CNS Spectrums

www.cambridge.org/cns

The revival of psilocybin between scientific excitement, evidence of efficacy, and real-world challenges

Mauro Scala[1,2], Chiara Fabbri[1], Paolo Fusar-Poli[3,4,5,6], Giorgio Di Lorenzo[7,8], Maria Ferrara[9], Andrea Amerio[10,11], Laura Fusar-Poli[4], Anna Pichiecchio[4,12], Carlo Asteggiano[12], Marco Menchetti[1], Diana De Ronchi[1], MNESYS - Mood and Psychosis Sub-Project (Spoke 5)[#], Giuseppe Fanelli[1,13] and Alessandro Serretti[14,15]

[1]Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy; [2]Health Research Institute Hospital 12 de Octubre (imas12), Madrid, Spain; [3]Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, King's College London, London, United Kingdom; [4]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [5]OASIS Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom; [6]Department of Psychiatry and Psychotherapy, University Hospital, Ludwig-Maximilian-University, Munich, Germany; [7]Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; [8]IRCCS Fondazione Santa Lucia, Rome, Italy; [9]Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy; [10]Health Research Institute Hospital 12 de Octubre (imas12), Madrid, Spain; [11]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [12]Advanced Imaging and Artificial Intelligence Center, Department of Neuroradiology, IRCCS Mondino Foundation, Pavia, Italy; [13]Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands; [14]Department of Medicine and Surgery, Kore University of Enna, Italy and [15]Oasi Research Institute-IRCCS, Troina, Italy

Abstract

The revival of psilocybin in psychopharmacological research heralds a potential paradigm shift for treating mood and anxiety disorders, and other psychiatric conditions beyond the psychotic spectrum. This critical review evaluates current evidence on psilocybin's efficacy, juxtaposing potential benefits with the practical aspects of psychedelic-assisted psychotherapy (PAP) and the methodological constraints of existing research.

An electronic literature search was conducted using PubMed/MEDLINE, selecting studies published up to December 2023 that explored the clinical use of psilocybin in mood and anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, and substance use disorder. Despite promising preliminary results suggesting psilocybin's efficacy in alleviating depression and anxiety, as well as obsessions, compulsions, and addictive behaviors, significant evidence gaps persist. These include evaluating the efficacy of psilocybin compared to standard antidepressants or anxiolytic molecules and identifying patient subpopulations that might benefit most from PAP. Concerns about psilocybin's safety, long-term efficacy, and optimal dosage remain unclear due to previous trials' limitations. Real-world implementation faces challenges, including infrastructural requirements, personnel training, and unresolved legal and ethical issues. This paper argues for further research to substantiate the evidence base, emphasizing the need for larger studies that overcome current methodological limitations and explore psilocybin's full therapeutic potential. While psilocybin holds promise for psychiatry, its successful translation from research to clinical practice demands more robust evidence on efficacy, safety, and methodological rigor. In addition, other factors, such as cultural stigma and legal/ethical issues, need to be successfully addressed to facilitate psilocybin's implementation in healthcare systems.

Review

Cite this article: Scala M, Fabbri C, Fusar-Poli P, Di Lorenzo G, Ferrara M, Amerio A, Fusar-Poli L, Pichiecchio A, Asteggiano C, Menchetti M, De Ronchi D, MNESYS - Mood and Psychosis Sub-Project (Spoke 5), Fanelli G, and Serretti A (2024). The revival of psilocybin between scientific excitement, evidence of efficacy, and real-world challenges. *CNS Spectrums* **29**(6), 570–584.
https://doi.org/10.1017/S1092852924002268

Received: 24 May 2024
Accepted: 17 October 2024

Keywords:
rapid-acting antidepressants; psilocin; pharmacotherapy; synaptic plasticity; personality; cognitive flexibility

Corresponding author:
Giuseppe Fanelli;
Emails: giuseppe.fanelli5@unibo.it; drgiuseppefanelli@gmail.com

[#]MNESYS—Mood and Psychosis Sub-Project (Spoke 5) [Collaborative Author Group]: Luigi Grassi (University of Ferrara, Ferrara, Italy); Alessio Maria Monteleone and Silvana Galderisi (University of Campania, Naples, Italy); Alessandro Bertolino (University of Bari, Bari, Italy); Mirella Ruggeri and Sarah Tosato (University of Verona, Verona, Italy); Valdo Ricca (University of Florence, Florence, Italy); Gianluca Serafini (University of Genoa, Genoa, Italy); Cinzia Niolu (Tor Vergata University of Rome, Rome, Italy); Pierluigi Politi (University of Pavia, Pavia, Italy).

Introduction

The need for new treatments for psychiatric disorders is evidenced by increased research into novel pharmacological approaches.[1-3] Standard antidepressant drugs are widely used in depressive disorders but not without drawbacks. These include high nonresponse rates, the persistence of some residual symptoms (e.g., cognitive and sleep disturbances), undesirable metabolic and sexual side effects,[4-7] as well as the delayed onset of therapeutic effects.[8] Antidepressants are also used to treat other psychiatric disorders including obsessive-compulsive disorder (OCD),[9] post-traumatic stress disorder (PTSD),[10] and substance use disorder (SUD).[11] However, despite the establishment of an appropriate treatment paradigm with current antidepressants, up to 60% of patients with OCD continue to experience debilitating residual symptoms,[9] and less than 30% of

patients with PTSD achieve clinical remission.[10] Standard antidepressants produce inconsistent improvements when treating depression associated with SUD.[11] These challenges highlight the need for novel, rapid-acting pharmacological approaches to possibly overcome the limitations of standard antidepressants.

Within this context, psychedelics have received much attention over the past few years. Although researchers started to explore the effects of psychedelics in the 1950s,[12] psilocybin only recently was granted the status of breakthrough therapy by the Food and Drug Administration (FDA) for treatment-resistant depression (TRD).[13] The latter was not an endorsement for clinical use, but an invitation to provide further evidence on which clinical decisions can be based. The principal reason for this caution can be identified in previous trials' methodological issues that have contributed to classifying psilocybin as a drug of abuse with no medical value over the past 50 years.[14] Furthermore, the psychoactive effects of psilocybin, including disturbances of consciousness, mood, perception, and thought, left this drug for recreational use rather than a potential psychopharmacological treatment.[15] Indeed, the historical primary use of psilocybin in ancient indigenous rituals intended to induce mystical experiences and a simultaneous altered state of consciousness, thus allowing for better processing of unconscious memories.[16]

More recently, these effects were found to be closely dependent on plasma psilocin levels (i.e., psilocybin's active metabolite) and serotonin $5HT_{2A}$ receptor occupancy rates,[17] which increases glutamate tone, thus leading to more active synaptic plasticity.[18] Despite these compelling pharmacodynamic properties, a 2016 survey revealed conflicting opinions among clinicians regarding the possible use of psilocybin for therapeutic purposes. Only 43% of the participants expressed support, while the majority of responders perceived the use of hallucinogens as potentially hazardous.[19]

However, recent brain imaging studies aimed at elucidating psilocybin's therapeutic mechanisms showed significant changes in brain connectivity.[20,21] Functional magnetic resonance imaging (fMRI) and perfusion studies conducted before and after treatment showed decreased activation and reduced cerebral blood flow in the amygdala,[22] as well as variations in prefrontal-limbic functional connectivity.[23,24] Psilocybin also decreases brain modularity, correlating with clinical outcomes, unlike the selective serotonin reuptake inhibitor (SSRI) escitalopram.[25,26] Electrophysiology studies also revealed that psilocybin reduces alpha, beta, and delta band activity in both healthy and depressed individuals, while an increase in theta power correlates with depressive symptoms improvement in major depressive disorder (MDD).[27,28]

Preliminary literature provides converging evidence about the potential therapeutic efficacy of psilocybin after one or two administrations, particularly in mood disorders.[29] Psilocybin might also represent a treatment alternative for depression and anxiety comorbid with life-threatening cancers – conditions often resistant to other psychopharmacological therapies –[30] as demonstrated in some randomized, crossover trials, despite their small sample sizes.[31-33] However, these clinical trials showed several limitations that require careful consideration when drawing conclusions about efficacy. Moreover, only one randomized clinical trial (RCT) directly compared the efficacy of psilocybin with escitalopram without demonstrating a significant difference between the two.[26]

After these preliminary findings, Australia has recently become the first country in the world to approve psilocybin for the treatment of TRD, albeit with stringent regulatory oversight requiring ethics committee approval for use in each patient.[34] Despite these advancements and the ensuing enthusiasm, psilocybin has not been approved for the treatment of depression or other mental disorders (i.e., anxiety disorders, OCD, PTSD, and SUD) in other countries, and its use in real-world clinical settings will have to face several unresolved issues, which have not been frequently discussed in the literature.[35-37]

The present critical review aims to offer an evidence-informed clinical opinion on the possible implementation of psilocybin-based treatment strategies in psychiatric clinical settings, examining the shortcomings of previous studies that assessed the clinical efficacy of psilocybin, as well as discussing the possible obstacles to its use in real-world psychiatric practice. Some suggestions for the potential use of psilocybin in clinical practice will also be made, with particular attention to feasibility and acceptability. The psilocybin's unique strengths and innovative potential will also be discussed.

Materials and methods

An electronic literature search was conducted using PubMed/MEDLINE for English-language articles published from inception to December 2023. We used the keyword "psilocybin" combined with terms related to depressive disorders, bipolar depression, anxiety disorders, OCD, PTSD, and SUD.

This critical review does not intend to systematically summarize the extent of the effect of psilocybin, given the number of reviews already available in the literature,[29,38] but rather to offer an expert clinical opinion on the available evidence and possible future perspectives. Key aspects evaluated include its safety profile, addictive potential, optimal dosing, and the altered states of consciousness that may arise during psychedelic-induced mystical experiences. Moreover, this review evaluates the uncertainty about the efficacy of psilocybin independent of concomitant psychotherapy, as well as the positioning of psilocybin-based therapy within treatment paradigms, its comparative efficacy versus standard antidepressants, the appropriate infrastructure and personnel expertise for its safe and effective implementation, and ethical and legal challenges related to psilocybin use.

Results

Barriers to clinical implementation of psilocybin-based treatments, along with psilocybin's potential strengths and innovations, are presented in Table 1 and described in the following paragraphs.

Safety profile and addictive potential

In evaluating the incorporation of psilocybin into clinical psychiatric practice, a thorough assessment of its safety profile and addictive potential is imperative. In this section, we present the safety warnings related to psilocybin use, providing an opinion on the risk of adverse events when psilocybin is administered in controlled settings.

Overall, the compound was well tolerated in most clinical trials.[8] The most common adverse events include nausea, headache, and minimal reductions in cardiovascular parameters (such as basal heart rate and blood pressure), with frequencies up to 33%, 67%, and 76%, respectively, according to the available trials.[8] A mild activation syndrome characterized by moderate anxiety or fear, tremors, and emotional liability affects between 17 and 23.2% of participants at the beginning of the treatment.[8] When this syndrome is accompanied by transient paranoid ideation, it is

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 1. Evidence-based strengths and challenges of potential use of psilocybin in real-world clinical practice

	Strengths	Challenges
PAP	Short-term treatment with one or few sessions	Unknown benefits of psilocybin without PAP
	Limited/no risk of poor treatment adherence	Operator-dependent approach
	Rapid onset of action	Patients' motivation
	Alleged sustained therapeutic effect over time	Need for strong therapeutic alliance
	Possible implementation of different psychotherapeutic approaches	Unclear optimal duration
		Economic and human resources to train clinicians
		Need for culturally adapted versions
		Long duration of a PAP session
		Unknown benefits in depressed patients with comorbid personality disorders
Safety profile	Dose-dependent AEs	Transient and self-limiting fatigue, hypertension, tachycardia, vomiting, insomnia, and psychological discomfort during PAP
	Rare serious AEs	Risk of serious AEs if simultaneous ingestion of alcohol and/or other psychedelics
	Rare "bad trips"	Lack of a "rescue" drug
	Low risk of HPPD	Paucity of data about long-term safety profile
	No sexual dysfunction, cognitive impairments, weight gain, metabolic changes, or manic switch	
	No withdrawal symptoms	
	Low risk of serotonin toxicity	
	No risk of dependency and/or addiction	
Dosing	Possibility of adapting the dose (macro- or micro-dosing)	Incomplete knowledge about dose–response therapeutic relationship
		Lack of multi-arms RCTs
		Unknown interactions with antidepressants and other psychotropic drugs
		Lack of psilocin-level measures
		Influence of subjective experiences
Mystical experience and personality domains	Improvement in cognitive flexibility	Possibility of being influenced by one's thoughts
	Rapid decrease in depressive ruminations	Brainwash and inappropriate behaviors
	Increase in empathy, self-acceptance, and social life	Potentially unwanted personality changes
	Effects in personality domains (neuroticism, extroversion, and openness)	
Trial confounders and limitations		Stringent inclusion criteria
		Small sample size
		Risk of selection, performance, and detection biases
		Short follow-up
		No comparison with placebo or TAU
		Open-label and crossover designs
		Pilot and proof-of-concept studies
		Single-dose protocols
Ethical challenges and legal considerations		Appropriate delivery of informed consent
		Recreational use
		Self-medication use without medical support
		Equitable access to PAP
		Need of psychoeducation
		Cultural and social stigma
		Impossibility of patenting psilocybin

Abbreviations: AE, adverse event; HPPD, hallucinogen persisting perception disorder; PAP, psychedelic-assisted psychotherapy; RCT, randomized clinical trial; TAU, treatment as usual.

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

colloquially referred to as a "bad trip". Anxiety, mainly due to psychological discomfort during psychedelic-assisted psychotherapy (PAP), is generally acute and transient and improves with therapists' reassurance.[39] Rates of fatigue and insomnia were found to be above 5%.[8] A major concern is related to the risk of developing hallucinogen-persisting perception disorder (HPPD), which includes two major subtypes. HPPD I, also known as "benign flashback" or "flashback type", has a short-term, reversible, and benign course.[40] In a study involving a small sample of male patients with AIDS, one participant experienced a post-traumatic stress flashback of a sexual assault two days after the PAP, which may be attributed to HPPD I.[39] HPPD II, conversely, usually presents as recurrent, long-term, distressing, and pervasive perceptive disturbances. It's noteworthy that the Diagnostic and Statistical Manual of Mental Disorders (DSM) does not differentiate between HPPD I and II, and the issue is still controversial.[40] The common symptomatology across both types of HPPD includes recurring visual hallucinations (e.g., flashes and intensified color perception, palinopsia, micropsia, and macropsia), false perceptions of movement, recurrent synesthesia, dissociation, auras, depersonalization, and derealization.[15] HPPD has mainly been associated with the use of lysergic acid diethylamide (LSD).[40] However, it has also been reported after recreational psilocybin use, often together with alcohol and cannabis consumption.[15] Despite the limited occurrence of HPPD in clinical studies with therapeutic dosages of psilocybin (10–25 mg), further controlled trials should better explore the clinical implications. It is essential to understand whether the potential occurrence of these transient or enduring psychotic symptoms may represent an obstacle to the therapeutic use of psilocybin.

Regarding possible serotonin toxicity, psilocybin shows a lower risk compared to other psychedelics.[41] Both psychedelic effects and serotonin syndrome are associated with an increase in 5-HT_{2A} neurotransmission[42,43] that is responsible for transient serotonin-related symptoms such as nausea, anxiety, hypertension, tachycardia, visual deficits, motor incoordination, and mild tremors, even at therapeutic doses. These symptoms usually subside within a few hours and typically do not need hospitalization.[44] However, there is a tipping point at which 5-HT_{2A} receptor stimulation can occasionally lead to severe intoxications, marked by symptoms such as myoclonus, rigidity, severe hyperthermia, and impaired mental status persisting beyond the psilocybin sessions. In such cases, serotonin syndrome should be considered.

Overall, all the mentioned adverse events display a dose-dependent relationship and can cause significant impairment when combined with alcohol or other psychedelics during recreational use.

Despite the potential for adverse effects, clinical findings remain encouraging. During trials, participants do not express a desire for further PAP sessions or dose increases. Hence, despite psilocybin being classified as a drug of abuse, the US Drug Enforcement Administration (DEA) does not include it among the drugs that can cause dependence and/or addiction.[45] Based on the evidence so far, a high risk of physical addiction could be excluded. At most, in uncontrolled settings, there is a potential for behavioral dependence, where dopamine release would not be triggered by the drug itself but by an external factor (i.e., the state of mind or the gesture of assumption).[46]

A potential limitation of psilocybin use in clinical settings is the lack of a specific antagonist medication to counteract adverse experiences. Benzodiazepines could be a viable solution in case of mild activation or occasional insomnia after PAP, while low doses of typical (i.e., haloperidol, perphenazine, or sulpiride) or atypical antipsychotics (i.e., aripiprazole)[40] may be used if transient psychotic symptoms occur.

In summary, patients treated with psilocybin generally experience mild and transient side effects, which can be partially alleviated through psychological support provided during PAP. Long-term side effects cannot be well quantified and evaluated at present, given the current lack of well-powered studies. Therefore, we suggest carefully considering the safety profile of psilocybin, but also balancing the risks with the pros; for example, in medical and research settings there is no risk of withdrawal symptoms for psilocybin, and the drug has a sexually and metabolically safe profile.[8] However, further research is needed to understand the safety profile of psilocybin in naturalistic contexts.

Dosing

Establishing a safe and effective dose is fundamental for the medical use of psilocybin. Whether higher dosing or micro-dosing has a better therapeutic effect remains controversial, and the dose–response relationship of psilocybin is still a debated issue. According to two recent dose–response meta-analyses, the most effective dose for depressive disorders appears to be between 24.68 mg/70 kg[47] and 35 mg/70 kg.[48] For TRD, the optimal dose is suggested to be higher, with an effective dose of 40 mg/70 kg, whereas for anxiety lower doses should be considered 22.78 mg/70 kg.[47] However, these results were likely influenced by publication and reporting bias. While higher dosages may be more effective in some groups of patients, such as those with alcohol use disorders, they may be responsible for more frequent adverse events such as dysphoria and anxiety, particularly troublesome for patients with advanced cancer.[49] Multi-arms studies testing psilocybin across various psychiatric conditions could help to address this issue.

We suggest here some aspects that researchers and clinicians should consider when tailoring psilocybin dose in clinical settings. First, micro-dosing sessions should be considered before prescribing a macro-dose, considering the patient's expected sensitivity to adverse events. Second, measuring plasma psilocin levels, as is done with current antidepressants,[50] may help optimize the dose.[17] However, it remains to be clarified whether administering another antidepressant in combination therapy influences therapeutic response, regardless of psilocybin's blood levels.[51] Lastly, assessing patients' genetic polymorphisms in psilocybin pharmacodynamic targets might help to predict response.[52] Nonetheless, the introspective and subjective experiences (i.e., significant changes in perception, cognition, affect, volition, and somesthesia)[16] induced by this compound may go beyond the dosage, pharmacokinetic, and pharmacodynamic mechanisms, as discussed in the next paragraph.

Mystical experience and personality domains

During PAP, therapists aim to support patients to access an enduring mystic state where they can reprocess unconscious memories. Music and a supportive environment during PAP facilitate this process, increasing psychological and cognitive flexibility, which is the main mediator of psilocybin benefits in mood disorders.[53] During these processes, rigid thought patterns are loosened and experiences of ego-dissolution and deep universal connections are reported.[54] Within the phenomenon of ego-dissolution, patients experience a profound disintegration of their perception of being a separate self from their surroundings. Ego-dissolution involves the breakdown of typical cognitive structures that contribute to

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

individual consciousness, ultimately leading to a sense of loss of personal identity, as well as a more fluid perception of subjective experience.[55] However, under these conditions, there is a possibility of individuals being influenced in their thoughts, and there have been occasional attempts to brainwash individuals.[56] One way to prevent inappropriate behaviors during PAP sessions could be to ensure the constant presence of at least two therapists per session. Despite these negative occurrences, we emphasize that mystical experiences appear relevant to decrease depressive ruminations and increase empathy, self-acceptance, social life, and openness. A single PAP session has indeed been found to decrease neuroticism and increase both extroversion and openness when personality was assessed using the Revised NEO Personality Inventory (NEO-PI-R) at 3 months of follow-up.[57] While standard antidepressants can also slightly mitigate neuroticism in MDD, extroversion and openness are specifically related to the effect of PAP.[58,59] These variations in personality domains, if durable, reshape the patient's interactions with the environment and may explain the sustained effect of psilocybin over time only after a few sessions. On the other hand, the possibility of long-lasting personality effects may raise ethical issues.[32,57] We underline that the available studies have a maximum follow-up duration of 12 months,[60] with only two secondary analyses providing data on 4.5 years of follow-up,[61,62] This temporal limitation underscores the necessity for extended longitudinal studies to comprehensively evaluate the durability of psilocybin's therapeutic benefits.

The relevance of these findings derives from the fact that they overcome the traditional assumption that personality changes can only occur slowly and gradually.[63] The effect of psilocybin appears even more intriguing when considering the stability of personality traits in healthy adults, as well as the greater rigidity of personality in patients with psychiatric disorders[64] compared to the general population.[65] According to the above, we glimpse the potential benefits of using the PAP paradigm in personality disorders, especially considering that to date no drugs are specifically approved to treat these conditions. However, we also underline that there is currently no experimental evidence from clinical trials supporting this hypothesis. Future research would help to bridge the gap between psychopathology and neurobiology, by studying the possible link between changes in psychopathological dimensions of personality (assessed, for instance, with the NEO-PI-R or the Personality Inventory for DSM-5 (PID-5)) and variations in specific functional brain networks induced by psilocybin in neuroimaging studies. Despite neuroplasticity phenomena mainly occurring in the prefrontal cortex, amygdala, and hippocampus,[66] the molecular mechanisms underlying these effects remain essentially unknown.

Psychedelic-assisted psychotherapy

According to the current trial protocols, psilocybin is typically administered alongside a psychological support called PAP. The only exception is a trial of psilocybin for OCD where no concomitant psychotherapy or psychosocial intervention was provided to participants.[67]

PAP includes three phases: preparation, psilocybin session, and integration. During preparation, patients are given information about the upcoming drug therapy session and guidance on how to maximize benefits while minimizing adverse events. This increases patients' expectations and suggestibility toward the treatment, posing challenges in obtaining accurate informed consent. Since the surrounding setting significantly influences the experience and the adverse events, PAP sessions are delivered in a calm and relaxing environment with a preselected music program. If future trials confirm the importance of these setting requirements, this could limit widespread clinical application, as only a few healthcare centers may be adapted in a feasible way, and provide the personnel needed. In the weeks after treatment, psychotherapy is used to integrate thoughts, unconscious memories, and other psychopathological phenomena that arise during the sessions.[68] While cognitive-behavioral therapies (CBTs) have the strongest evidence in PAP,[69] the unconscious processes during session and integration phases are also related to psychodynamic theories. Despite differences, PAP sessions contain elements of psychodynamic treatment where unconscious material is revealed. In the integration phase, patients report to nondirective therapists all thoughts and perceptions previously arisen without exerting any censorship or giving a conscious direction as if they were free associations, an essential tool of psychoanalytical practices.[70] It is indeed interesting to consider that elements from different psychotherapeutic approaches merge into an innovative approach that is, however, rooted in previous theories. PAP may offer another potential advantage. Traditional psychotherapeutic interventions often require multiple weekly sessions, sometimes lasting up to 12 months, to achieve a therapeutic effect.[71] Intriguingly, when combined with psilocybin, enduring benefits over even 6 months can be achieved after only one or two sessions, resulting in less time consuming and potentially more cost-effective for the healthcare systems. Additionally, the rapid onset of action (as early as 8 hours[62]) and the lack of a daily pill intake can improve treatment adherence.

However, PAP shows some potential challenges. First, the psychological support hinders the quantification of psilocybin's benefit itself. Given the paucity of studies without psychotherapy, the benefits of the drug itself remain to be demonstrated still if not associated with psychotherapy. Second, PAP is an operator-dependent approach, leading to significant heterogeneity and outcome differences. Third, future studies should determine the optimal psychotherapeutic approach in terms of intervention type and session frequency, as well as the possible benefits of different psychologically oriented interventions and settings. For instance, depressed patients with comorbid borderline personality disorder (BPD) were excluded from the majority of trials, while a study showed the benefits of PAP in this group.[39] Possible integration of PAP with specific CBT approaches (e.g., dialectical behavioral therapy or DBT) may further improve outcomes in patients with personality disorders. Furthermore, integrating PAP with specific skills of the DBT modules (i.e., mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness) might be beneficial for all patients, providing them with tools to deal with unpleasant memories or to face changes to achieve new goals in their lives.[69] Undoubtedly, significant economic and human resources are needed in the short term to train and certify clinicians and to set the environment for preparatory and integrative sessions. This may constitute a challenge in implementing PAP in developing countries or culturally diverse nations. Developing a culturally adapted version of PAP is crucial for worldwide accessibility, as it was investigated mostly in the United States (US) and Western countries. Finally, yet importantly, as PAP sessions can last several hours or even an entire workday, working shifts will have to consider this aspect.

Evidence of efficacy, confounders, and limitations of clinical trials

The evidence previously presented should be interpreted considering that it derives from a mix of RCTs not always well-designed,

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

non-randomized studies, open-label trials, and pilot studies. Details regarding the main findings and limitations of the available studies investigating psilocybin use in psychiatric disorders are summarized in Table 2.

Research on MDD, anxiety and depressive symptoms associated with life-threatening cancer, and TRD showed the most robust evidence, supported by a non-randomized study[72] and several RCTs.[26,31-33,60,73-77] Open-label studies[25,39,57,78-81] and two follow-up analyses[61,62] supported the overall positive findings of RCTs. Among all the studies conducted, five were pilot studies.[25,31,39,72,80] Concerning the outcome, two trials reported no significant difference in the antidepressant effect between psilocybin and escitalopram[26] or placebo,[72] whereas another one showed improvement in depression only at month 6.[31] According to a recent meta-analysis, which included three RCTs and three open-label studies, the use of psilocybin (at doses ranging from 1 mg to 25 mg) to patients not currently taking any other psychotropic medications resulted in significant reductions in depressive symptoms.[38]

However, these studies have significant limitations and do not clearly provide conclusive evidence on the antidepressant efficacy of psilocybin, particularly in the long term. Concerning the recruitment phase, there are clear limitations such as small sample sizes[25,31-33,39,57,60,72-74,77-81] with lack of diversity among participants[32,33,39,57,60,72,75-79] and potential selection biases.[26,31,39,72-74,76] These issues limit the generalizability of findings and impede a comprehensive assessment of rare adverse events, as well as the precise evaluation of the number needed to harm, and the number needed to treat. One study only recruited healthy subjects.[74] In terms of methodology, some studies showed inconsistent application of correction for multiple testing,[26,74] no consideration of confounding factors,[57,78] lack of randomization,[72] and relatively short-term follow-up periods were often observed,[25,26,31-33,39,57,72-81] generally between one and 6 months after one or two single active psilocybin treatments. Only one RCT has a 12-month follow-up.[60] Furthermore, the intake of other antidepressants during follow-up periods could confound results, and it remains uncertain whether the maintenance of medium-term therapeutic effect can be solely attributable to the PAP.[60] Only two long-term 4.5-year follow-up studies are available, involving 4 and 14 patients, respectively.[61,62] One of these shows a sustained reduction in demoralization,[62] while the other presents the clinical response rates for depression and anxiety.[61] This lack of information on long-term safety, tolerability, and efficacy represents an important obstacle to the use of psilocybin in clinical practice, as mood disorders are typically chronic and recurrent. In terms of study design, the use of open-label[25,39,57,78-81] and crossover designs,[31-33,74,80] as well as a single-dose protocol,[31,33,39,72-77] was frequently noted. Blinding procedures were not consistently robust,[26,32,60,72-76] and comparison with placebo or standard treatments was lacking in many studies.[25,26,31-33,39,57,60,72,73,75-81] Potential detection bias was sometimes observed due to differences in outcome measurement between the treatment and control groups.[31,33] In some instances, control groups consisted of waiting lists rather than active comparators,[60,73] and therapeutic settings were sometimes not consistently provided.[74,76] Finally, in one RCT not all questionnaires used for data collection were validated, introducing an additional source of bias.[32]

Evidence of efficacy for OCD,[67] body dysmorphic disorder (BDD),[82] alcohol dependence,[83] and tobacco addiction[84,85] is promising but limited due to the absence of RCTs. To address this limitation, two RCTs assessing the effects of PAP in alcohol-dependent volunteers[86] and smokers (NCT01943994) have been conducted, albeit results have not been published yet. To date, no study has investigated PAP treatment for PTSD. An open-label pilot study of psilocybin for bipolar depression II (BDII) (NCT05065294) is currently recruiting participants, while another one (NCT04433845) with a single-dose design has been already published.[87] Additionally, two qualitative analyses of follow-up interviews[88] and web-survey[89] of anecdotal use of psilocybin in individuals with putative BD reported that the drug was perceived to be more helpful than harmful. However, it is important to note several limitations of qualitative studies including self-reported diagnosis, selection, recall bias, and reporting bias, which may primarily emphasize positive experiences limiting the understanding of negative ones.

Besides these intrinsic limitations of the study design, another common limitation among available trials is the strict inclusion criteria, which severely reduces the results' generalizability. Common exclusion criteria include a family history of psychotic and bipolar disorders, current psychotic symptoms, concomitant antidepressant drugs during PAP, and active suicidal ideation or intent.[32] The exclusion of patients with psychotic symptoms and/or suicidal ideation aims to avoid the rare possibility of inducing psychotomimetic adverse events and suicidal behavior in patients with congruent ideation. However, excluding depressed patients treated with other antidepressants may be considered overly conservative, preventing a comprehensive understanding of psilocybin's safety and effects in combination therapy, as well as the necessary tapering or washout periods to avoid pharmacological interactions upon switching medications. To the best of our knowledge, only two recent clinical trials (NCT03429075 and NCT03912974) included two separate treatment sessions with psilocybin and an SSRI. In the former, there was no concomitant administration of the two drugs[26]; in the latter, psilocybin was administrated only on the last day of the two-week escitalopram pretreatment period.[74] Consequently, the relative efficacy of psilocybin in combination with another antidepressant has not yet been established in RCTs. Moreover, standard antidepressants typically show limited efficacy in reducing suicidal ideation in the first phase of treatment.[90] In this regard, one of the mentioned clinical trials compared psilocybin to the SSRI escitalopram.[26] The study did not demonstrate the superiority of psilocybin over escitalopram in reducing depressive symptoms, its primary outcome. Although secondary outcomes, including suicidal ideation, clinical remission, other measures of depressive symptoms, anxiety, and anhedonia, tended to favor psilocybin, the analysis was not corrected for multiple comparisons. Therefore, drawing firm conclusions from these findings may be questionable.[26] In terms of safety, psilocybin was better tolerated than escitalopram,[26] although the latter contributed to mitigating psilocybin-induced acute autonomic adverse events in the study arm evaluating the response to psilocybin after pretreatment with escitalopram.[74] Although this finding does not result from a sustained and combined drug administration, it suggests that combining psilocybin with a standard antidepressant may not only be safe but also beneficial in terms of side effects. However, this may not apply to all antidepressants, and potential interactions should be considered carefully. For instance, since psilocin is metabolized by the liver monoamine oxidase (MAO),[91] MAO inhibitors may intensify the effects, and this combination should be avoided. Conversely, a recent retrospective online survey found that psilocybin's effect was attenuated up to 3 months after discontinuing SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs).[92] This attenuation might be due to

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 2. Completed Clinical Trials and Secondary Analyses with Results Published in Peer-Reviewed Journals until December 2023

Reference	Year	Trial registration identifier	Sample size and clinical presentation	Study design	Main findings	Limitations
Carhart-Harris et al.	2021	NCT03429075	n 59 MDD	Randomized double-blind controlled trial	No difference in antidepressant effect between PSY 25 mg and ESC by wk 6 QIDS-SR–16: −8.0 for PSY vs. −6.0 for ESC (p = 0.17)	- Possible selection bias - Moderate depression at baseline - Brief duration of escitalopram treatment - Blinding effectiveness not assessed within each treatment group - No comparison with placebo - Lack of correction for multiple comparisons for secondary outcomes - Medium-term follow-up (6 mth) - Follow-up data not fully collected
Davis et al.	2021	NCT03181529	n 24 MDD	Randomized, waiting-list controlled clinical trial	Greater ↓ of depressive symptoms in GRID-HDRS in the immediate treatment group (PSY 20 mg/ and 30 mg/kg) by wks 1 and 4 (SD 8.0 [7.1] and 8.5 [5.7]) compared to delayed treatment group by wks 5 and 8 (SD 23.8 [5.4] and 23.5 [6.0])	- Small sample size - Possible selection bias - Moderate depression at baseline - Psychotherapy was delivered by facilitators without formal clinical training - Single-blinded - Waiting list - No comparison with placebo or TAU - Possible attrition bias - Short-term follow-up (1 mth)
Becker et al.,	2022	NCT03912974	n 27 MDD	Randomized double-blind placebo-controlled crossover study	ESC (10–20 mg) pretreatment (14 d) reduced PSY (25 mg) bad effects, AEs (p = 0.004), fear (p = 0.004), anxiety (p < 0.05), and autonomic AEs (p < 0.02) compared with placebo pretreatment	- Crossover design - Small sample size - HS only - Possible selection bias - Brief duration of escitalopram treatment - No therapeutic setting - No correction for multiple testing - No follow-up
Gukasyan et al.	2022	NA	n 24 MDD	Randomized-waiting-list controlled clinical trial	PSY 20 and 30 mg/70 kg 2 wks apart: antidepressant response rate of 75% and remission of 58% in GRID-HDRS by mth 12	- Small sample size - Lack of diversity among participants - Single-blinded - Waiting list - No comparison with placebo or TAU - Lack of a long-term comparison group - 33% of participants used other ADs during follow-up - Medium-term follow-up (12 mth)
von Rotz et al.	2023	NCT03715127	n 52 MDD	Randomized, double-blind, placebo-controlled, parallel-group trial	Greater ↓ of depressive symptoms with PSY (0.215 mg/kg) compared with placebo by d 14MADRS: −15.0 to −1.3 (Cohens' d = 0.97, p = 0.0011) for PSY	- Small sample size - Lack of diversity among participants - Single-dose protocol - No comparison with TAU - Short-term follow-up (2 wk)
Sloshower et al.	2023	NCT03554174	n 19 MDD	Placebo-controlled, within-subject, fixed-order trial	No significant difference in the improvement of depression and anxiety between PSY 0.3 mg/kg compared with placebo by wk 6 GRID-HDRS: Δ = 6.3–8.7, Cohens' d = 1.02–2.27 for PSY vs. Δ = 4.4–5.8, and Cohens' d = 0.65–0.99 for placebo	- Pilot study - Small sample size - Potential selection bias - Lack of diversity among participants - Lack of randomization - Single-blinded - Fixed-order design - Single-dose protocol - No comparison with TAU - Short-term follow-up (16 wk)

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 2. *Continued*

Reference	Year	Trial registration identifier	Sample size and clinical presentation	Study design	Main findings	Limitations
Raison et al.	2023	NCT03866174	n 104 MDD	Randomized double-blind active placebo-controlled	PSY 25 mg ↓ depressive symptoms by d 43 compared with niacin MADRS: MD −12.3 [95% CI, −17.5 to −7.2]; p < 0.001)	- Lack of diversity among participants - Potential selection bias - Ineffective blinding - Niacin as an active placebo may have amplified the placebo response - Single-dose protocol - Facilitator adherence to psychological support protocol not assessed - No comparison with TAU - Short-term follow-up (43-d)
Carhart-Harris et al.	2016	ISRCTN14426797	n 12 TRD	Open-label uncontrolled study	PSY 10 and 25 mg 7 days apart ↓ depressive symptoms by 1 wk and mth 3 QIDS: mean change wk 1–11.8, 95% CI –9.15 to −14.35, p = 0.002, Hedges'g = 3.1) and mth 3–9.2, 95% CI –5.69 to −12.71, p = 0.003, Hedges' g = 2	- Pilot study - Open-label design - Small sample size - Within-group analyses only - No comparison with placebo or TAU - No enduring improvements after 3 mths - Short-term follow-up (3 mth)
Carhart-Harris et al.	2017	NA	n 16 TRD	Open-label uncontrolled study	PSY 10 and 25 mg/70 kg 1 wk apart ↓ depressive symptoms by wk 5 QIDS-SR16: mean change −8 ± 5.1, t = −6.3, p < 0.001	- Open-label design - Small sample size - Lack of diversity among participants - No consideration of confounding factors - No comparison with placebo or TAU - Short-term follow-up (5 wk)
Carhart-Harris et al.	2018	NA	n 20 TRD	Open-label uncontrolled follow-up study	PSY 10 and 25 mg 7 d apart ↓ depressive symptoms (BDI and QIDS-SR16) by mth 3 and 6 (Cohen's d = 1.5 and 1.4, p < 0.001)	- Open-label design - Small sample size - Lack of diversity among participants - Variability in patients' assessment of current depressive episode duration - No comparison with placebo or TAU - Medium-term follow-up (6 mth)
Erritzoe et al.	2018	NA	n 20 TRD	Open-label uncontrolled study	PSY 10 and 25 mg 7 d apart modulates personality structure (NEO-PI-R) by mth 3 ↓ neuroticism (MD –5.7, p = 0.002, Cohen's d = 0.571) ↑ extraversion (MD 6.5, p = 0.001, Cohen's d = 0.716) and ↑ openness (MD 4.9, p = 0.012, Cohen's d = 0.437)	- Open-label design - Small sample size - Lack of diversity among participants - No consideration of confounding factors - No comparison with placebo or TAU - Short-term follow-up (3 mth)
Lyons et al.	2018	NA	n 15 TRD	Open-label study	PSY 10 and 25 mg 7 d apart ↓ pessimism bias (POFLE) by wk 1[t(14 = −2.714, p = 0.017; 95% CI (−0.21, −0.02), g = 0.7] ↓ depressive symptoms (BDI) by wk 1 [t^{14} = 7.900, p < 0.001; 95% CI (16.17, 28.23), g = 1.9]	- Pilot study - Open-label and cross-sectional design - Small sample size - It is part of another open-label study (Carhart-Harris et al., 2016) - HS control group (n = 15), not exposed to the same treatment procedures - No comparison with placebo or TAU - Uncertain improvement in cognitive (pessimism) bias, as it may be an epiphenomenon of the core effects of treatment on depressive symptoms - Short-term follow-up (1 wk)

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 2. *Continued*

Reference	Year	Trial registration identifier	Sample size and clinical presentation	Study design	Main findings	Limitations
Goodwin et al.	2022	NCT03775200	n 233 TRD	Randomized double-blind, dose-finding, parallel-group, clinical trial	PSY 25 mg, but not 10 mg, reduced depression more than a 1-mg dose by 3 wk MADRS MD between PSY25 mg and PSY 1 mg was −6.6 (p < 0.001)No difference between PSY 10 mg and 1 mg MADRS MD between PSY 10 mg and PSY 1 mg was −2.5 (p = 0.18)	- Dose–response study - Lack of diversity among participants - Moderate depression at baseline - Incomplete blinding - Single-dose protocol - Variability in session monitors' background and education - No comparison with placebo or TAU - Short-term follow-up (12 wk)
Grob et al.	2011	NCT00302744	n 12 Cancer-related anxiety and depressive symptoms	Randomized double-blind active placebo-controlled crossover study	PSY 0.2 mg/kg failed to improve depressive symptoms and anxiety symptoms by wk 2 Depression (BDI) decreased at mth 6 (t_7 = 2.71, p = 0.03) Anxiety (STAI trait) decreased at mth 1 (t_{11} = 4.36, p = 0.001)	- Pilot study - Crossover design - Small sample size - Potential selection bias - Single-dose protocol - No comparison with TAU - No data of the between-group comparison - Variability in posttreatment subject contact - Potential detection bias - Medium-term follow-up (6 mth)
Griffiths et al.	2016	NCT00465595	n 51 Cancer-related anxiety and depressive symptoms	Randomized double-blind crossover study	PSY 1 or 3 mg/70 kg vs. PSY 22 or 30 mg/70 kg 5 wks apart Depression (GRID-HDRS–17): clinical response rate of 78% and treatment remission 65% 6 mths Anxiety (HAM-A): clinical response rates of 83% and treatment remission 57% by 6 mths	- Crossover design - Small sample size - Lack of diversity among participants - Not all questionnaires are validated - No double-blind assessment after crossover - No comparison with placebo or TAU - Medium-term follow-up (6 mth)
Ross et al.	2016	NCT00957359	n 29 Cancer-related anxiety and depressive symptoms	Randomized double-blind active placebo-controlled crossover study	PSY 0.3 mg/kg vs. niacin 7 wks apartDepression (BDI): clinical response rate of 83% by wk 7 Anxiety (HAD-A): clinical response rate of 58% by wk 7	- Crossover design - Small sample size - Lack of diversity among participants - Possible detection bias in the control group - Single-dose protocol - No comparison with TAU - Medium-term follow-up (6.5 mth)
Agin-Liebes et al.	2020	NA	n 15 Cancer-related anxiety and depressive symptoms	Long-term within-subject follow-up analysis of Ross et al., 2016	PSY 0.3 mg/kg vs. niacin 7 wks apart Depression (BDI): clinical response rate of 79% at 4.5-yr follow-up Anxiety (HADS): clinical response rate of 57% at 4.5-yr follow-up	- Crossover design - Small sample size - Lack of diversity among participants - Possible detection bias in the control group - Single-dose protocol - No comparison with TAU - Intake of other ADs during follow-up - Potential reporting bias
Ross. et al.	2021	NA	n 11 Cancer-related anxiety and depressive symptoms	Follow-up analysis ofRoss et al., 2016	PSY 0.3 mg/kg vs. niacin 7 wks apart ↓ in SI (BDI and BSI) by 8 h [p < 0.001] and sustained for 6.5 mths [p < 0.001] ↓ LoM (DS) by wk 2 [p = 0.005] and sustained by mth 6.5 [p < 0.001], yr 3.2 [p < 0.001], and yr 4.5 [p < 0.001]	- Crossover design - Small sample size - Lack of diversity among participants - Possible detection bias in the control group - Single-dose protocol - No comparison with TAU - The parent trial was not designed to assess the antisuicidal effects of PSY - underpowered analyses - Only 4 patients completed 4.5-yr follow-up

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 2. *Continued*

Reference	Year	Trial registration identifier	Sample size and clinical presentation	Study design	Main findings	Limitations
Agrawal et al.	2023	NA	n 30 MDD associated with cancer	Fixed-dose open-label study	PSY 25 mg ↓ depressive symptoms by wk 8 MADRS: mean change 19.1 (95% CI, −22.3 to −16.0; p < 0.001) by wk 8. Antidepressant response rate of 80% and treatment remission of 50% by wk 8	- Open-label design - Small sample size - Single-dose protocol - No comparison with placebo or TAU - Short-term follow-up (8 wks)
Anderson et al.	2020	NCT02950467	n 18 AIDS-related demoralization	Open-label uncontrolled study	PSY 0.3–0.36 mg/kg ↓ demoralization by mth 3 DS-II: mean difference − 5.78 [SD 6.01], partial eta squared = 0.47, 90% CI 0.21–0.60 by mth 3	- Pilot study - Open-label design - Small sample size - Lack of diversity among participants - Possible selection bias - Single-dose protocol - No comparison with placebo or TAU - Short-term follow-up (3 mth)
Moreno et al.	2006	NA	n 9 OCD	Modified double-blind trial	PSY escalating dosage sequence 1 wk apart (25–100–200–300 μg/kg) ↓ OCD symptoms (23%–100% decrease in YBOCS score). No significant effect of dose (F = 2.25, df = 3,3; p = .261) orinteraction of time and dose (F = 0.923, df = 9,45; p = .515)	- Proof-of-concept study - Pre/posttest design - Small sample size - Potential selection bias - Lack of randomization - The study was designed primarily to assess safety and tolerability, but clinical data were also collected. - No comparison with placebo or TAU - No comparison between groups - Modified blinded procedures - Only one participant with medium-term follow-up (6 mth)
Schneier et al.	2023	NA	n 12 BDD	Open-label uncontrolled study	PSY 25 mg ↓ BDD symptoms (BDD-YBOCS) by wk 12 (p < 0.001, partial eta squared = 0.54)	- Pilot study - Open-label design - Small sample size - Limited diversity among participants - Potential selection bias - Single-dose protocol - No comparison with placebo or TAU - Lack of systematic assessment of non-serious AEs - Short-term follow-up (12-wk)
Bogenschutz et al.	2015	NCT02061293	n 10 Alcohol dependence	Open-label uncontrolled study	↓ in percentage drinking days (mean difference SD = 27.2 (23.7), 95% CI 9.0–45.4, t^8 = 3.449, p = 0.009) and heavy drinking days (mean difference SD = 26.0 (22.4), 95% CI 8.7–43.2, t^8 = 3.477, p = 0.008) during wks 5–12	- Proof-of-concept study - Open-label design - Small sample size - Lack of biological verification of alcohol use (only self-reported-only measures) - No comparison with placebo or TAU - Medium-term follow-up (36 wk)
Johnson et al.	2014	NA	n 15 Tobacco addiction	Open-label, uncontrolled study	After PSY 20 mg/70 kg at wk 1, PSY 30 mg/70 at wk 7 and 13; 80% of participants showed seven-day point prevalence abstinence at 6 mth	- Pilot study - Open-label design - Small sample size - Lack of diversity among participants - Self-selection bias - No comparison with placebo or TAU - Unable to differentiate effects of moderate vs. high PSY doses - Medium-term follow-up (6 mth)
Johnson et al.	2017	NA	n 15 Tobacco addiction	Long-term within-subject follow-up analysis of Johnson et al., 2014	After PSY 20 mg/70 kg at wk 1, PSY 30 mg/70 at wk 7, and 13, 67% of the participants were still abstinent at mth 12 (F 2,23 = 81.4, p < 0.001)	- Small sample size - Lack of diversity among participants - Self-selection bias - Possible reporting bias - No comparison with placebo or TAU

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Table 2. *Continued*

Reference	Year	Trial registration identifier	Sample size and clinical presentation	Study design	Main findings	Limitations
Aaronson et al.	2023	NCT04433845	n 15 BD	Open-label uncontrolled study	PSY 25 mg ↓ BDII depression by wk 3 and remission persisted by wk 12. MADRS: mean (SD) change −24.00 (9.23), Cohen d = 4.08, 95% CI, −29.11 to −18.89, p < 0.001 by wk 3	- Open-label design - Small sample size - Possible selection bias - Single-dose protocol - No comparison with placebo or TAU - Short-term follow-up (12 wk)

For some studies, some data is not available (i.e., p-value, effect size, SD, and MD).
Abbreviations: AE, adverse event; AIDS, acquired immune deficiency syndrome; BD, bipolar depression; BDD, body dysmorphic disorder; BDD-YBOCS, Yale Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder; BDI, Beck Depression Inventory total score; BDII, bipolar depression II; BSI, Brief Symptom Inventory; CI, confidence interval; df, degrees of freedom; DS, Demoralization Scale, DS-II, Demoralization Scale-II; ESC, escitalopram; F, F-statistic; GRID-HDRS, Grid-Hamilton Depression Rating Scale total score; HADS, Hospital Anxiety and Depression Scale total score; HAM-A, Hamilton Anxiety Rating Scale total score; h, hour; HS, healthy subjects; MADRS, Montgomery-Asberg Depression Rating Scale total score; MD, mean deviation; MDD, major depressive disorder; mth, month; N, sample size; NA, not available; NEO-PI-R, revised NEO Personality Inventory; OCD, obsessive-compulsive disorder; p, p-value; POFLE, Prediction Of Future Life Events task; PSY, psilocybin; QIDS, Quick Inventory of Depressive Symptomatology total score; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Reported total score; SD, standard deviation; STAI, State–Trait Anxiety Inventory total score; TAU, treatment as usual; TRD, treatment resistant depression; wk, week; YBOCS, Yale-Brown Obsessive Compulsive Scale; yr, year.

postsynaptic serotonergic receptor downregulation following chronic antidepressant use.[93] Thus, regardless of the drug class, attention should be paid to the duration of standard antidepressant treatment: an acute administration may intensify the psychedelic effect and exacerbate adverse events, whereas a chronic administration may decrease the therapeutic effects of psilocybin.

Another challenge is conducting high-quality trials with a blinded control group treated with a psychoactive placebo that mimics subjective experiences and potential adverse events during PAP. Additionally, enhancing our understanding of how placebo effects influence psilocybin's antidepressant efficacy could be achieved by using active comparators like ketamine, which induce similar immediate antidepressant response rates (71% at 28 hours for ketamine vs. 69% at 48 hours for psilocybin)[94] to assist with blinding, whereas it typically does not produce the sustained antidepressant response of psilocybin (35% at week 1 for ketamine vs. 71% at 1 month for psilocybin).[73,94,95] The difficulty of blinding studies on psychedelics also includes the possibility that positive results of psilocybin may have been enhanced by a nocebo effect in the control group. To reduce the impact of the nocebo effect, it has been recommended that in clinical trials, every patient randomized should receive an effective dose of psilocybin after the primary endpoint is assessed.[96] Furthermore, overcoming performance and detection bias in future studies will be of valuable importance, given the subjective effects induced by psilocybin and the self-rated scales used to detect them. In this respect, excluding participants with prior psychedelic exposure is essential to reduce expectancy bias, as many patients included in clinical trials reported previous psychedelic use.

Addressing these limitations will be essential for establishing the efficacy and safety profile of psilocybin as a treatment for psychiatric disorders.

Ethical challenges and legal considerations

Despite the therapeutic potential, psilocybin remains a prohibited and controlled substance in many countries. Nowadays, the legal use of psilocybin is limited to a few countries such as Jamaica, and the Netherlands, as well as in the context of research clinical trials.

As clinical studies yield promising results, the benefits and popularity of this psychedelic are growing faster than the ethical and legislative processes necessary for its proper use. An estimated 21 million people in the US use psilocybin, with some stating they use it for recreational purposes and others for self-medication.[97] The pressing need for novel therapeutic options for treatment-resistant psychiatric disorders is leading many patients to self-administer this drug, rather than waiting for further evidence of efficacy, legal medical, and protected access.[98] Social and cultural stigma, arising from both recreational and therapeutic misuse, presents another significant barrier to the potential use of psilocybin in clinical practice.

An ethical issue that may arise if psilocybin is approved by regulatory authorities for medical use is the need to standardize access to PAP sessions. If the benefits of this drug extend beyond psychiatry to conditions such as migraine headaches, organ transplantation, cancer, and immune diseases,[68] ensuring fair access to treatment will be crucial. Priority should likely be given to life-threatening conditions initially (e.g., TRD with suicidal ideation and cancer).

A final issue that may slow the approval of psilocybin for medical use is the impossibility of patenting this drug since it is a naturally occurring compound. Therefore, psilocybin is not attractive to pharmaceutical companies, and the high involvement of institutional stakeholders is important.

Discussion

Despite the issues and challenges discussed above, there is increasing evidence suggesting the therapeutic potential of psilocybin in several conditions, characterized by a transdiagnostic profile with internalizing symptoms and ruminations. In depression, common ruminations include passive and negative thoughts about feelings of guilt, inefficacy, negative topics, and self-criticism.[99] Ruminative brooding was consistently linked to a more severe substance use profile,[100] while ruminations about one's obsessions can make obsessions even more intrusive and ego-dystonic in OCD.[101]

Psilocybin is typically administered for a few weeks, a considerably shorter duration compared to treatment with SSRIs/SNRIs, which can last several months or years to show and maintain antidepressant effects.[102] Despite this more desirable shorter treatment period, PAP needs a specific therapeutic setting, making its

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

administration more complicated compared to standard antidepressants that are generally taken by patients at home.

In our opinion, the potential benefits of psilocybin may also be considered with cautious optimism in other conditions, such as autism spectrum disorder (ASD). LSD showed potential efficacy in ASD during the "first wave" of psychedelic research.[103] Psilocybin's empathogenic effects may alleviate social anxiety, and depression, as well as rigid cognitive and behavioral patterns associated with ASD while increasing emotional empathy and sociability. Given the significant impact of social withdrawal as an early manifestation in various neuropsychiatric disorders, and its trans-diagnostic association with a decreased likelihood of short-term symptom remission,[104] the use of psilocybin to engage directly with social impairments presents a compelling therapeutic avenue. Additionally, a recent preclinical research involving a rat model reported that serotonin-modulating drugs such as psilocybin may be effective in ameliorating ASD-related cognitive deficits.[105] Based on the evidence of psilocybin's efficacy in ameliorating ego-dystonic obsessions in OCD,[67] it may also be useful in reducing the pervasive interests and repetitive behaviors in ASD, though obsessive and compulsive-like symptoms in ASD differ from those in OCD and present unique psychopathological experiences.[106] While these effects are desirable in ASD, a potential challenge of PAP in this population could be the risk of triggering aggressive behavior due to the difficulties in interacting with therapists and communicating the deeper consciousness contents.[107] Considering that psychotic experiences are significantly higher in people with ASD compared to neurotypical individuals, another risk of using PAP in the ASD population may be related to the rare psychotic-like symptoms potentially induced by psilocybin.[108] Therefore, a tailored PAP protocol for neurodevelopmental disorders may involve microdosing to minimize adverse events, and repeated sessions to facilitate the processing of unconscious material.

Nevertheless, before implementing psilocybin in the real world, further evidence of its safety and efficacy is required to support informed clinical decision-making. Future well-powered and designed RCTs should randomize patients to receive PAP, standard antidepressant drugs (i.e., SSRIs or SNRIs), and/or psychotherapy (i.e., CBT). Standardized psychometric scales should be used to assess symptom improvement/remission as the primary outcome. To ensure the validity of results, the assessment should be conducted at baseline, approximately 1 month after treatment initiation (to compare the onset of action), and periodically up to 1 year (to evaluate medium-term effects). Double-blinding procedures should be maintained throughout the study duration and the follow-up to eliminate potential detection biases. Considering that the different time periods between PAPs may impact treatment outcomes, RCTs should compare psilocybin effects when used with various time intervals between dosing sessions, such as once a week or once a month. Furthermore, RCTs may identify distinct subpopulations responding optimally to psilocybin, SSRIs/SNRIs, or CBT. By evaluating the impact of assignment to one of these three treatment groups on the outcomes, we might be able to explore whether these therapeutic pathways serve as the causal mediators through which treatment effectiveness is achieved.

We need to further investigate dose optimization, the optimal duration of washout periods to sustain the therapeutic effect between PAP sessions, the ideal number of sessions, as well as the most relevant elements and strategies of psychological intervention. This will allow us to understand if it is possible to minimize mild hallucinogenic effects and alterations in consciousness while still benefiting from neuroplasticity mechanisms. If this is possible, we would have a pure psychoplastogen agent.[109] However, it is possible that the psychedelic experience is necessary to produce the therapeutic benefits, and neuroplasticity itself can partly contribute.[110] Since mystic experiences may direct the effects of neuroplasticity toward a beneficial change, providing supporting therapeutic settings seems necessary to obtain the full therapeutic potential of psilocybin. Enrolled patients should be willing to actively undergo this mystical experience, rather than passively hoping that psilocybin will change their thoughts and behavioral patterns. Therefore, patients' motivation for this treatment and the therapeutic alliance with clinicians remain indispensable conditions for ensuring the benefits of the treatment itself.

A major effort from the scientific community is pivotal to strengthen boundaries, both legal and ethical, between the clinical and recreational use of psilocybin. This entails the development of appropriate ethical principles and guidelines, as well as legislative measures to prevent the misuse of psychedelics. Learning from the therapeutic use of ketamine, it is essential to carefully balance the risks and benefits associated with psilocybin.

It is important to temper excessive media enthusiasm surrounding psilocybin and comprehensively assess its potential interactions with other drugs, as well as the duration of its therapeutic effects. Furthermore, exploring other possible mechanisms of action, such as potential anti-inflammatory properties,[111] may provide additional support for benefits in various disorders, including depressive[112] and anxiety disorders.[113]

Conclusions

This review critically examined essential aspects related to the implementation of psilocybin in real-world settings, extending beyond its efficacy in treating major psychiatric disorders. While further evidence of efficacy is needed for the treatment of OCD and SUD, the use of psilocybin may present a potential alternative to current antidepressants, improving depressive and anxiety symptoms with mild and transient side effects, as well as a shorter onset of action and treatment duration. However, the integration of psilocybin into clinical practice still faces significant challenges, including the need for larger, well-powered RCTs to validate its efficacy and safety in a comprehensive manner. These future studies should also explore optimal dosing, treatment frequency, and the integration of psychological therapies to maximize therapeutic benefits. Moreover, it is imperative to establish clear ethical and legal frameworks to differentiate clinical use of psilocybin from its recreational misuse. Advancing psilocybin research will therefore require a concerted effort to accumulate robust, evidence-based data supporting its therapeutic application in psychiatry. This endeavor will not only help delineate the precise therapeutic niche of psilocybin but also potentially augment the armamentarium of available psychiatric treatments.

Ethical considerations. Since this review included only published data, ethics approval was not sought.

Funding and acknowledgments. This work was supported by #NEXTGENERATIONEU (NGEU) and funded by the Italian Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006)—a multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553, October 11, 2022).

Author contribution. Conceptualization: A.S., C.F., M.S., G.F.; Data curation: A.S., C.F., M.S., G.F.; Funding acquisition: A.S., C.F., M.a.P.S.(.5.M., G.F.;

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

Investigation: A.S., C.F., M.S., G.F.; Methodology: A.S., C.F., M.S., G.F.; Project administration: A.S., C.F., G.F.; Resources: A.S., C.F., M.S., G.F.; Software: A.S., G.F.; Supervision: A.S., A.A., A.P., C.F., L.F., G.F.; Validation: A.S., A.A., A.P., C.F., L.F., M.S., G.F.; Writing – review & editing: A.S., A.A., A.P., C.A., C.F., G.D.L., D.D.R., M.a.P.S.(.5.M., L.F., M.M., M.F., M.S., P.F., G.F.; Writing – original draft: A.A., A.P., L.F., M.S.; Visualization: C.F., M.S.; Formal analysis: M.S.

Competing interest. AS is or has been a consultant to or has received honoraria or grants unrelated to the present work from Abbott, AbbVie, Angelini, Astra Zeneca, Clinical Data, Boehringer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, InnovaPharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, Servier, and Taliaz. CF was a speaker for Janssen. The other authors declare no potential conflicts of interest.

References

1. Cole EJ, Phillips AL, Bentzley BS, et al. Stanford Neuromodulation Therapy (SNT): a double-blind randomized controlled trial. *Am J Psychiatry.* 2022;**179**(2):132–141.
2. Serretti A. Advances in the treatment of depression. *Int Clin Psychopharmacol.* 2022;**37**(5):183–184.
3. Serretti A. Psychopharmacology: past, present and future. *Int Clin Psychopharmacol.* 2022;**37**(3):82–83.
4. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol.* 2009;**29**(3): 259–266.
5. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry.* 2010;**71**(10):1259–1272.
6. Conradi HJ, Ormel J, De Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med.* 2011;**41**(6):1165–1174.
7. Sforzini L, Worrell C, Kose M, et al. A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Mol Psychiatry.* 2022;**27**(3):1286–1299.
8. Scala M, Fanelli G, De Ronchi D, Serretti A, Fabbri C. Clinical specificity profile for novel rapid acting antidepressant drugs. *Int Clin Psychopharmacol.* 2023;**38**(5):297–328.
9. Del Casale A, Sorice S, Padovano A, et al. Psychopharmacological treatment of obsessive-compulsive disorder (OCD). *Curr Neuropharmacol.* 2019;**17**(8):710–736.
10. Akiki TJ, Abdallah CG. Are there effective psychopharmacologic treatments for PTSD? *J Clin Psychiatry.* 2018;**80**(3):18ac12473.
11. Iqbal MN, Levin CJ, Levin FR. Treatment for substance use disorder with co-occurring mental illness. *FOCUS.* 2019;**17**(2):88–97.
12. Meyer TD, Meir P, Lex C, Soares JC. Magic Mushrooms—an exploratory look at how mental health professionals feel and think about Psilocybin. *Psychiatry Res.* 2022;**316**:114727.
13. Rahhal N. Second psilocybin trial gets FDA 'breakthrough' status. *Mail Online.* https://www.dailymail.co.uk/health/article-7733255/Second-psilocybin-trial-gets-FDA-breakthrough-status.html; 2019 Accessed April 26, 2024.
14. Phelps J. Developing guidelines and competencies for the training of psychedelic therapists. *J Humanist Psychol.* 2017;**57**:450–487.
15. Dodd S, Norman TR, Eyre HA, et al. Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy. *CNS Spectr.* 2022; 1–11.
16. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl).* 2006; **187**(3):268–283.
17. Madsen MK, Fisher PM, Burmester D, et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. *Neuropsychopharmacology.* 2019;**44**(7):1328–1334.
18. Jakab RL, Goldman-Rakic PS. 5-Hydroxytryptamine $_{2A}$ serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proc Natl Acad Sci.* 1998;**95**(2):735–740.
19. Barnett BS, Siu WO, Pope HG. A survey of American Psychiatrists' attitudes toward classic hallucinogens. *J Nerv Ment Dis.* 2018;**206**(6): 476–480.
20. Wall MB, Harding R, Zafar R, Rabiner EA, Nutt DJ, Erritzoe D. Neuroimaging in psychedelic drug development: past, present, and future. *Mol Psychiatry.* 2023;**28**(9):3573–3580.
21. Preller KH, Duerler P, Burt JB, et al. Psilocybin induces time-dependent changes in global functional connectivity. *Biol Psychiatry.* 2020;**88**(2): 197–207.
22. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci.* 2012;**109**(6):2138–2143.
23. Mertens LJ, Wall MB, Roseman L, Demetriou L, Nutt DJ, Carhart-Harris RL. Therapeutic mechanisms of psilocybin: changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. *J Psychopharmacol (Oxf).* 2020;**34**(2):167–180.
24. Gill H, Puramat P, Patel P, et al. The effects of psilocybin in adults with major depressive disorder and the general population: findings from neuroimaging studies. *Psychiatry Res.* 2022;**313**:114577.
25. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry.* 2016;**3**(7):619–627.
26. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med.* 2021;**384**(15):1402–1411.
27. Le GH, Wong S, Badulescu S, et al. Spectral signatures of psilocybin, lysergic acid diethylamide (LSD) and ketamine in healthy volunteers and persons with major depressive disorder and treatment-resistant depression: a systematic review. *J Affect Disord.* 2024;**355**:342–354.
28. Skosnik PD, Sloshower J, Safi-Aghdam H, et al. Sub-acute effects of psilocybin on EEG correlates of neural plasticity in major depression: relationship to symptoms. *J Psychopharmacol (Oxf).* 2023;**37**(7):687–697.
29. Haikazian S, Chen-Li DCJ, Johnson DE, et al. Psilocybin-assisted therapy for depression: a systematic review and meta-analysis. *Psychiatry Res.* 2023;**329**:115531.
30. Grassi L, Caruso R, Hammelef K, Nanni MG, Riba M. Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. *Int Rev Psychiatry.* 2014;**26**(1):44–62.
31. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry.* 2011;**68**(1):71–78.
32. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol (Oxf).* 2016;**30**(12):1181–1197.
33. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol (Oxf).* 2016;**30**(12):1165–1180.
34. Nogrady B. Australia's approval of MDMA and psilocybin for PTSD and depression is premature, say critics, https://doi.org/10.1136/bmj.p1599; 2023 Accessed 26 April 2024.
35. Bienemann B, Ruschel NS, Campos ML, Negreiros MA, Mograbi DC. Self-reported negative outcomes of psilocybin users: a quantitative textual analysis. *PLOS ONE.* 2020;**15**(2):e0229067.
36. Eisenstein M. The psychedelic escape from depression. *Nature.* 2022;**609** (7929):S87–S89.
37. Rossi GN, Hallak JEC, Bouso Saiz JC, Dos Santos RG. Safety issues of psilocybin and LSD as potential rapid acting antidepressants and potential challenges. *Expert Opin Drug Saf.* 2022;**21**(6):761–776.
38. Watford T, Masood N. Psilocybin, an effective treatment for major depressive disorder in adults - a systematic review. *Clin Psychopharmacol Neurosci.* 2024;**22**(1):2–12.
39. Anderson BT, Danforth A, Daroff PR, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. *EClinicalMedicine.* 2020;**27**: 100538.

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

40. Martinotti G, Santacroce R, Pettorruso M, et al. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. *Brain Sci.* 2018;**8**(3):47.
41. Malcolm B, Thomas K. Serotonin toxicity of serotonergic psychedelics. *Psychopharmacology (Berl).* 2022;**239**(6):1881–1891.
42. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;**352**(11):1112–1120.
43. Thomas K, Malcolm B, Lastra D. Psilocybin-assisted therapy: a review of a novel treatment for psychiatric disorders. *J Psychoactive Drugs.* 2017;**49**(5):446–455.
44. Honyiglo E, Franchi A, Cartiser N, et al. Unpredictable behavior under the influence of "Magic Mushrooms": a case report and review of the literature. *J Forensic Sci.* 2019;**64**(4):1266–1270.
45. Johnson MW, Griffiths RR, Hendricks PS, Henningfield JE. The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology.* 2018;**142**:143–66.
46. Zou Z, Wang H, d'Oleire Uquillas F, Wang X, Ding J, Chen H. Definition of substance and non-substance addiction. *Adv Exp Med Biol.* 2017;**1010**:21–41.
47. Perez N, Langlest F, Mallet L, et al. Psilocybin-assisted therapy for depression: a systematic review and dose-response meta-analysis of human studies. *Eur Neuropsychopharmacol.* 2023;**76**:61–76.
48. Li NX, Hu YR, Chen WN, Zhang B. Dose effect of psilocybin on primary and secondary depression: a preliminary systematic review and meta-analysis. *J Affect Disord.* 2022;**296**:26–34.
49. Bender D, Hellerstein DJ. Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research. *Psychopharmacology (Berl).* 2022;**239**(6):1907–1932.
50. Cellini L, De Donatis D, Zernig G, et al. Antidepressant efficacy is correlated with plasma levels: mega-analysis and further evidence. *Int Clin Psychopharmacol.* 2022;**37**(2):29–37.
51. Sarparast A, Thomas K, Malcolm B, Stauffer CS. Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review. *Psychopharmacology (Berl).* 2022;**239**(6):1945–1976.
52. Schmitz GP, Jain MK, Slocum ST, Roth BL. 5-HT $_{2A}$ SNPs alter the pharmacological signaling of potentially therapeutic psychedelics. *ACS Chem Neurosci.* 2022;**13**(16):2386–2398.
53. Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *J Context Behav Sci.* 2020;**15**:39–45.
54. Smigielski L, Scheidegger M, Kometer M, Vollenweider FX. Psilocybin-assisted mindfulness training modulates self-consciousness and brain default mode network connectivity with lasting effects. *NeuroImage.* 2019;**196**:207–215.
55. Letheby C, Gerrans P. Self unbound: ego dissolution in psychedelic experience. *Neurosci Conscious*. 2017(1); nix016.
56. Dimsdale JE. *Dark Persuasion: A History of Brainwashing from Pavlov to Social Media*. New Haven: Yale University Press;2021.
57. Erritzoe D, Roseman L, Nour MM, et al. Effects of psilocybin therapy on personality structure. *Acta Psychiatr Scand.* 2018;**138**(5):368–378.
58. Jylhä P, Ketokivi M, Mantere O, et al. Do antidepressants change personality? —A five-year observational study. *J Affect Disord.* 2012;**142**(1–3):200–207.
59. Tsigkaropoulou E, Michopoulos I, Porichi E, Dafnas K, Serretti A, Ferentinos P. Temperament and character dimensions explain self-reported resilience deficits in patients with affective disorders. *Int Clin Psychopharmacol.* 2023;**39**(2):59–69.
60. Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: prospective 12-month follow-up. *J Psychopharmacol (Oxf).* 2022;**36**(2):151–158.
61. 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 (Oxf).* 2020;**34**(2):155–166.
62. Ross S, Agin-Liebes G, Lo S, et al. Acute and sustained reductions in loss of meaning and suicidal ideation following psilocybin-assisted psychotherapy for psychiatric and existential distress in life-threatening cancer. *ACS Pharmacol Transl Sci.* 2021;**4**(2):553–562.
63. Roberts BW, Luo J, Briley DA, Chow PI, Su R, Hill PL. A systematic review of personality trait change through intervention. *Psychol Bull.* 2017;**143**(2):117–141.
64. McNeil DC, Reddon JR. Utility and stability of the basic personality inventory in psychiatric patients with longstanding psychotic disorders in a new psychiatric rehabilitation program over a two-year period. *Psychol Rep.* 2000;**87**(3 Pt 1):767–775.
65. Roberts BW, Walton KE, Viechtbauer W. Patterns of mean-level change in personality traits across the life course: a meta-analysis of longitudinal studies. *Psychol Bull.* 2006;**132**(1):1–25.
66. Ling S, Ceban F, Lui LMW, et al. Molecular mechanisms of psilocybin and implications for the treatment of depression. *CNS Drugs.* 2022;**36**(1):17–30.
67. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry.* 2006;**67**(11):1735–1740.
68. Barnett BS, Greer GR. Psychedelic psychiatry and the consult-liaison psychiatrist: a primer. *J Acad Consult-Liaison Psychiatry.* 2021;**62**(4):460–471.
69. Yaden DB, Earp D, Graziosi M, Friedman-Wheeler D, Luoma JB, Johnson MW. Psychedelics and psychotherapy: cognitive-behavioral approaches as default. *Front Psychol.* 2022;**13**:873279.
70. Rabeyron T, Massicotte C. Entropy, Free energy, and symbolization: free association at the intersection of psychoanalysis and neuroscience. *Front Psychol.* 2020;**11**:366.
71. Stoffers-Winterling JM, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst. Rev.* 2012(8):CD005652.
72. Sloshower J, Skosnik PD, Safi-Aghdam H, et al. Psilocybin-assisted therapy for major depressive disorder: an exploratory placebo-controlled, fixed-order trial. J *Psychopharmacol (Oxf).* 2023;**37**(7):698–706.
73. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry.* 2021;**78**(5):481–489.
74. Becker AM, Holze F, Grandinetti T, 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;**111**(4):886–895.
75. Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *N Engl J Med.* 2022;**387**(18):1637–1648.
76. Raison CL, Sanacora G, Woolley J, et al. Single-dose psilocybin treatment for major depressive disorder: a randomized clinical trial. *JAMA.* 2023;**330**(9):843–853.
77. Von Rotz R, Schindowski EM, Jungwirth J, et al. Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. *EClinicalMedicine.* 2023;**56**:101809.
78. Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Sci Rep.* 2017;**7**(1):13187.
79. Carhart-Harris RL, Bolstridge M, Day CMJ, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl).* 2018;**235**(2):399–408.
80. Lyons T, Carhart-Harris RL. More realistic forecasting of future life events after psilocybin for treatment-resistant depression. *Front Psychol.* 2018;**9**:1721.
81. Agrawal M, Emanuel E, Richards B, Richards W, Roddy K, Thambi P. Assessment of psilocybin therapy for patients with cancer and major depression disorder. *JAMA Oncol.* 2023;**9**(6):864–866.
82. Schneier FR, Feusner J, Wheaton MG, et al. Pilot study of single-dose psilocybin for serotonin reuptake inhibitor-resistant body dysmorphic disorder. *J Psychiatr Res.* 2023;**161**:364–370.
83. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol (Oxf).* 2015;**29**(3):289–299.
84. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT $_{2A}$ R agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol (Oxf).* 2014;**28**(11):983–922.

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press

85. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse.* 2017; **43**(1):55–60.
86. O'Donnell KC, Mennenga SE, Owens LT, et al. Psilocybin for alcohol use disorder: rationale and design considerations for a randomized controlled trial. *Contemp Clin Trials.* 2022;**123**:106976.
87. Aaronson ST, Van Der Vaart A, Miller T, et al. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar Type II major depressive episodes: a nonrandomized controlled trial. *JAMA Psychiatry.* 2023:e234685.
88. DellaCrosse M, Pleet M, Morton E, et al. "A sense of the bigger picture:" a qualitative analysis of follow-up interviews with people with bipolar disorder who self-reported psilocybin use. *PLOS ONE.* 2022;**17**(12): e0279073.
89. Morton E, Sakai K, Ashtari A, Pleet M, Michalak EE, Woolley J. Risks and benefits of psilocybin use in people with bipolar disorder: an international web-based survey on experiences of 'magic mushroom' consumption. *J Psychopharmacol (Oxf).* 2023;**37**(1):49–60.
90. Olgiati P, Serretti A. Persistence of suicidal ideation within acute phase treatment of major depressive disorder: analysis of clinical predictors. *Int Clin Psychopharmacol.* 2022;**37**(5):193–200.
91. Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. *Drug Metab Rev.* 2017;**49**(1):84–91.
92. Gukasyan N, Griffiths RR, Yaden DB, Antoine DG, Nayak SM. Attenuation of psilocybin mushroom effects during and after SSRI/SNRI antidepressant use. *J Psychopharmacol (Oxf).* 2023;**37**:707–716.
93. Bonson KR, Murphy DL. Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium. *Behav Brain Res.* 1995;**73**(1–2): 229–233.
94. Zarate CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry.* 2006;**63**(8):856–864.
95. Aan Het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biol Psychiatry.* 2010;**67**(2):139–145.
96. Mertens LJ, Koslowski M, Betzler F, et al. Methodological challenges in psychedelic drug trials: efficacy and safety of psilocybin in treatment-resistant major depression (EPIsoDE)—rationale and study design. *Neurosci Appl.* 2022;**1**:100104.
97. Krebs TS, Johansen PØ. Over 30 million psychedelic users in the United States. *F1000Research.* 2013 Mar 28;**2**:98.
98. Pilecki B, Luoma JB, Bathje GJ, Rhea J, Narloch VF. Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm Reduct J.* 2021;**18**(1):40.
99. Kennedy JC, Dunlop BW, Craighead LW, Nemeroff CB, Mayberg HS, Craighead WE. Assessing in-session rumination and its effects on CBT for depression. *Behav Res Ther.* 2022;**159**:104209.
100. Memedovic S, Slade T, Ross J, et al. Rumination and problematic substance use among individuals with a long-term history of illicit drug use. *Drug Alcohol Depend.* 2019;**203**:44–50.
101. Flaherty A, Katz D, Chosak A, et al. Treatment of overthinking: a multidisciplinary approach to rumination and obsession spectrum. *J Clin Psychiatry.* 2022;**83**(4): 21ct14543 .
102. Moret C, Isaac M, Briley M. Review: Problems associated with long-term treatment with selective serotonin reuptake inhibitors. *J Psychopharmacol (Oxf).* 2009;**23**(8):967–974.
103. Markopoulos A, Inserra A, De Gregorio D, Gobbi G. Evaluating the potential use of serotonergic psychedelics in autism spectrum disorder. *Front Pharmacol.* 2022;**12**:749068.
104. Oliva V, Fanelli G, Kasper S, et al. Social withdrawal as a trans-diagnostic predictor of short-term remission: a meta-analysis of five clinical cohorts. *Int Clin Psychopharmacol* 2022;**37**(2):38–45.
105. Buzzelli V, Carbone E, Manduca A, et al. Psilocybin mitigates the cognitive deficits observed in a rat model of Fragile X syndrome. *Psychopharmacology (Berl).* 2023;**240**(1):137–147.
106. Scala M, Biondi L, Serretti A, Fabbri C. Obsessive-compulsive, psychotic, and autism dimensions overlap in real world: a case report. *Clin Neuropharmacol.* 2023;**46**(4):149–152.
107. Bender L, Cobrinik L, Faretra, G. Biological Treatment of Mental Illness: Proceedings of the II International Conference of the Manfred Sakel Foundation;1963.
108. Kiyono T, Morita M, Morishima R, et al. The prevalence of psychotic experiences in autism spectrum disorder and autistic traits: a systematic review and meta-analysis. *Schizophr Bull Open.* 2020;**1**:sgaa046.
109. Vargas MV, Meyer R, Avanes AA, Rus M, Olson DE. Psychedelics and other psychoplastogens for treating mental illness. *Front Psychiatry.* 2021;**12**:727117.
110. Moliner R, Girych M, Brunello CA, et al. Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nat Neurosci.* 2023;**26**(6):1032–1041.
111. Nkadimeng SM, Steinmann CM, Eloff JN. Anti-inflammatory effects of four psilocybin-containing magic mushroom water extracts in vitro on 15-lipoxygenase activity and on lipopolysaccharide-induced cyclooxygenase-2 and inflammatory cytokines in human U937 macrophage cells. *J Inflamm Res.* 2021;**14**:3729–3738.
112. Benedetti F, Zanardi R, Mazza MG. Antidepressant psychopharmacology: is inflammation a future target? *Int Clin Psychopharmacol.* 2022;**37**(3):79–81.
113. Elnazer HY, Sampson AP, Baldwin DS. Effects of celecoxib augmentation of antidepressant or anxiolytic treatment on affective symptoms and inflammatory markers in patients with anxiety disorders: exploratory study. *Int Clin Psychopharmacol.* 2021;**36**(3):126–132.

https://doi.org/10.1017/S1092852924002268 Published online by Cambridge University Press