing for the Bursting of the Psychedelic Hype Bubble. *JAMA Psychiatry* **79**, 943–944 (2022).
10. E-Wen McCulloch, D. *et al.* Knowledge gaps in psychedelic medicalisation: Clinical studies and regulatory aspects. *Neurosci. Appl.* **3**, 103938 (2024).
11. Elliott, J. H. *et al.* Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap. *PLOS Med.* **11**, (2014).
12. Sterne, J. A. C. *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* **366**, l4898 (2019).
13. Nosek, B. A. *et al.* Replicability, Robustness, and Reproducibility in Psychological

Science.