Progress in Neuropsychopharmacology & Biological Psychiatry 143 (2025) 111541

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Adverse event reporting and management in psilocybin therapy clinical trials: A systematic review to guide clinical and research protocol development

Danielle Bukovsky [a,b], Aron Amaev [a], Jianmeng Song [a,b], Shannen Kyte [a,b], Edgardo Carmona-Torres [a,b], Fumihiko Ueno [a,b], Vincenzo Deluca [b,c,d], Antonio P. Strafella [a,b,e], Muhammad I. Husain [a,b,c,e,f], Ariel Graff-Guerrero [a,b,c,d,f,g], Philip Gerretsen [a,b,c,d,f,g,*]

[a] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH), 250 College Street, Toronto, Ontario M5T 1R8, Canada
[b] Institute of Medical Science, University of Toronto, 1 King's College Cir, Toronto, Ontario M5S 3K3, Canada
[c] Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario M5T 1R8, Canada
[d] Schizophrenia Division, CAMH, 1001 Queen St W, Toronto, Ontario M6J 1H1, Canada
[e] Krembil Brain Institute, University Health Network, 60 Leonard Avenue, Toronto, Ontario M5T 2S8, Canada
[f] Temerty Centre for Therapeutic Brain Intervention, CAMH, 1025 Queen St W, Toronto, Ontario M6J 1H1, Canada
[g] Adult Neurodevelopment and Geriatric Psychiatry, CAMH, 1025 Queen St W, Toronto, Ontario M6J 1H1, Canada

ARTICLE INFO

Keywords:
Psilocybin
Adverse event
Serious adverse event
Safety
Psychedelics

ABSTRACT

Psilocybin, a psychedelic prodrug, has gained renewed interest for its potential to treat various psychiatric disorders, including depression, anxiety, and substance use disorders. While promising, concerns remain regarding its safety profile and the management of potential adverse events (AEs). This systematic review aimed to evaluate the incidence, nature, and severity of adverse events and serious adverse events (SAEs) associated with psilocybin use across diverse clinical populations.

A comprehensive search was conducted across MEDLINE, Embase, and APA PsycInfo via the OVID platform, from database inception to June 5, 2024. A total of 42 clinical studies ($N = 1068$ participants) met inclusion criteria, all of which reported on AEs and/or SAEs following psilocybin administration. All studies were deemed to have a high risk of bias due to concerns regarding blinding. We synthesized information on common, uncommon, and SAEs, instances of suicidal ideation, methods of measuring AEs, and AEs requiring medical intervention. Reported AEs included headache, transient increases in blood pressure, and nausea, which typically resolved on their own. In rare instances, medical intervention was required. SAEs were reported infrequently in 2 of 42 studies and were limited to participants with underlying depressive disorders (e.g., suicidal behaviour, hospitalization).

Overall, psilocybin appears to have a favourable safety profile when administered in controlled settings. Based on our findings, we provide an outline of commonly reported AEs, uncommon AEs, SAEs, and considerations for future clinical and research protocols.

1. Introduction

Psilocybin is a psychedelic prodrug naturally occurring in over 150 mushroom species worldwide (Peredy and Bradford, 2014). While psilocybin has been used for hundreds if not thousands of years as part of spiritual and shamanic ceremonies (Nutt, 2019), it has recently regained attention as a potential treatment for various psychiatric disorders. Psilocybin, in conjunction with psychological support, has shown preliminary evidence for improving symptoms of major depressive disorder, treatment resistant depression, substance use disorders, anxiety, post-traumatic stress disorder (PTSD), and other mental disorders (Salvetti et al., 2024; van der Meer et al., 2023; Irizarry et al., 2025).

* Corresponding author at: 80 Workman Way; 6th floor Office 6320, Toronto, Ontario M6J 1H4, Canada.
E-mail addresses: philgerretsen@yahoo.com, philip.gerretsen@camh.ca (P. Gerretsen).

https://doi.org/10.1016/j.pnpbp.2025.111541
Received 20 June 2025; Received in revised form 20 October 2025; Accepted 21 October 2025
Available online 23 October 2025

Psilocybin's therapeutic effects are thought to be achieved via neuroplasticity, primarily induced through serotonin 2A receptor ($5HT_{2A}$-R) agonism (Nutt et al., 2020; Ly et al., 2018). Research has demonstrated a dose-response relationship of psilocybin, wherein higher doses are associated with stronger therapeutic effects (Bogenschutz et al., 2015; Griffiths et al., 2016; Roseman et al., 2017; Ross et al., 2016). Accordingly, psilocybin is typically administered in macrodoses ranging from 20 to 30 mg, inducing a psychedelic experience lasting approximately 4-to-8 h (Nutt et al., 2020).

While various clinical trials have shown promise for psychedelic use, recent regulatory decisions highlight the need for further assessment of their safety. Psilocybin remains a Schedule I controlled substance in the United States, reflecting ongoing concerns about its risk profile. In August 2024, the U.S. Food and Drug Administration (FDA) rejected 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for PTSD, citing insufficient evidence of safety and efficacy (Psychedelic Alpha, 2025). This decision has sparked renewed scrutiny of the safety of psychedelics, including psilocybin, emphasizing the need for a more thorough evaluation of their safety.

There are several safety considerations with psilocybin use. The principal physical risks include headache/migraine, tachycardia, hypertension, nausea and/or vomiting, and fatigue (Wsół, 2023; Yerubandi et al., 2024). Of greater concern are the psychiatric effects including extreme anxiety, fear, suicidality, depression, risk of self-harm, prolonged psychosis, and severe perceptual abnormalities, including hallucinogen persistent perception disorder (HPPD) (Rossi et al., 2022; Carbonaro et al., 2016). HPPD is characterized by hallucinations or perceptual disturbances that continue after the cessation of psychedelic use (Diagnostic and Statistical Manual of Mental Disorders, 2025). Nonetheless, risk of HPPD is considered extremely rare (Halpern and Pope, 2003) and has only been documented in cases of illicit psychedelic use (Espiard et al., 2005).

Given these concerns, psychedelic research has implemented several safeguards to minimize adverse events (AE). These include selecting participants with good cardiovascular health and excluding participants with a personal or family history of schizophrenia, other psychotic disorders, or bipolar I disorder (Johnson et al., 2008). Additionally, most studies include trained psychedelic therapists who provide psilocybin-assisted psychotherapy (PAP), which includes rapport building sessions with participants prior to dosing; psychoeducation on navigating the psychedelic experience; supervision and provision of support during dosing sessions; and post-treatment debriefing and integration sessions to ensure psychological safety and facilitate any beneficial psychotherapeutic effects following the psychedelic experience (Johnson et al., 2008). While ensuring safety, the protocols associated with PAP incur significant costs that may limit the broader implementation of psilocybin use for research and clinical purposes (Wolfgang and Hoge, 2023).

Though systematic reviews have been conducted since the resurgence of psychedelic therapy, many have key limitations. Existing reviews predominantly focus on studies that provide PAP (Romeo et al., 2024; Freitas et al., 2025), excluding studies where psilocybin is administered without such support. Throughout this review, we use the term psilocybin therapy (PT) to refer to psilocybin administered in research contexts, with or without the inclusion of a psychotherapeutic component. There has been a call, including from the FDA (Psychedelic Alpha, 2025), to evaluate the safety of psilocybin independently of psychological support (Earleywine et al., 2024). Additionally, existing reviews frequently group together multiple psychedelics (e.g., MDMA, psilocybin, lysergic acid diethylamide (LSD)), and include a limited number of psilocybin specific clinical trials (Breeksema et al., 2022; Hinkle et al., 2024), making it difficult to isolate psilocybin-specific safety outcomes. Further, published systematic reviews often assess both efficacy and safety conjointly (Yao et al., 2024; van Amsterdam and van den Brink, 2022; Goel and Zilate, 2025), providing a greater focus on the efficacy of psilocybin and only limited descriptions of AEs. Moreover, as many RCTs have been done in the context of depression and anxiety, reviews are limited to these disorders and fail to evaluate the safety of psilocybin in other contexts (Yerubandi et al., 2024; Perez et al., 2023).

As psilocybin research continues to expand with multiple phase III trials currently underway (National Library of Medicine, NCT05624268; National Library of Medicine, NCT06308653), there is a need to thoroughly reassess psilocybin's safety profile. The aim of this systematic review is to assess the current safety profile of psilocybin in clinical trials to guide future clinical and research protocol development toward balancing participant safety and costs toward increasing accessibility. Specifically, we aimed to: (i) assess common/expected AEs, unexpected/uncommon AEs, serious adverse events (SAE) and suicidality, AEs requiring medical intervention, treatment discontinuations and study withdrawals, and safety measures used; (ii) provide research informed considerations for clinical and research protocol development.

2. Methods

2.1. Literature search

This systematic review was conducted following the guidelines by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). English language publications from 2000 to June 2024 were searched for using Medline, Embase, and APA PsycInfo using the Ovid Database. Publications were limited to after the year 2000 as this was the first year in which regulatory approval was given to resume psychedelic research (Center for Psychedelic and Consciousness Research, 2020). The following search term was used: "safe* OR side* OR *adverse* AND Psilocybin".

2.2. Eligibility criteria

The eligibility criteria are described below through the PICO Framework:

i) Participants: The population of interest was adult participants of any sex, age, and health status.
ii) Interventions: Administration of a moderate-to-high dose of psilocybin, with or without supportive therapy.
iii) Comparators: Any clinical trial design was eligible for inclusion.
iv) Outcome Measures: Outcome measures included reported AEs and serious adverse events (SAEs); studies that did not report on these outcomes were excluded.

2.3. Risk of bias assessment

Risk of bias was assessed by two independent reviewers (AA and DB). Any discrepancies were resolved through discussion and by consulting with a third independent reviewer if necessary (PG).

The Cochrane revised risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019) was used to assess risk of bias in randomized studies. RoB 2 evaluates risk on five domains of bias: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Further, the RoB 2 tool for crossover trials was used for crossover clinical trials, which evaluated a 6th domain of bias (i.e., Domain S), bias arising from carryover effects. An overall RoB 2 risk-of-bias judgement of 'low risk', 'some concerns', or 'high risk' was determined based on the evaluation of the domains outlined above.

The Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (Sterne et al., 2016) was used to evaluate non-randomized studies. Consistent with previous investigations (Shapiro et al., 2024), the ROBINS-I tool was also used to evaluate single-arm open-label studies. ROBINS-I evaluates risk of bias across seven domains in non-randomized interventional studies: baseline confounding, selection of participants, classification of interventions,

deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. An overall ROBINS-I risk-of-bias judgement of 'low,' 'moderate,' 'serious,' or 'critical' was determined based on the evaluation of the specified domains. Risk of bias plots were generated using the Risk-Of-Bias VISualization (robvis) tool (McGuinness and Higgins, 2021).

2.4. Study identification and data extraction

Studies identified through the systematic search were imported into the Covidence software for reference management, and duplicates were automatically removed. Titles and abstracts were independently screened by AA and DB according to the predefined inclusion criteria. Articles that met the initial screening criteria were then moved forward for full-text review to confirm eligibility. Data were extracted on study design, sample characteristics (mean age, sex, population), psilocybin dose and frequency, AE measurement methods, dropouts and withdrawals, and reported AEs and SAEs. Study designs were recorded as described in each study. AE data were extracted from the main text and supplemental materials, if applicable, and categorized as expected/common or unexpected/uncommon based on their frequency and prior literature (Yerubandi et al., 2024; Breeksema et al., 2022). AEs explicitly listed as unrelated to psilocybin were excluded. AEs listed in Supplemental Tables 1–5 are presented as reported in each study and were not reclassified using a standardized framework to minimize reviewer bias.

Placebo conditions included inert and active controls (low dose psilocybin (25 μg/kg, 1 mg, 1 mg/70 kg, 3 mg/70 kg), diphenhydramine, niacin, and methylphenidate hydrochloride). Studies using microdoses (≤ 1 mg oral psilocybin) as the treatment condition were excluded; those using 1.5–2 mg intravenous psilocybin were included as these doses have been comparable to ~15 mg oral psilocybin (Hasler et al., 2004). All moderate-to-high therapeutic doses of psilocybin (e.g., 10 mg, 25 mg) were grouped for reporting. Similar AEs were grouped as such into the following categories: *paranoia*, included paranoid ideation and ideas of reference; *perceptual disturbances*, included visual distortions, visual changes, and hallucinations; and *motor and psychosomatic changes*, included motor dysfunction and spontaneous motor movement, impaired psychomotor skills, and psychomotor hyperactivity. For studies that reported AE frequencies across timepoints, the highest frequency reported was taken as the participant count.

3. Results

A total of 1190 articles were identified. After the removal of duplicates ($n = 443$), 747 articles were screened independently. Of these, 74 underwent full-text review, and 42 met inclusion criteria, consisting of 1068 participants who were allocated to receive psilocybin, 316 who received inert placebo and 257 who received active placebo. One study (Carhart-Harris et al., 2021) included an escitalopram comparator group, which was not categorized as placebo ($n = 29$). The PRISMA flow diagram is presented in Fig. 1.

Table 1 summarizes the included studies, detailing study designs, sample size, mean age, sex distribution, study population, psilocybin dose, comparator group, and prior psychedelic use. Supplemental Tables 1–5 outline reasons for participant discontinuations and withdrawals, safety assessments used, and reported AEs and SAEs per study, categorized by study population.

3.1. Risk of bias

A total of 12 studies were assessed using the RoB 2 tool for parallel trials (Figs. 2 and 3), and 10 studies were assessed with the RoB 2 tool for crossover trials (Figs. 4 and 5). Almost all the included crossover studies were judged to have 'some concerns' in the domain of bias arising from the randomization process, primarily due to insufficient detail on sequence generation or allocation concealment. Additionally, most studies, both crossover and parallel, were judged to have 'some concerns' in the domains of bias due to deviation from intended interventions and bias in measurement of the outcome. This was largely attributed to limited or unclear information on blinding procedures for participants and study staff. In cases where blinding integrity was assessed and participants or study personnel were able to correctly guess their treatment allocation, studies were judged as 'high risk' for these domains.

A total of 19 studies were assessed using the ROBINS-I tool (Table 2). Most studies exhibited 'serious risk' of bias for confounding due to inadequate control of confounding variables (e.g., participants' expectancy effects, prior psychedelic use, socioeconomic status, age, or relevant medical histories). Further, we judged all studies to have 'some concerns' regarding bias in the measurement of outcomes, as many did not measure or adjust for expectancy bias, an important consideration given that participants were aware they were receiving psilocybin. Taken together, these issues underpinned the 'serious' or 'critical' overall ratings.

3.2. Study populations and participant characteristics

Of the included studies, 16 were open-label (Bogenschutz et al., 2015; Hasler et al., 2002; Agrawal et al., 2024; Madsen et al., 2024; Aaronson et al., 2024; Lewis et al., 2023; Peck et al., 2023; Goodwin et al., 2023; Schneier et al., 2023; Shnayder et al., 2023; Dahmane et al., 2021; Anderson et al., 2020; Brown et al., 2017; Carhart-Harris et al., 2016; Johnson et al., 2014; Carhart-Harris et al., 2011), 12 were parallel group or waitlist randomized controlled trials (Carhart-Harris et al., 2021; Rosenblat et al., 2024; Raison et al., 2023; Heinzerling et al., 2023;von Rotz et al., 2023; Bogenschutz et al., 2022; Goodwin et al., 2022 Schindler et al., 2022; Rucker et al., 2022; Davis et al., 2021; Smigielski et al., 2019; Griffiths et al., 2018), 12 were crossover randomized controlled trials (Becker et al., 2022; Bravermanova et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2006, 2011, 2016; Grob et al., 2011; Hasler et al., 2004; Holze et al., 2022; Ley et al., 2023; Ross et al., 2016; Schindler et al., 2021), and 3 were fixed-ordered clinical trials (Moreno et al., 2006; Dahmane et al., 2021; Sloshower et al., 2023), one of which was also open-label (Dahmane et al., 2021). Across studies, study populations included: 1) healthy participants (Hasler et al., 2004; Dahmane et al., 2021; Brown et al., 2017; Carhart-Harris et al., 2011; Ley et al., 2023; Rucker et al., 2022; Smigielski et al., 2019; Griffiths et al., 2018; Becker et al., 2022; Bravermanova et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006; Hasler et al., 2002; Holze et al., 2022) ($n = 15$), 2) Major depressive disorder (MDD) (Carhart-Harris et al., 2021; Raison et al., 2023; von Rotz et al., 2023; Davis et al., 2021; Sloshower et al., 2023) ($n = 5$), 3) Treatment resistant depression (TRD) (Goodwin et al., 2023; Carhart-Harris et al., 2016; Rosenblat et al., 2024; Goodwin et al., 2022) ($n = 4$, Rosenblat et al., 2024 included participants with major depression or bipolar II disorder), 4) Treatment resistant bipolar disorder type II with current depressive episode (Aaronson et al., 2024) ($n = 1$), 5) Life-threatening illness with associated depression, anxiety, and/or existential distress (Griffiths et al., 2016; Ross et al., 2016; Agrawal et al., 2024; Lewis et al., 2023; Anderson et al., 2020; Grob et al., 2011) ($n = 6$), 6) Alcohol use disorder/DSM-IV alcohol dependence ($n = 3$) (Bogenschutz et al., 2015; Heinzerling et al., 2023; Bogenschutz et al., 2022), 7) nicotine dependence ($n = 1$) (Johnson et al., 2014), 8) headache and migraine disorders (Madsen et al., 2024; Schindler et al., 2021, 2022) ($n = 3$), 9) Body dysmorphic disorder (Schneier et al., 2023) ($n = 1$), 10) Obsessive compulsive disorder (Moreno et al., 2006) ($n = 1$), 11) Anorexia nervosa (Peck et al., 2023) ($n = 1$), and 12) Acquired immunodeficiency syndrome (AIDS) survivor men (Anderson et al., 2020)

Study design among included studies also varied. Of all studies, 9 (21%) compared psilocybin with an inert placebo (Bravermanova et al., 2018; Griffiths et al., 2011; Hasler et al., 2004; Rucker et al., 2022; Schindler et al., 2021, 2022; Sloshower et al., 2023; Smigielski et al.,

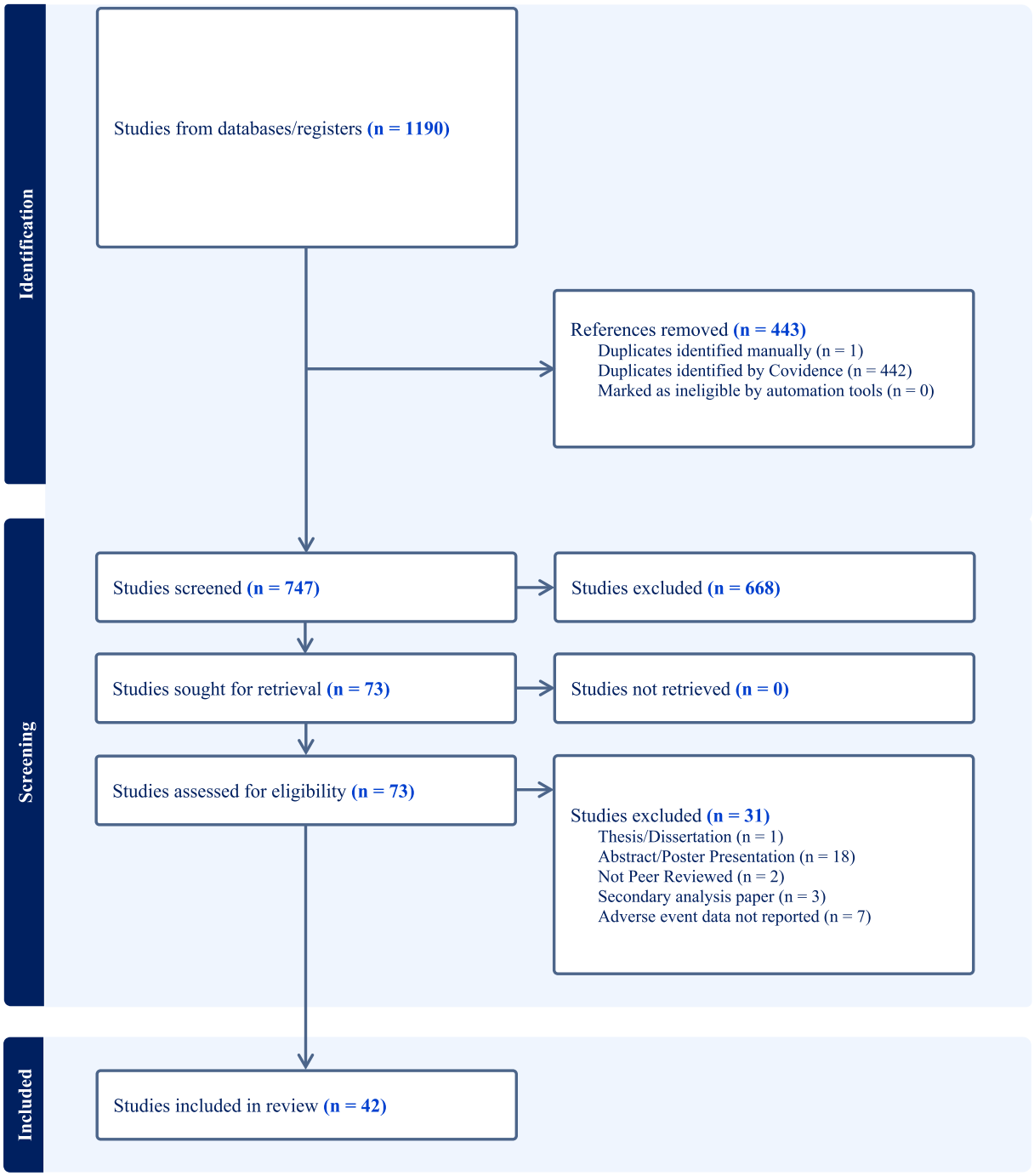

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing review search strategy.

2019; von Rotz et al., 2023), 9 (21%) with an active placebo (Bogenschutz et al., 2022; Goodwin et al., 2022; Griffiths et al., 2006, 2016, 2018; Grob et al., 2011; Moreno et al., 2006; Raison et al., 2023; Ross et al., 2016), 3 (7%) with other psychoactive substance and placebo (Carbonaro et al., 2018; Holze et al., 2022; Ley et al., 2023), one (2%) study compared pre-treatment with escitalopram versus placebo prior to psilocybin administration (Becker et al., 2022), one (2%) compared escitalopram plus 1 mg psilocybin to 25 mg psilocybin (Carhart-Harris et al., 2021), and 19 (45%) did not have a comparator drug group (Aaronson et al., 2024; Agrawal et al., 2024; Anderson et al., 2020; Bogenschutz et al., 2015; Brown et al., 2017; Carhart-Harris et al., 2011, 2016; Dahmane et al., 2021; Davis et al., 2021; Goodwin et al., 2023; Hasler et al., 2002; Heinzerling et al., 2023; Johnson et al., 2008; Lewis et al., 2023; Madsen et al., 2024; Peck et al., 2023; Rosenblat et al., 2024; Schneier et al., 2023; Shnayder et al., 2023). Of the studies reviewed, 34 incorporated psilocybin in the context of PAP, while 8 did not explicitly describe supportive psychotherapy or were unclear about psychological support given (Hasler et al., 2004; Dahmane et al., 2021; Carhart-Harris et al., 2011; Ley et al., 2023; Becker et al., 2022; Hasler et al., 2002; Holze et al., 2022; Schindler et al., 2021). In all studies, participants were monitored during peak dose effects. Of the included studies, 30 studies included participants with prior psychedelic use (Griffiths et al., 2016; Ross et al., 2016; Carhart-Harris et al., 2021; Aaronson et al., 2024; Lewis et al., 2023; Schneier et al., 2023; Anderson et al., 2020; Brown et al., 2017; Carhart-Harris et al., 2016; Johnson et al., 2014; Carhart-Harris et al., 2011; Rosenblat et al., 2024; Raison

Table 1
Demographic and study design details of included studies.

Study	Study Design (as reported)	n	Mean Age (SD)	% Male	Study Population	Frequency and Dose of Psilocybin	Comparator Group	Prior Psychedelic Use
Treatment resistant depression and major depressive disorder								
Rosenblat et al. (2024)	Randomized, waiting list–controlled clinical trial	Immediate group = 16 Delayed group = 15	Immediate group: 40.3 (13.3) Delayed Group: 48.5 (13.3)	Total Sample: 61% Immediate group: 73% Delayed Group: 47%	TRD as part of major depressive or bipolar II disorder	Up to three 25 mg doses	Waitlist control	Prior psychedelic use 6/31 (19%)
Goodwin et al. (2023)	Phase II, exploratory, fixed-dose, open-label study	Psilocybin =19	42.2 (10.8)	32%	TRD	Single 25 mg dose	N/A	NR
Sloshower et al. (2023)	Placebo-controlled, within-subject, fixed-order study	Enrolled = 22 Placebo = 19 Psilocybin =15	42.8 (13.8)	32%	MDD	Single 0.3 mg/kg dose	Placebo (microcrystalline cellulose)	Prior psychedelic exposure 8/19 (42%), Prior psilocybin exposure 7/19 (37%)
Raison et al. (2023)	Randomized, 2-group, phase 2 clinical trial	Psilocybin = 51 Niacin = 53	Total sample: 41.1 (11.3) Psilocybin: 40.4 (10.9) Niacin: 41.8 (11.7)	Total Sample: 50% Psilocybin: 53% Niacin: 47%	MDD	Single 25 mg dose	Niacin 100 mg	Prior psychedelic use 10/51 (20%) in psilocybin group
von Rotz et al. (2023)	Double-blind, randomized clinical trial	Psilocybin = 26 Placebo = 26	Psilocybin: 37.6 (10.9) Placebo: 35.9 (9.80)	Psilocybin: 39% Placebo: 35%	MDD	Single 0.215 mg/kg body weight dose	Placebo (mannitol)	Prior psychedelic use 5/26 (19%) in psilocybin group
Goodwin et al. (2022)	Phase 2 double-blind trial	25 mg Psilocybin = 79 10 mg Psilocybin = 75 1 mg Psilocybin = 79	25 mg Psilocybin: 40.2 (12.2) 10 mg Psilocybin: 40.6 (12.8) 1 mg Psilocybin: 38.7 (11.7)	25 mg Psilocybin: 44% 10 mg Psilocybin: 45% 1 mg Psilocybin: 54%	TRD	25 mg, 10 mg or 1 mg dose	1 mg psilocybin	Prior psilocybin use 14/233 (6%)
Davis et al. (2021)	Randomized, waiting list–controlled clinical trial	Immediate treatment = 13 Delayed treatment = 11	Total sample: 39.8 (12.2) Immediate treatment: 43.6 (13.0) Delayed treatment: 35.2 (9.9)	Immediate treatment: 31% Delayed treatment: 36%	MDD	Session 1: 20 mg/70 kg Session 2: 30 mg/70 kg	Delayed treatment group	Prior psychedelic use 0.8 (1.9%)
Carhart-Harris et al. (2021)	Phase 2, double-blind, randomized, controlled trial	Psilocybin = 30 Escitalopram = 29	Psilocybin: 43.3 (11.7) Escitalopram: 39.1 (9.7)	Psilocybin: 63% Escitalopram: 69%	Moderate-to-severe MDD	Two 25 mg doses, 3 weeks apart (plus daily placebo)	1 mg psilocybin (plus 6 weeks of daily oral escitalopram)	Prior psilocybin use 8/30 (27%) in the psilocybin group
Carhart-Harris et al. (2016)	Open-label feasibility study	Psilocybin = 12	42.7 (10.2)	50%	TRD	Two oral doses: 10 mg and 25 mg dose, 7 days apart	N/A	Prior psilocybin use 5/12 (42%)
Healthy participants								
Ley et al. (2023)	Randomized, double-blind, placebo-controlled, crossover design	Psilocybin = 32	29 (4)	50%	Healthy participants	Single 20 mg dose	(i) 300 mg or 500 mg mescaline, (ii) 100 μg LSD and (iii) placebo	Prior psychedelic use 20/32 (63%). Prior psilocybin use 12/32 (38%)
Rucker et al. (2022)	Phase 1, randomized, double-blind, placebo-controlled study	25 mg Psilocybin = 30 10 mg Psilocybin = 30 Placebo = 29	Total sample: 36.1 (9.1) 25 mg Psilocybin: 36.6 (10.3) 10 mg Psilocybin: 36.1 (9.3) Placebo: 35.6 (7.7)	Total sample: 54% 25 mg Psilocybin: 53% 10 mg Psilocybin: 53% Placebo: 55%	Healthy participants	Single 10 or 25 mg dose	Placebo	Prior psilocybin use 26/28 (43%) in psilocybin groups

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design (as reported)	n	Mean Age (SD)	% Male	Study Population	Frequency and Dose of Psilocybin	Comparator Group	Prior Psychedelic Use
Holze et al. (2022)	Double-blind, randomized, placebo-controlled, crossover	Psilocybin = 28	35 (9.4)	50%	Healthy participants	5 sessions: Placebo, LSD (100 and 200 μg), and psilocybin (15 and 30 mg) separated by at least 10 days.	Placebo, LSD (100 and 200 μg).	Prior psychedelic use 14/28 (50%). Prior psilocybin use 6/28 (21%)
Becker et al. (2022).	Double-blind, placebo-controlled, crossover design	Psilocybin = 23	34 (10)	52%	Healthy participants	Single 25 mg psilocybin dose; pre-treatment 10 mg escitalopram 7 days, 20 mg escitalopram 7 days.	Single 25 mg psilocybin dose; pre-treatment placebo 14 days.	Prior psilocybin use 6/23 (22%), MDMA use 8/23 (30%)
Dahmane et al. (2021)	Phase I single-center, open-label, single ascending oral dose study	Psilocybin = 12 (all 12 received the first dose)	NR	83%	Healthy participants	3 oral doses: 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg	N/A	NR
Smigielski et al. (2019)	Double-blind, placebo-controlled, between-subject design	Psilocybin = 20 Placebo = 20	Psilocybin: 52.80 (1.55) Placebo: 50.47 (2.15)	Psilocybin: 60% Placebo: 58%	Healthy Buddhist meditation practitioners	Single 315 μg/kg oral dose	Placebo (lactose)	Prior consciousness altering drug use 4/20 (20%) in the psilocybin group ≤3 times, over 20 years ago; 5/20 (25%) ≤3 times in the last 20 years
Bravermanova et al. (2018)	Placebo-controlled double-blind crossover design	Psilocybin = 20	36.81	50%	Healthy participants	Single 0.26 mg/kg dose	Placebo	Prior psychedelic use 14/20 (70%). 1 participant did not fill out the form of previous experience
Carbonaro et al. (2018)	Double-blind, within-subject crossover design	Psilocybin = 20	28.5	45%	Healthy participants	3 doses: 10, 20, 30 mg/70 kg (given 48 h–1 week apart)	DXM (400 mg/70 kg), and placebo (lactose or microcrystalline cellulose)	All participants had a history of psychedelic drug use; 20/20 (100%)
Griffiths et al. (2018)	Double-blinded randomized controlled trial	Low-dose psilocybin, standard support for spiritual practice = 25 High-dose psilocybin, standard support for spiritual practice = 25 High-dose psilocybin, high support for spiritual practice = 25	Low-dose psilocybin, standard support for spiritual practice: 40.2 (2.5) High-dose psilocybin, standard support for spiritual practice: 41.0 (2.7) High-dose, high support for spiritual practice: 45.6 (2.3)	Low-dose, standard support for spiritual practice: 36% High-dose, standard support for spiritual practice: 52% High-dose, high support for spiritual practice: 32%	Healthy participants	Two doses dependent on condition. High-dose psilocybin, standard support for spiritual practice: 20 and 30 mg/70 kg High-dose, high support for spiritual practice: 20 and 30 mg/70 kg on sessions 1 and 2, respectively	Active placebo of 1 mg/70 kg psilocybin with moderate level ("standard" support for spiritual practice)	Past lifetime use of psychedelics: High-dose psilocybin, standard support for spiritual practice: 7/25 (28%) High-dose psilocybin, high support for spiritual practice: 5/25 (20%)
Brown et al., (2017)	Open-label study	Psilocybin = 12	43 (range 24–61)	83%	Healthy participants	Three escalating oral doses of 0.3, 0.45, and 0.6 mg/kg psilocybin at monthly intervals	N/A	12/12 (100%). "Subjects must have had at least one substantial prior experience with a psychedelic"
Carhart-Harris et al. (2011)	Open-label pilot study	Psilocybin: 1.5 mg = 3 2 mg = 6	Total sample: 35.8 (4.9) 1.5 mg: 37.3 (2.3) 2 mg: 35 (5.8)	Total sample: 78% 1.5 mg: 100% 2 mg: 67%	Healthy hallucinogen experienced volunteers	1.5 mg (n = 3) or 2 mg (n = 6)	N/A	9/9 (100%) "All subjects were required to have taken a hallucinogenic drug on at least one occasion without adverse reaction"
Griffiths et al. (2011)	Double-blind, between-group, crossover design	Psilocybin = 18	46 (range 29–62)	44%	Healthy participants	Five doses: 0, 5, 10, 20, 30 mg/70 kg, p.o.) ~1 month apart	Placebo (lactose)	1/18 (6%) participant had previous psilocybin use
Griffiths et al. (2006)	Double-blind study	Psilocybin = 36	46 (range 24–64)	39%	Healthy hallucinogen-naïve adults reporting	Orally administered psilocybin 30 mg/70 kg	Methylphenidate hydrochloride (40 mg/70 kg)	0/36 (0%). "Hallucinogen-naïve adults"

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design (as reported)	n	Mean Age (SD)	% Male	Study Population	Frequency and Dose of Psilocybin	Comparator Group	Prior Psychedelic Use
					regular participation in religious or spiritual activities			
Hasler et al. (2004)	Double-blind, placebo-controlled, dose-effect study	Psilocybin = 8	29.5 (range 22–44)	50%	Healthy participants	Four psilocybin doses in random order: 45 μg/kg body weight, 115 μg/kg, 215 μg/kg, 315 μg/kg over 5 visits, at least 2 weeks apart.	Placebo (lactose)	"Our subjects had no or very limited experience with psychoactive drugs"
Hasler et al. (2002)	Clinical study	Psilocybin = 8	33 (6)	50%	Healthy participants	Single oral dose of 212 ± 25 μg/kg body weight.	N/A	NR. "Subjects with a history of illicit drug abuse were excluded from the study"
Patients with life-threatening illness								
Agrawal et al. (2024)	Phase 2, open-label trial	Psilocybin = 30	56.1 (12.4)	30%	Curable and incurable cancer and MDD	Single 25 mg dose	N/A	NR. Prior psychedelic use was permitted if >12 months before screening
Lewis et al. (2023)	Single-arm, open-label pilot study	Psilocybin = 12	48.2 (11.5)	33%	Cancer patients with DSM-5 depressive disorder	Single 25 mg dose	N/A	Prior psychedelic use 5/12 (42%)
Shnayder et al. (2023)	Phase II, single-center, fixed-dose, open-label trial	Psilocybin = 30	56.1 (12.4)	30%	Cancer patients with MDD	Single 25 mg dose	N/A	NR
Griffiths et al. (2016)	Randomized, double-blind, crossover trial	High dose first = 26 Low dose first = 25	Total sample: 56.3 (1.4) High dose first: 56.5 (1.8) Low dose first: 56.1 (2.3)	Total sample: 51% High dose first: 50% Low dose first: 52%	Cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety	Two doses: 1 dose of 1 or 3 mg/70 kg psilocybin, 1 dose of 22 or 30 mg/70 kg	Low dose (1 or 3 mg/70 kg) psilocybin	Prior hallucinogen use 23/51 (45%)
Ross et al. (2016)	Double blind placebo-controlled crossover RCT	Psilocybin first = 14 Niacin first = 15	Total sample: 56.28 (13.93) Psilocybin first: 52 (15.03) Niacin first: 60.27 (9.45)	Psilocybin first: 50% Niacin first: 27%	Patients with anxiety and depression in life-threatening cancer	Single 0.3 mg/kg oral dose	Niacin 250 mg	Prior hallucinogen use 16/29 (55%)
Grob et al. (2011)	Double-blind, within-subject placebo-controlled study	Psilocybin = 12	Ages ranged from 36 to 58 years	8%	Adults with advanced stage cancer and reactive anxiety	Single 0.2 mg/kg dose	Niacin placebo (250 mg)	Prior hallucinogen use 8/12 (67%). Prior use with hallucinogenic mushrooms 5/12 (42%)
Substance-use disorders								
Heinzerling et al. (2023)	Pilot randomized controlled trial	Visual Healing + Psilocybin = 10 Standard Group (psilocybin only) = 10	Visual Healing + Psilocybin: 46.9 (8.5) Standard Group (psilocybin only): 51.0 (13.2)	Visual Healing + Psilocybin: 40% Standard Group (psilocybin only): 40%	AUD	Two 25 mg doses	Standard set and setting procedures (compared to Visual Healing procedures)	NR. "Psychedelic use (not including ketamine) in the past 12 months or > 25 times lifetime not permitted"
Bogenschutz et al. (2022)	Double-blind randomized clinical trial	Psilocybin = 49 Diphenhydramine = 46	Total sample: 45.78 (11.56) Psilocybin: 47.18 (10.93) Diphenhydramine: 44.24 (12.15)	Total sample: 56% Psilocybin: 57% Diphenhydramine: 54%	AUD	Two doses: 25 mg/70 kg and 25–40 mg/70 kg, 4 weeks apart	Diphenhydramine	NR
Bogenschutz et al. (2015)	Open-label, single-group, proof of	Psilocybin = 10	40.1 (10.3)	60%	DSM-IV Alcohol Dependence	Two doses: 0.3 mg/kg, and was 0.4 mg/kg, orally 4 weeks apart	N/A	NR. "Participants not permitted to have history of

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design (as reported)	n	Mean Age (SD)	% Male	Study Population	Frequency and Dose of Psilocybin	Comparator Group	Prior Psychedelic Use
	concept within-subjects design							using hallucinogens more than 10 times"
Johnson et al. (2014)	Open-label pilot study	Psilocybin = 15	51 (10.5)	67%	Nicotine-dependent smokers	One moderate dose 20 mg/70 kg followed by a default high dose (30 mg/70 kg) at Week 7 and optionally at Week 13. Participants could opt to repeat the moderate dose at session 2 and 3.	N/A	Minimal past hallucinogenic use 10/15 (67%)
Other conditions								
Madsen et al. (2024)	Open-label clinical trial	Psilocybin = 10	49.4 (12.9)	50%	Chronic cluster headache	Three 0.14 mg/kg doses of peroral psilocybin	N/A	NR. Prior serotonin hallucinogen use for chronic cluster headache not permitted
Aaronson et al. (2024)	Nonrandomized open-label trial	Psilocybin = 15	37.8 (11.6)	40%	Treatment-resistant bipolar type II major depressive episodes	Single 25 mg dose	N/A	Prior lifetime psychedelic use 5/15 (33%)
Peck et al. (2023)	Open-label pilot study	Psilocybin = 10	28.3 (3.7)	0%	Anorexia nervosa	Single 25 mg dose	N/A	NR
Schneier et al. (2023)	Open-label study	Psilocybin = 12	34.31 (8.86)	33%	Body dysmorphic disorder	Single 25 mg dose	N/A	Prior psilocybin use 1/12 (8%)
Schindler et al. (2022)	Randomized, double-blind, placebo-controlled study	Psilocybin = 8 Placebo = 8	Total sample: 49.1 (10.7) Psilocybin: 52.6 (11.2) Placebo: 44.5 (8.6)	Total sample: 64% Psilocybin: 50% Placebo: 83%	Cluster headache	Psilocybin (0.143 mg/kg) in a pulse of three doses, each ~5 days apart.	Placebo (microcrystalline cellulose)	Prior psilocybin and related substance use 2/8 (25%) in psilocybin group
Schindler et al. (2021)	Exploratory double-blind, placebo-controlled, crossover study	Psilocybin = 10	40.5 (4.4)	30%	Adults with migraine	Psilocybin (0.143 mg/kg) was administered in 2 test sessions spaced 2 weeks apart.	Placebo (microcrystalline cellulose)	Prior use of psilocybin and related drugs (2/10) (20%)
Anderson et al. (2020)	Open-label safety and feasibility pilot study	Psilocybin = 18	59.2 (4.4)	100%	Older long-term AIDS survivor men	Single 0.3–0.36 mg/kg dose orally	N/A	Lifetime history of classic psychedelic use 7/18 (38.9%) ≥10 times, 3/18 (16.7%) ≥100 times, and 1/18 (5.5%) had used entactogens (e.g., MDA) 'hundreds' of times
Moreno et al. (2006)	Modified double-blind study	Psilocybin = 9	40.9 (13.2)	78%	DSM-IV-defined OCD	4 doses: Low (100 μg/kg), medium (200 μg/kg), and high (300 μg/kg) assigned in that order and a very low dose (25 μg/kg) randomly inserted in a double-blind fashion	Psilocybin 25 μg/kg	9/9 (100%). "Subject required to have tolerated well at least 1 prior exposure to indole-based psychedelics"

Abbreviations: N/A = not applicable; NR = not reported; MDD = major depressive disorder; TRD = treatment resistant depression; MDMA = 3,4-Methylenedioxymethamphetamine; AUD = alcohol use disorder; DSM-IV; The Diagnostic and Statistical Manual of Mental Disorders 4th edition; OCD = obsessive compulsive disorder; AIDS = acquired immunodeficiency syndrome.

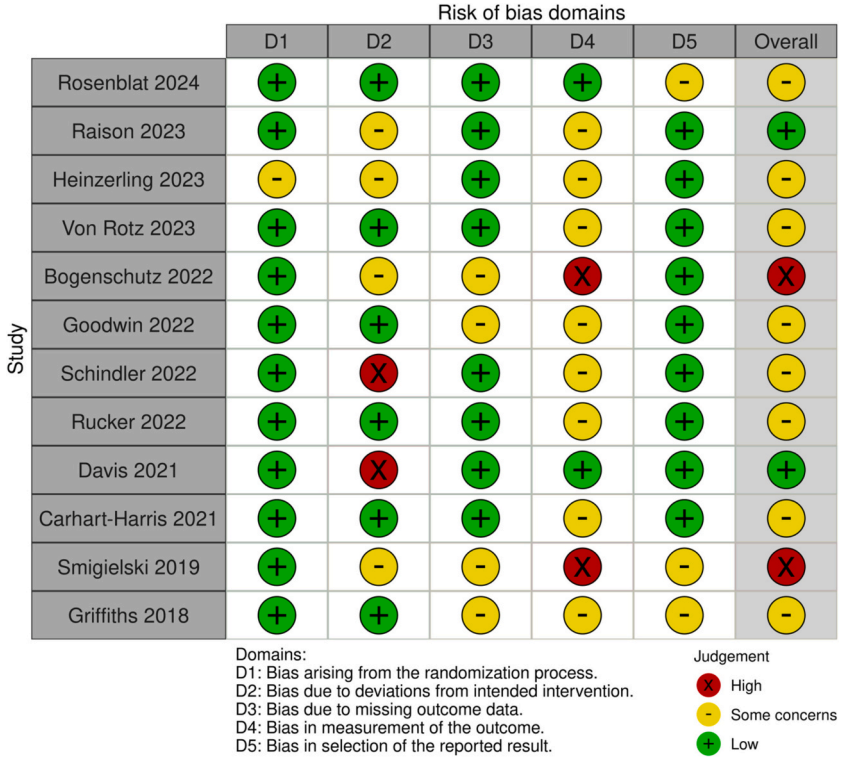

Fig. 2. Traffic light plot for RoB 2 for parallel trials.

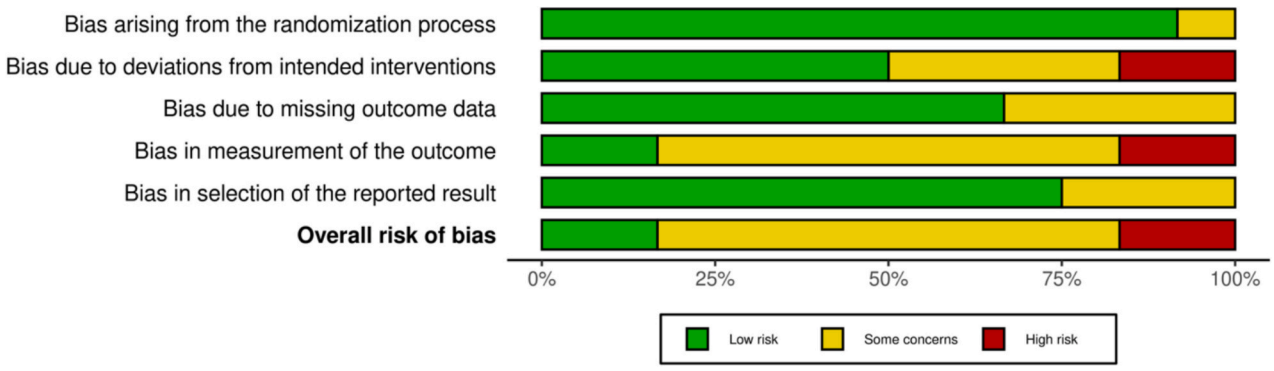

Fig. 3. Summary graph for RoB 2 for parallel trials.

et al., 2023; Ley et al., 2023; von Rotz et al., 2023; Goodwin et al., 2022; Schindler et al., 2022; Rucker et al., 2022; Griffiths et al., 2018; Moreno et al., 2006; Sloshower et al., 2023; Becker et al., 2022; Bravermanova et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2011; Holze et al., 2022; Grob et al., 2011; Schindler et al., 2021; Davis et al., 2021), 10 did not report participants' prior psychedelic use (Bogenschutz et al., 2015; Agrawal et al., 2024; Madsen et al., 2024; Peck et al., 2023; Goodwin et al., 2023; Shnayder et al., 2023; Dahmane et al., 2021; Heinzerling et al., 2023; Bogenschutz et al., 2022; Hasler et al., 2002), one study explicitly stated that none of the participants had prior psychedelic experience (Griffiths et al., 2006), and another reported that participants had "very limited or no experience with psychoactive drugs" (Hasler et al., 2004).

3.3. Expected, common adverse events

The most commonly reported expected AEs mentioned in at least one participant across studies included headache (71%), nausea (64%), elevated blood pressure (52%), anxiety (45%), increased heart rate (36%), fatigue (33%), dizziness (26%), and perceptual disturbances (26%). These findings are summarized in Fig. 6. Most commonly reported AEs across psilocybin and placebo conditions are reported in Table 3 and illustrated in Fig. 7.

Seven studies reported differences in psilocybin and placebo conditions using statistical significance (Hasler et al., 2004; Griffiths et al., 2018; Bravermanova et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006; Grob et al., 2011), rather than reporting frequency or participant counts and are thus excluded from Table 3 and Fig. 7. All seven studies found significant increases in blood pressure following psilocybin administration, and six also report significant increases in heart rate (Griffiths et al., 2018; Bravermanova et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006; Grob et al., 2011). Significant differences were reported in derealization, yawning, tearing or crying, and nausea (Griffiths et al., 2018; Carbonaro et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006). Griffiths et al. (2006, 2011) reported significant differences in anxiety/fearfulness, unresponsiveness to questions, stimulation/arousal, and spontaneous motor activity, with Griffiths et al. (2011) also reporting significant

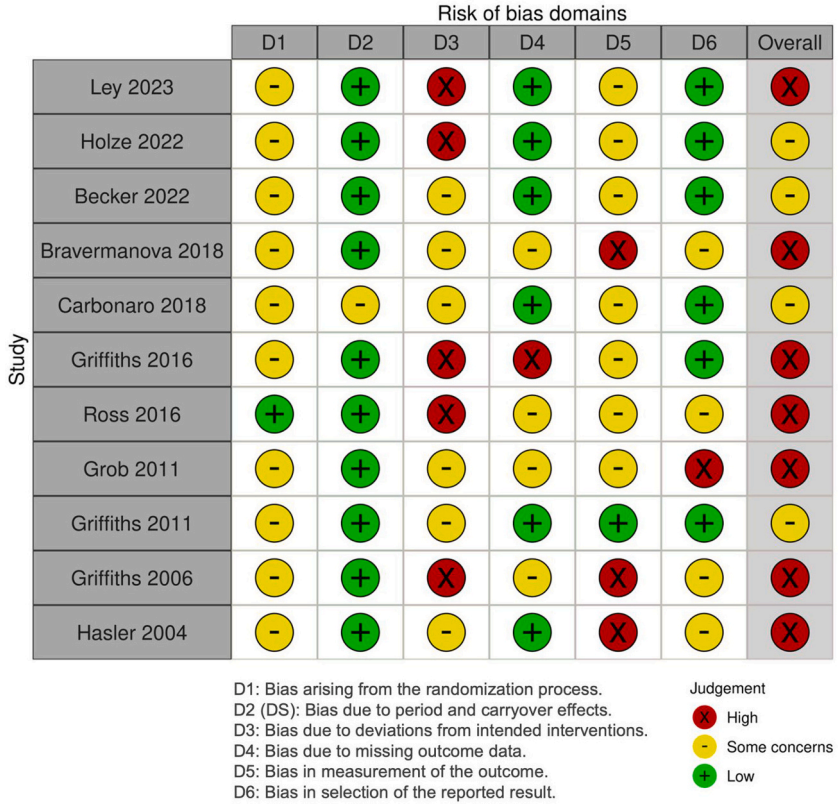

Fig. 4. Traffic light plot for RoB 2 crossover tool.

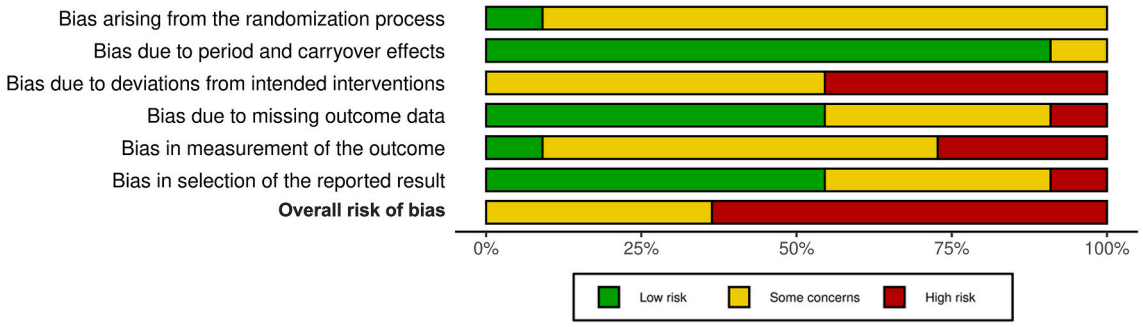

Fig. 5. Summary graph for RoB 2 crossover tool.

Table 2
ROBINS-I risk of bias assessment.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Madsen 2024	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Aaronson 2024	Serious	Low	Low	Low	Critical	Moderate	Moderate	Critical
Agrawal 2024	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Sloshower 2023	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Lewis 2023	Serious	Low	Low	Low	Moderate	Moderate	Low	Serious
Peck 2023	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Goodwin 2023	Serious	Low	Low	Low	Low	Serious	Low	Serious
Schneier 2023	Serious	Low	Low	Low	Moderate	Moderate	Low	Serious
Shnayder 2023	Serious	Low	Low	Low	Moderate	Moderate	Moderate	Serious
Schindler 2021	Serious	Low	Low	Low	Low	moderate	Low	Serious
Dahmane 2021	Serious	Serious	Low	Low	Critical	Moderate	Critical	Critical
Anderson 2020	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Brown 2017	Serious	Low	Low	Low	Serious	Moderate	Serious	Serious
Carhart-Harris 2016	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Bogenschutz 2015	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Johnson 2014	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Carhart-Harris 2011	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious	Serious
Moreno 2006	Serious	Low	Low	Low	Moderate	Moderate	Moderate	Serious
Hasler 2002	Serious	Moderate	Low	Low	Critical	Moderate	Critical	Critical

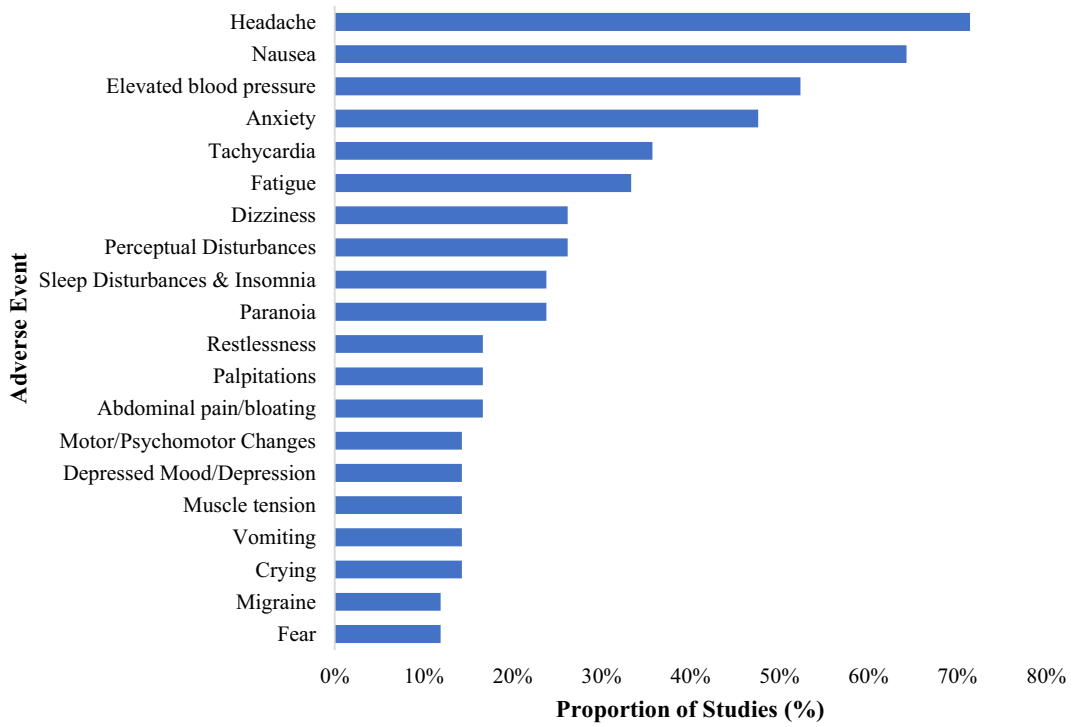

Fig. 6. Percentage of studies reporting most common adverse events associated with psilocybin. Adverse events reported in more than 10% of all studies are displayed.

Table 3
Common adverse events reported for that included both psilocybin and placebo conditions.

Adverse Event	Psilocybin $N = 433$ (%)	Placebo* $N = 370$ (%)
Headache	171 (39)	72 (19)
Fatigue	103 (24)	44 (12)
Nausea or Vomiting	93 (21)	10 (3)
Anxiety	46 (11)	9 (2)
Insomnia	39 (9)	7 (2)
Elevated blood pressure	23 (5)	11 (3)
Dry mouth	27 (6)	2 (1)
Dizziness	19 (4)	1 (<1)

Adverse events presented from 11 studies that reported data for both psilocybin and placebo conditions (Griffiths et al., 2016; Raison et al., 2023; Ley et al., 2023; von Rotz et al., 2023; Bogenschutz et al., 2022; Goodwin et al., 2022; Schindler et al., 2022; Rucker et al., 2022; Holze et al., 2022; Schindler et al., 2021; Sloshower et al., 2023).
* Placebo includes inert and active placebo conditions.

increases in ideas of reference or paranoid thinking and restlessness/fidgetiness. Carbonaro et al. (2018) similarly found significant differences in restlessness/fidgetiness, but no significant differences in unresponsiveness to questions, anxiety/fearfulness, or delusions/paranoid thinking. Griffiths et al. (2018) report significant differences in increases in anxiety/fearfulness, derealization, and delusions/paranoid thinking. Hasler et al. (2004) report significant increase in drowsiness, while both Hasler et al. (2004) and Grob et al. (2011) report significant difference in changes in sensory perceptions.

All frequently reported AEs align with the known acute effects of psilocybin (Yerubandi et al., 2024; Breeksema et al., 2022). AEs were generally transient and resolved within 24 h of administration. Few studies reported on the severity of AEs, though severe AEs were reported in five studies and included hypertension, anxiety, nausea, headache, illusion and panic attack, and paranoia (Agrawal et al., 2024; Carhart-Harris et al., 2016; Raison et al., 2023; Anderson et al., 2020; Goodwin et al., 2022). In most studies, increases in blood pressure and heart rate occurred in a dose-dependent manner, typically peaking during the acute effects of psilocybin and resolving thereafter. An exception was noted by Peck et al. (2023), who reported one case of increased orthostatic heart rate response at a three-month follow-up.

3.4. Unexpected, uncommon adverse events

Unexpected or uncommon AEs that were reported in more than one study included: chest tightness/heaviness/pain, abnormal/vivid dreams, shivering/cold, back pain, bruxism/jaw rigidity, tension/sore muscles, hypotension, pain, freezing, hypersensitivity to odours, trembling, forgetfulness/memory impairments, perspiration, increased appetite, cluster headache (CH) attack (in participants with pre-existing CH), corona virus, pneumonia, influenza, and oropharyngeal pain (Table 4). Of the studies included in Table 4, 8 included placebo conditions (Ley et al., 2023; Bogenschutz et al., 2022; Goodwin et al., 2022; Schindler et al., 2022; Carbonaro et al., 2018; Holze et al., 2022; Schindler et al., 2021; Sloshower et al., 2023), of which one did not report counts, but significant differences between AEs in psilocybin versus placebo conditions (Carbonaro et al., 2018). The overall frequency of uncommon AEs being present in placebo conditions was typically <1%. The uncommon AEs reported in more than one participant in placebo conditions included back pain ($n = 7$) (Bogenschutz et al., 2022; Holze et al., 2022), cluster headache attack ($n = 5$) (Schindler et al., 2022), tension/sore muscles ($n = 4$) (Schindler et al., 2022; Schindler et al., 2021), freezing ($n = 2$) (Ley et al., 2023; Holze et al., 2022), neck and shoulder pain ($n = 4$) (Holze et al., 2022), viral upper respiratory tract infection ($n = 3$) (Bogenschutz et al., 2022), general pain ($n = 3$) (Bogenschutz et al., 2022), alcohol withdrawal syndrome ($n = 2$) (Bogenschutz et al., 2022), and oropharyngeal pain ($n = 2$). Uncommon or unexpected AEs reported in a single participant in placebo conditions included bruxism, increased appetite, jaw soreness, gingivitis and hot flashes. Of note, hypotension was observed in single participants across three studies: Rosenblat et al. (2024), Heinzerling et al. (2023), and Lewis et al. (2023), representing 3.3%, 5%, and 8.5% of their respective samples. Rosenblat et al. (2024) also reported a novel case of persistent genital arousal lasting for six months in a participant

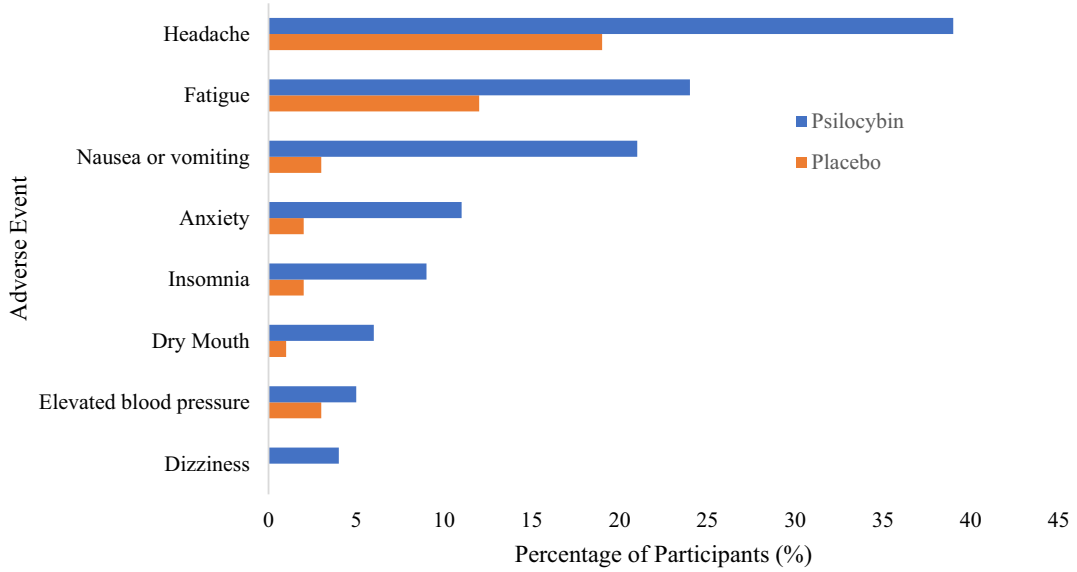

Fig. 7. Mean percentage of participants reporting adverse events from 11 studies that provided data for both psilocybin and placebo conditions (Griffiths et al., 2016; Raison et al., 2023; Ley et al., 2023; von Rotz et al., 2023; Bogenschutz et al., 2022; Goodwin et al., 2022; Schindler et al., 2022; Rucker et al., 2022; Holze et al., 2022; Schindler et al., 2021; Sloshower et al., 2023).

with treatment resistant depression. While unusual, the event resolved without sequelae and was not classified as serious. Anderson et al. (2020) reported two atypical AEs in individuals with AIDS. One participant experienced a post-traumatic flashback related to a prior sexual assault two days after dosing, and another with decades of polysubstance use developed severe anxiety and relapsed into methamphetamine use ten days after dosing, despite initial improvement in anxiety. As these unexpected or uncommon AEs were not clearly deemed related to study intervention, it is unclear whether they can be attributed to psilocybin itself.

3.5. Adverse events requiring medical intervention

3.5.1. Hypertension

Adverse events requiring medical intervention are detailed below and outlined in Table 5.

Four cases of elevated blood pressure required pharmacologic intervention. Goodwin et al. (2023) reported two instances of severe treatment-emergent AEs involving hypertension, both of which were managed with clonidine. Lewis et al. (2023) documented one participant who received 10 mg of propranolol for sustained high blood pressure. Griffiths et al. (2018) described one case in which a participant was withdrawn from the study after requiring nitroglycerin for critically elevated diastolic blood pressure.

3.5.2. Headache

While most studies reported that headaches were self-limiting, the use of over the counter (OTC) medications was noted in some studies. Brown et al. (2017) reported successful headache treatment with acetaminophen but did not specify in how many participants. Lewis et al. (2023) reported 325 mg of acetaminophen was given to a participant experiencing headache. Johnson et al. (2014) found that 50% of participants ($n = 5$) used OTC medications to alleviate headache symptoms. Goodwin et al. (2023) stated that mild to moderate headaches generally resolved spontaneously or were treated with ibuprofen or paracetamol/acetaminophen, typically on the dosing day or the following day. One participant in their study treated with clonidine for hypertension also experienced a co-occurring headache that resolved with blood pressure management.

3.5.3. Nausea

Lewis et al. (2023) reported two participants were treated with 25 mg of promethazine to manage nausea.

3.5.4. Anxiety

Goodwin et al. (2022) reported one participant in a group that received 25 mg psilocybin was treated with lorazepam for acute anxiety. Bogenschutz et al. (2022) reported two participants received 10 mg of diazepam for anxiety during their second dosing session, which resolved within 45 and 210 min post-diazepam administration, respectively.

3.5.5. Psychotic disorder

Rucker et al. (2022) reported a participant received 2.5 mg of oromucosal midazolam for substance-induced psychosis and behavioral disinhibition during the acute phase of the psilocybin experience. The event resolved without sequelae, and the participant was discharged 11 h post psilocybin dosing. It was not considered an SAE and there were no noted significant effects at follow-up.

3.6. Serious adverse events & suicidality

Of the 42 included studies, only two reported related or potentially related SAEs that occurred in participants with major depressive disorder and treatment resistant depression (Goodwin et al., 2022; Sloshower et al., 2023) (See Supplemental Table 1). Goodwin et al. (2022) reported a total of 16 SAEs from day 2 to 12 weeks post-treatment in participants with TRD. From day 2 to 3 weeks post-dosing, SAEs included suicidal ideation ($n = 4$), intentional self-injury ($n = 3$) and hospitalization for severe depression ($n = 1$). Between weeks 3 to 12, AEs included suicidal behaviour ($n = 3$), codeine withdrawal syndrome ($n = 1$), adjustment disorder with anxiety and depression ($n = 1$), suicidal ideation ($n = 1$), intentional self-injury ($n = 1$), and depression ($n = 1$). All participants reporting suicidal behaviour during follow-up had a prior history of suicidal behaviour and did not show a treatment response at week 3 post-dosing. Sloshower et al. (2023) reported one SAE involving hospitalization in a participant with treatment refractory MDD. Although the participant initially experienced a reduction in depressive symptoms following psilocybin dosing, her symptoms worsened in the following weeks, and she voluntarily admitted herself to a psychiatric hospital for worsening depressive symptoms and suicidal ideation. The SAE was

Table 4
Uncommon/unexpected adverse events reported across studies.

Adverse Event	Number of Participants (% total sample)	Number of Reported Studies	Reported Studies	Study Population
Chest tightness/heaviness/ pain	5 (0.47%)	4	Goodwin et al. 2023, Ley et al. 2023, Sloshower et al. 2023, Davis et al. 2021	TRD, Healthy participants, MDD
Abnormal/Vivid dreams	4 (0.34%)	4	Goodwin et al. 2022[3], Carhart-Harris et al. 2021, Davis et al. 2021, Heinzerling et al. 2021	TRD, MDD, AUD
Shivering/cold	3 (0.28%)	4	Goodwin et al. 2022, Schindler et al. 2022, Schindler et al. 2021, Carbonaro et al. 2018	TRD, Cluster headache, Migraine, Healthy participants
Back pain	10 (0.94%)	3	Bogenschutz et al. 2022, Holze et al. 2022, Carhart-Harris et al. 2021[3]	AUD, Healthy participants, MDD
Bruxism/Jaw rigidity	8 (0.75%)	3	Heinzerling et al. 2023, Ley et al. 2023, Holze et al. 2022	AUD, Healthy participants
Tension/sore muscles	5 (0.47%)	3	Schindler et al. 2022, Davis et al. 2021, Schindler et al. 2021	Cluster headache, MDD, Migraine
Hypotension[1]	3 (0.28%)	3	Rosenblat et al. 2024, Heinzerling et al. 2023, Lewis et al. 2023	TRD, AUD, Cancer & Depressive disorder
Pain (General)	3 (0.28%)	3	Peck et al. 2023, Bogenschutz et al. 2022, Carhart-Harris et al. 2021	MDD, Alcohol Dependence, Anorexia nervosa
Freezing	26 (2.43%)	2	Ley et al. 2023, Holze et al. 2022	Healthy participants
Hypersensitivity to odours	17 (1.59%)			
Trembling	12 (1.12%)			
Forgetfulness/memory impairment	14 (1.31%)	2	Holze et al. 2022, Rucker et al. 2022	Healthy participants
Perspiration	14 (1.31%)	2	Ley et al. 2023, Holze et al. 2022	Healthy participants
Increased appetite	5 (0.47%)	2	Ley et al. 2023, Goodwin et al. 2022	Healthy participants, TRD
Cluster headache	5 (0.47%)	2	Madsen et al. 2024, Schindler et al. 2022	Cluster headache
Corona virus	3 (0.28%)	2	Schneier et al. 2023, Bogenschutz et al. 2022	AUD, BDD
Pneumonia	3 (0.28%)	2	Schneier et al. 2023, Bogenschutz et al. 2022	AUD, BDD
Influenza	2 (0.19%)	2	Bogenschutz et al. 2022, Carhart-Harris et al. 2021, Bogenschutz et al. 2015	AUD, MDD, Alcohol dependence
Oropharyngeal pain	2 (0.19%)	2	Bogenschutz et al. 2022, Carhart-Harris et al. 2021	AUD, MDD
Brooding	15 (1.40%)			
Neck/shoulder pain	12 (1.12%)	1	Holze et al. 2022	Healthy participants
Hot flashes	9 (0.84%)			
Fizziness	16 (1.50%)			
Dissociative identity disorder	2 (1.31%)	1	Rucker et al. 2022	Healthy participants
Shortness of breath	6 (0.56%)	1	Ley et al. 2023	Healthy participants
Rhinorrhea	3 (0.28%)	1	Agrawal et al. 2024	Cancer & MDD
Dehydration	3 (0.28%)			
Hypoglycemia[2]	2 (0.19%)	1	Peck et al. 2023	Anorexia =nervosa
Cataract	1 (0.09%)			
Photopsia	1 (0.09%)			
Diverticulitis	1 (0.09%)			
Toothache	1 (0.09%)			
Gingivitis	1 (0.09%)			
URTI	2 (0.19%)			
Viral URTI	2 (0.19%)			
Alcohol poisoning	2 (0.19%)			
Myalgia	1 (0.09%)	1	Bogenschutz et al. 2022	AUD
Testicular pain	1 (0.09%)			
Limb injury	1 (0.09%)			
Muscle strain	1 (0.09%)			
Dyspnea	1 (0.09%)			
Nasal congestion	1 (0.09%)			
Food allergy	1 (0.09%)			
Food poisoning	1 (0.09%)			
Alcohol withdrawal syndrome	1 (0.09%)			
Malignant melanoma stage II	1 (0.09%)	1	Goodwin et al. 2022	TRD
Tooth abscess	1 (0.09%)	1		TRD
Persistent genital arousal[3]	1 (0.09%)	1	Rosenblat et al. 2024	TRD
Skin abrasion	1 (0.09%)	1	Goodwin et al. 2023	TRD
Joint pain	1 (0.09%)	1	Sloshower et al. 2023	MDD
Limb discomfort	1 (0.09%)	1	Carhart-Harris et al. 2021	MDD
Dysmenorrhea	1 (0.09%)			

(*continued on next page*)

Table 4 (*continued*)

Adverse Event	Number of Participants (% total sample)	Number of Reported Studies	Reported Studies	Study Population
Musculoskeletal stiffness	1 (0.09%)			
Jaw clenching/pain	1 (0.09%)			
Bradycardia	1 (0.09%)	1	Heinzerling et al. 2023	AUD
Tinnitus	1 (0.09%)			
Facial muscle spasm	1 (0.09%)	1	Madsen et al. 2024	Cluster headache
Low libido[4]	1 (0.09%)	1	Schneier et al. 2023	BDD
Jaw soreness[5]	1 (0.09%)	1	Schindler et al. 2022	Cluster headache
Ear fullness[5]	1 (0.09%)			
Methamphetamine relapse[6]	1 (0.09%)	1	Anderson et al. 2020	AIDS survivor men
PTSD flashback[7]	1 (0.09%)			

Abbreviations: TRD = treatment resistance depression; MDD = major depressive disorder; AUD = alcohol use disorder; BDD = body dysmorphic disorder; UTRI = upper respiratory tract infection; AIDS = acquired immunodeficiency syndrome.

[1] Lewis et al. (2023) reported hypotension in one participant who also experienced nausea, vomiting, and diarrhea the day after dosing. Given a concurrent case of viral gastroenteritis in the participant's household, the event was not clearly attributable to psilocybin.

[2] Hypoglycemia was hypothesized to result from prolonged fasting on the dosing day rather than a direct pharmacological effect of psilocybin, given the participant's malnutrition and reduced carbohydrate stores related to anorexia nervosa.

[3] The adverse event persisted throughout the 6-month follow-up period.

[4] Low libido began in the first week and persisted for two weeks.

[5] Incidence reported not to be significantly higher than placebo.

[6] Reported 10 days after dosing. The participant was diagnosed with generalized anxiety disorder, panic disorder, and borderline personality disorder, with a history of polysubstance use. Although initial anxiolysis was observed, the participant later reported severe anxiety and a sense of rejection, which led to a methamphetamine relapse and withdrawal from the intervention.

[7] Two days after the medication visit, the participant experienced a vivid post-traumatic flashback involving prior sexual assaults. Symptoms include nausea, tinnitus, panic, and insomnia, resulting in two days of work absence. A similar flashback had previously occurred after starting efavirenz, an antiretroviral and 5-HT_2A receptor agonist.

Table 5
Pharmacological management of adverse events reported across studies.

Study	Population	Adverse Event	Management	Outcome
Goodwin et al., 2023	TRD	Hypertension ($n = 2$)	Clonidine	Resolved
		Headache	Ibuprofen or paracetamol	Resolved
		Anxiety ($n = 1$)	Lorazepam	Resolved
Lewis et al., 2023	MDD	Hypertension ($n = 1$)	10 mg propranolol	Resolved
		Headache ($n = 1$)	325 mg acetaminophen	Resolved
		Nausea ($n = 2$)	25 mg promethazine	Resolved
Bogenschutz et al., 2022	AUD	Anxiety ($n = 2$)	10 mg diazepam	Resolved within 45 min and 210 min
Rucker et al., 2022	Healthy participants	Substance induced psychotic disorder ($n = 1$)	2.5 mg oromucosal midazolam	Resolved
Griffiths et al., 2018	Healthy participants	Severe hypertension ($n = 1$)	Nitroglycerin	Withdrawn from study
Brown et al., 2017	Healthy participants	Headache	Acetaminophen	Resolved
Johnson et al., 2014	Nicotine dependent smokers	Headache ($n = 5$)	Over-the-counter medication (unspecified)	Resolved

Abbreviations: TRD = treatment resistant depression; MDD = major depressive disorder; AUD = alcohol use disorder.

anticipated due to her high baseline depression scores.

3.7. Reports of suicidal ideation as non-serious adverse events

A number of studies reported instances of suicidal ideation as non-serious AEs due to their transient nature or lack of need for clinical intervention. Rosenblat et al. (2024) reported transient increases of suicidality for 24 to 48 h post dosing in two participants, neither of which required further intervention. Raison et al. (2023) reported that one participant with MDD exhibited an increase in suicidal ideation from baseline to the end of the trial (43 days post-treatment) as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). However, they did not report any cases of suicidal or self-injurious behaviour and noted that any cases of suicidal ideation were passive. Peck et al. (2023) reported that one participant with anorexia nervosa and a history of MDD displayed an increased C-SSRS score after a 3-month follow-up. However, they deemed that the increased score was not study related due to the participant's history. In a study of participants with alcohol use disorder (AUD), Bogenschutz et al. (2022) reported a brief episode of passive suicidal ideation lasting 15 min in one participant during dosing, as well as suicidal ideation in four participants between weeks 4 and 36 post-dosing, none of which were classified as SAEs. Rucker et al. (2022) reported mild suicidal ideation (Sheehan Suicidality Tracking Scale (SSTS) = 1) in one healthy participant 19 days after treatment (10 mg psilocybin) which resolved the same day and was deemed possibly related to the study drug.

3.8. Treatment discontinuation/study withdrawal

Majority of the studies reviewed reported at least one participant who did not complete the study intervention as planned (See Supplemental Tables 1-5). Rosenblat et al. (2024) ($n = 1$) and Goodwin et al. (2022) ($n = 4$, $n = 2$ in 25 mg psilocybin group, $n = 2$ in 10 mg psilocybin group) report discontinuation or incompletion of the study due to an AE, without further specification. Heinzerling et al. (2023) reported one participant with a history of prior alcohol treatment episodes who withdrew due to an alcohol relapse that required inpatient detoxification and treatment. Similarly, Anderson et al. (2020) reported one participant who withdrew following a methamphetamine relapse. Two studies, Dahmane et al. (2021) and Brown et al. (2017) each reported white-coat hypertension in one participant, resulting in the participant's removal before the initial and second dosing session, respectively. One

participant in Sloshower et al. (2023) also dropped out before receiving psilocybin due to uncontrolled hypertension, though no further details are given. Additional treatment discontinuations were due to psychological reactions such as paranoia ($n = 1$) (Schindler et al., 2022) and anxiety ($n = 3$) (Griffiths et al., 2016; Davis et al., 2021). One participant discontinued due to vomiting after capsule administration (Griffiths et al., 2016). A small number of participants withdrew to resume antidepressant treatment ($n = 2$) (Ross et al., 2016; von Rotz et al., 2023) or to pursue other treatments ($n = 8$) (Rosenblat et al., 2024).

3.9. Measures

AE measures varied across studies, particularly concerning the assessment of psychological AEs. Vital signs were reported across 35 studies (83%) (See Supplemental Tables 1–5). AE data were commonly collected through study monitor observations during and after dosing, and participant self-report. However, there was no standardized AE measurement scale used across studies. Four studies included the list of complaints (LC) as a measure of AEs (Hasler et al., 2004; Ley et al., 2023; Becker et al., 2022; Holze et al., 2022). Few studies by the same authors used the Monitor Rating Questionnaire (MRQ) (Griffiths et al., 2016; Johnson et al., 2014; Davis et al., 2021; Griffiths et al., 2018; Griffiths et al., 2011; Griffiths et al., 2006), or the Challenging Experience Questionnaire (CEQ) (Anderson et al., 2020; Davis et al., 2021; Sloshower et al., 2023; Heinzerling et al., 2023). The CEQ assesses adverse psychological reactions to psychedelic effects across seven factors: grief, fear, death, insanity, isolation, physical distress and paranoia (Barrett et al., 2016). The Altered State of Consciousness (ASC) scale was used in 18 studies to assess subjective psychedelic experience, with the 5-Dimensional ASC Rating Scale (5D-ASC) the most frequently used variation of the measure. The 5D-ASC measures five domains: oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations, and reduction of vigilance. The interpretation of 5D-ASC outcomes varies among researchers. For instance, Smigielski et al. (2019) focused on the 'anxious ego dissolution' dimension to measure anxiety levels during psilocybin sessions. In contrast, other studies do not classify such psychological experiences as AEs, especially when they are transient and align with anticipated psychedelic effects. For instance, Sloshower et al. (2023) did not report acute subjective effects related to the psychedelic experience as AEs, citing evidence that these effects may mediate positive therapeutic outcomes. Similarly, Schneier et al. (2023) did not record transient, non-serious psychological experiences during dosing sessions as AEs unless they persisted at the 8-h post-dosing assessment. Smigielski et al. (2019) also reported two participants feeling transiently emotionally overwhelmed during the peak effect of psilocybin but note that the participants did not consider the experience as negative.

4. Discussion

We systematically reviewed 42 published, peer reviewed studies in which psilocybin was given to patients with psychiatric disorders, life-threatening illness, or healthy participants. To our knowledge, this is the largest systematic review to date evaluating the AEs of PT. In summary, our main findings were: (1) acute AEs are common after psilocybin administration; (2) the most common AEs were headache, elevated blood pressure, and nausea; (3) the majority of the AEs were mild and/or transient and resolved without pharmacological intervention; and (4) only 2 of 42 studies reported SAEs that were potentially related to psilocybin, including suicidal ideation, intentional self-injury, and hospitalization for severe depression in participants with MDD or TRD. There were no AEs or SAEs of suicidal ideation or self-injury reported in participants without pre-existing depression.

The common AEs reported in our systematic review are consistent with those observed in other reviews assessing psilocybin's safety. For instance, Yerubandi et al. (2024) similarly found that psilocybin dosing was associated with significant transient incidences of headache, nausea, anxiety, dizziness, and elevated blood pressure. Likewise, Breeksema et al. (2022) reported moderate to severe anxiety, headache, and nausea as the most common acute AEs associated with psilocybin and report that acute psychological AEs frequently resolved during dosing days. Nonetheless, our review is broader in scope, as it includes all studies that administered psilocybin, regardless of population, and incorporates a substantially larger number of studies than these previous reviews.

4.1. Defining psychological AEs – Need for standardized reporting

Defining and categorizing AEs in psilocybin research can be uniquely challenging. For example, psychological effects that may be classified as AEs in other clinical contexts are often an expected part of the psilocybin experience. The lack of standardized AE reporting frameworks further contributes to inconsistencies, with some studies reporting transient psychological effects as AEs and others omitting them. For example, Sloshower et al. (2023) argue that these effects may facilitate therapeutic outcomes rather than being classed as AEs. Smigielski et al., (2019) reported that two participants experienced emotional overwhelm, though the participants did not interpret the experience as negative and Schneier et al., (2023) did not consider transient, non-serious psychological experiences during dosing sessions as AEs. Qualitative studies show that participants generally perceive their psilocybin experiences as meaningful and positive, even when accompanied by transient psychological discomfort or perceptual alterations (Agin-Liebes et al., 2024; Smith et al., 2022; Turton et al., 2014). Relatedly, greater subjective intensity during dosing has been associated with stronger therapeutic outcomes (Griffiths et al., 2016; Ross et al., 2016; Griffiths et al., 2008). However, whether psychedelic effects are necessary for psilocybin's therapeutic benefit remains under investigation (Husain et al., 2023). Moreover, even studies that were judged to be low risk of bias reported AEs poorly, further underscoring the need for standardized and systematic AE reporting.

There is a need for widespread use of a psychedelic-specific AE scale to standardize AE reporting in psilocybin research (U.S. Food and Drug Administration, 2024). A psychedelic-specific AE scale should be capable of distinguishing between typical psychological effects, such as altered perception and intense emotional states, which are generally not harmful, and instances that are deemed adverse. Commonly used tools in psychotropic drug research, like the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987), do not capture the unique effects of psychedelics. The Swiss Psychedelic Side Effects Inventory (SPSI) (Calder and Hasler, 2024) is a newer instrument that assesses the severity, impact (positive, neutral, or negative), duration, and treatment-relatedness of 32 psychedelic specific side effects, though it requires further replication to assess its validity. We also recommend the use of existing validated tools such as the CEQ to evaluate potential adverse reactions to the psychedelic experience.

4.2. Impact of expectancy effects and functional unblinding on psilocybin safety outcomes

Though suggesting overall safety, fully assessing psilocybin's safety profile remains complicated due to confounding expectancy effects and functional unblinding in placebo-controlled studies (Muthukumaraswamy et al., 2021; Szigeti and Heifets, 2024). The FDA has raised concerns regarding interpreting the positive results of psychedelic research given the high prevalence of functional unblinding (U.S. Food and Drug Administration, 2024). Our risk of bias analysis similarly identified several studies with a high risk of bias due to functional unblinding, where participants and/or study staff were able to discern their treatment allocation. Compromised blinding may lead to biases AE reporting, specifically inflating the presence of AEs, due to both participant and staff expectations (Flameling et al., 2023; Aday

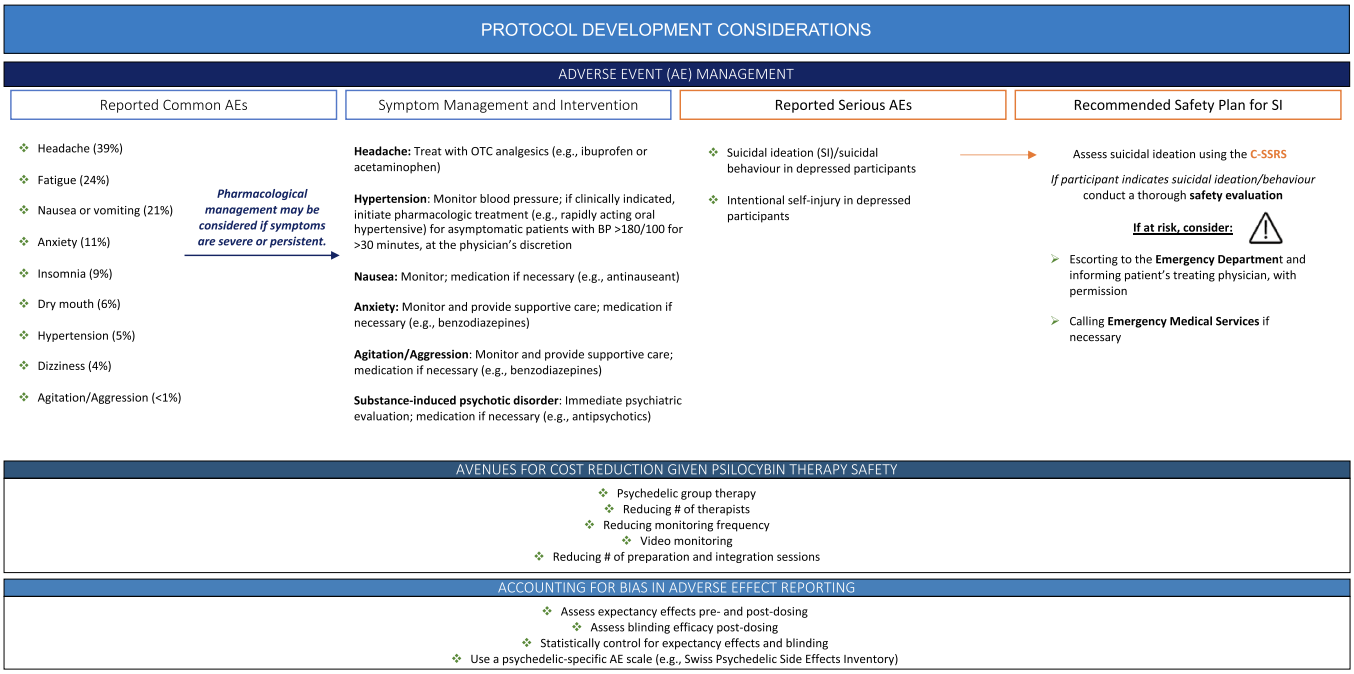

Fig. 8. Protocol development considerations, including adverse event management. Abbreviations: AE = adverse event; SI = suicidal ideation; C-SSRS = Columbia Suicide Severity Scale. Reported percentages on common AEs reflect the proportion of participants reporting each adverse event in studies that reported both psilocybin and placebo conditions.

et al., 2022). Accordingly, our results show that some AEs including headache, fatigue, nausea, and elevated blood pressure were also present in placebo conditions, albeit at lower frequencies. The extensive preparatory sessions common in psilocybin studies may also play a role in amplifying participant expectancy effects (Aday et al., 2022). Although functional unblinding challenges the interpretation of efficacy data, it does not negate safety findings. Rather, it's likely that functional unblinding will contribute to an exaggeration of psilocybin associated AEs. We recommend using validated tools to account for participant expectations (e.g., the Stanford Expectations of Treatment Scale (SETS) (Younger et al., 2012)), to assess for blinding efficacy of study staff and participants after each psilocybin dose, and to statistical control for these variables when possible (See Fig. 8).

4.3. Safety considerations and adverse event management

Overall, psilocybin use in supervised settings appears safe across populations with most AEs time-limited and resolving without intervention. We recommend a stepped approach to AE management (Fig. 8). Monitoring of AEs should occur to assess whether symptoms become distressing or prolonged. Pharmacological intervention may be required for headache, and less likely for hypertension, nausea, anxiety, or psychosis. Across all studies, four cases of hypertension required medical intervention and were successfully treated with clonidine, propranolol, or nitroglycerin. Headaches were effectively managed with OTC medications and may be recommended to participants if headaches occur within 48 h post dosing. In a couple of cases, nausea was treated with an antinauseant. There were rare instances where pharmacological intervention was required for anxiety in individuals with AUD and TRD, suggesting that such interventions may be a relevant consideration for individuals with these psychiatric comorbidities. The only reported case of substance-induced psychosis requiring pharmacological intervention resolved after administration of the short-acting amnestic benzodiazepine midazolam. No rescue medications were administered for agitation or aggression, persistent psychosis was not reported, and no antipsychotics were administered across all studies for any indication. However, psychedelic induced persistent psychosis remains a concern with psychedelic research, and individuals with history of psychosis are often excluded from trials (Griffiths et al., 2016; Ross et al., 2016; Carhart-Harris et al., 2021; Anderson et al., 2020; Carhart-Harris et al., 2016; Johnson et al., 2014; Raison et al., 2023; von Rotz et al., 2023; Bogenschutz et al., 2022; Davis et al., 2021; Schindler et al., 2021). Further, current PT protocols require antipsychotic medications to be available to manage extreme psychiatric instances (Johnson et al., 2008). The results of this review suggest antipsychotics may not be necessary and that benzodiazepines may be sufficient to address severe psychological distress.

A small number of SAEs occurred in participants with pre-existing depression, specifically suicidal ideation, intentional self-injury, and hospitalization. To minimize potential risks, we recommend assessing participants for suicidality using the C-SSRS across all participants, though individuals with pre-existing depression are of greater risk for suicidality (Posner et al., 2011). If a participant endorses active suicidal ideation, a thorough safety evaluation should be conducted be a study physician. In these instances, the clinician should consider escorting the participant to the Emergency Department, informing their primary care provider (with consent), or calling Emergency Medical Services if warranted. Implementing these safety protocols minimizes the risk associated with psilocybin across clinical populations.

4.4. Future psilocybin therapy protocol development: Balancing safety considerations and cost implications

Psilocybin has been used in cultural and spiritual contexts without the use of extensive safety protocols employed in modern psychedelic trials. Many studies follow the 2008 guidelines established by Johnson et al. (2008), emphasizing the use of supportive measures, such as two study monitors being present during sessions, and extensive preparation and integration sessions. However, these protocols incur significant costs. For instance, a Phase 3 MDMA-assisted therapy trial for PTSD estimated a cost of $11,537 per patient, raising questions about the sustainability of such an approach for broader therapeutic use (Marseille et al., 2022). As this review only reported SAEs in individuals with pre-existing depression and did not report any cases of persistent psychosis,

there is a compelling case for investigating psilocybin administration with less resource-heavy support, especially in individuals without co-occurring psychiatric disorders. Below we outline potential cost reduction strategies given PT's safety.

Group therapy is a promising approach to reduce costs and maintain existing safety protocols. Two studies in this review used group-based therapy components. Anderson et al. (2020) implemented group preparation and post-dosing integration sessions held in groups of six in their sample of older AIDS survivors. Agrawal et al. (2024) used a combination of both group (3–4 people) and individual preparation and integration sessions in participants with cancer and MDD. On the dosing day, participants were monitored by therapists in a 1:1 ratio, with oversight from two lead therapists observing from a separate room via cameras who could intervene if necessary. The of use of group therapy in Agrawal et al. (2024) was estimated to reduce costs by nearly 35% (Marseille et al., 2023). Neither of these studies reported any SAEs, suggesting that group-based protocols may be a safe, cost-effective alternative to fully individualized PT approaches.

Current guidelines require a minimum of two study therapists to be present for each dosing session (Health Canada, 2022; Guss et al., 2020). However, based on our review, and support by Agrawal et al. (2024), this level of monitoring may be disproportionate to the actual risks associated with psilocybin. Reducing the number of therapists present during dosing from two to one may be sufficient to ensure participant safety, especially for low-risk populations. Additionally, costs may be reduced by decreasing the frequency of monitoring. Monitors may check in with participants periodically rather than continuously as long as a) participants have a way to contact the therapist in case of emergencies and b) supervision is maintained during the peak dosing period (60–90 min post-psilocybin administration). Agrawal et al. (2024) also demonstrated the promise of using video monitoring by a secondary therapist, which would not only reduce staffing costs, but also enhance both participant and therapist safety and accountability. In a previous trial conducted by the Multidisciplinary Association for Psychedelic Studies (MAPS), a therapist was accused of sexual misconduct, which was investigated by use of video recording (Lindsay, 2022). While recordings alone cannot prevent harm, they can support investigations of protocol fidelity and ensure safety of both participants and clinicians by providing clear documentation of the dosing session. Last, multiple preparation and integration sessions may be unnecessary in many protocols, especially for healthy participants, presenting another opportunity to reduce costs. Future studies should carefully investigate psilocybin administration with less resource-heavy support, especially in individuals without co-occurring psychiatric disorders.

4.5. Limitations

This systematic review must be taken into consideration with its limitations. The definition of AEs, specifically psychological AEs, differ between included studies, and the lack of standardized reporting frameworks make it difficult to accurately synthesize the prevalence of psychological AEs. Additionally, we grouped all psilocybin macrodoses and did not stratify by dose, which may contribute to the differential AEs reported. We also do not report on concomitant medications that may influence the safety profile of psilocybin. Many of the included studies did not focus on AEs as an outcome and include minimal detail about AEs and their frequencies. Inconsistencies in reporting (i.e., number of instances versus number of participants affected) further complicated our ability to accurately summarize AEs across studies. Moreover, few studies explicitly categorized AEs as related or unrelated to psilocybin, making it unclear if some of the uncommon AEs were due to psilocybin or other external factors. Finally, as previously discussed, functional unblinding and expectancy effects may have influences on clinical outcomes and AE reporting by both participants and study staff (Muthukumaraswamy et al., 2021).

4.6. Conclusion & future directions

Psilocybin's pharmacological qualities make it a potentially useful intervention for the treatment of various neuropsychiatric disorders. Acute AEs related to psilocybin are common, however, they are typically mild, transient, and resolve without pharmacological treatment. SAEs are rare and occurred in participants with pre-existing depression, including suicidal ideation and behaviour, and hospitalization for severe depression.

We call for future psilocybin safety research to address several key factors:

1) The use of a validated, psychedelic-specific AE scale to improve the accuracy and consistency of AE reporting.
2) Careful assessment, and statistical accounting of, where possible, the impact of unblinding and expectancy effects, as these may influence psilocybin outcomes and AEs by both participants and study staff.
3) Evaluate condition-specific AEs. This will become more feasible as the number of psilocybin studies specific to different conditions increases.
4) Investigate the need for robust safety protocols to balance participant safety with cost-effectiveness and accessibility. The development of scalable treatment models that minimize the need for intensive psychological support could make PT more accessible to a wider population, particularly among low-risk groups.
5) Cautious investigation of psilocybin as a novel treatment option for other treatment resistance disorders, as AEs associated with PT are generally mild and transient. No studies have reported psilocybin associated persistent psychosis or negative cognitive effects. Further, no studies reported antipsychotic administration for agitation, aggression, or psychosis, supporting cautious investigation of psilocybin in more vulnerable populations.

Overall, available evidence suggests that psilocybin is safe in controlled settings, with a low incidence of SAEs or long-term psychiatric complications.

Funding sources

This work was supported in part by funding from the Alzheimer Society Research Program (0000000081), the Canadian Institute of Health Research (PJT-159807), and the Academic Health Science Centre Alternative Funding Plan Innovation Fund

CRediT authorship contribution statement

Danielle Bukovsky: Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Aron Amaev:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Jianmeng Song:** Writing – review & editing, Conceptualization. **Shannen Kyte:** Writing – review & editing, Conceptualization. **Edgardo Carmona-Torres:** Writing – review & editing, Conceptualization. **Fumihiko Ueno:** Writing – review & editing, Conceptualization. **Vincenzo Deluca:** Writing – review & editing, Conceptualization. **Antonio P. Strafella:** Writing – review & editing, Supervision, Conceptualization. **Muhammad Ishrat Husain:** Writing – review & editing, Supervision, Conceptualization. **Ariel Graff-Guerrero:** Writing – review & editing, Supervision, Conceptualization. **Philip Gerretsen:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Muhammad Ishrat Husain leads contracted research for COMPASS Pathways Limited.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2025.111541.

References

Aaronson, S.T., van der Vaart, A., Miller, T., et al., 2024. Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a nonrandomized open-label trial. JAMA Psychiatry 81, 555–562. https://doi.org/10.1001/jamapsychiatry.2023.4685.

Aday, J.S., Heifets, B.D., Pratscher, S.D., et al., 2022. Great expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. Psychopharmacology (Berl) 239, 1989–2010. https://doi.org/10.1007/s00213-022-06123-7.

Agin-Liebes, G., Nielson, E.M., Zingman, M., Kim, K., Haas, A., Owens, L.T., Rogers, U., Bogenschutz, M., 2024. Reports of self-compassion and affect regulation in psilocybin-assisted therapy for alcohol use disorder: An interpretive phenomenological analysis. Psychol. addict. behav.: J. Soc. Psychol. Addict. Behav. 38 (1), 101–113. https://doi.org/10.1037/adb0000935.

Agrawal, M., Richards, W., Beaussant, Y., et al., 2024. Psilocybin-assisted group therapy in patients with cancer diagnosed with a major depressive disorder. Cancer 130, 1137–1146. https://doi.org/10.1002/cncr.35010.

Turton, S., Nutt, D.J., Carhart-Harris, R.L., 2014. A qualitative report on the subjective experience of intravenous psilocybin administered in an FMRI environment. Curr. Drug Abuse Rev. 7 (2), 117–127. https://doi.org/10.2174/1874473708666150107120930.

U.S. Food and Drug Administration (FDA), 2024. FDA issues first draft guidance on clinical trials with psychedelic drugs. https://www.fda.gov/news-events/press-announcements/fda-issues-first-draft-guidance-clinical-trials-psychedelic-drugs (accessed January 24, 2025).

van Amsterdam, J., van den Brink, W., 2022. The therapeutic potential of psilocybin: a systematic review. Expert Opin. Drug Saf. 21, 833–840. https://doi.org/10.1080/14740338.2022.2047929.

Anderson, B.T., Danforth, A., Daroff, P.R., et al., 2020. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: an open-label safety and feasibility pilot study. EClinicalMedicine 27. https://doi.org/10.1016/j.eclinm.2020.100538.

Barrett, F.S., Bradstreet, M.P., Leoutsakos, J.-M.S., et al., 2016. The challenging experience questionnaire: characterization of challenging experiences with psilocybin mushrooms. J. Psychopharmacol. 30, 1279–1295. https://doi.org/10.1177/0269881116678781.

Becker, A.M., Holze, F., Grandinetti, T., et al., 2022. Acute effects of psilocybin after escitalopram or placebo Pretreatment in a randomized, double-blind, placebo-controlled, crossover study in healthy subjects. Clin. Pharmacol. Ther. 111, 886–895. https://doi.org/10.1002/cpt.2487.

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., et al., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J. Psychopharmacol. 29, 289–299. https://doi.org/10.1177/0269881114565144.

Bogenschutz, M.P., Ross, S., Bhatt, S., et al., 2022. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry 79, 953–962. https://doi.org/10.1001/jamapsychiatry.2022.2096.

Bravermanova, A., Viktorinova, M., Tyls, F., et al., 2018. Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing-study on P300 and mismatch negativity in healthy volunteers. Psychopharmacology (Berl) 235, 491–503. https://doi.org/10.1007/s00213-017-4807-2.

Psychedelic Alpha, BREAKING: FDA Publishes Lykos Therapeutics' MDMA Complete Response Letter (CRL), 2025 (accessed September 10, 2025). https://psychedelicalpha.com/news/breaking-fda-publishes-lykos-therapeutics-mdma-complete-response-letter-crl.

Breeksema, J.J., Kuin, B.W., Kamphuis, J., et al., 2022. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: a mixed-methods systematic review. J. Psychopharmacol. 36, 1100–1117. https://doi.org/10.1177/02698811221116926.

Brown, R.T., Nicholas, C.R., Cozzi, N.V., et al., 2017. Pharmacokinetics of escalating doses of Oral psilocybin in healthy adults. Clin. Pharmacokinet. 56, 1543–1554. https://doi.org/10.1007/s40262-017-0540-6.

Calder, A.E., Hasler, G., 2024. Validation of the Swiss psychedelic side effects inventory: standardized assessment of adverse effects in studies of psychedelics and MDMA. J. Affect. Disord. 365, 258–264. https://doi.org/10.1016/j.jad.2024.08.091.

Carbonaro, T.M., Bradstreet, M.P., Barrett, F.S., et al., 2016. Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. J. Psychopharmacol. 30, 1268–1278. https://doi.org/10.1177/0269881116662634.

Carbonaro, T.M., Johnson, M.W., Hurwitz, E., et al., 2018. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. Psychopharmacology 235, 521–534. https://doi.org/10.1007/s00213-017-4769-4.

Carhart-Harris, R., Giribaldi, B., Watts, R., et al., 2021. Trial of psilocybin versus escitalopram for depression. N. Engl. J. Med. 384, 1402–1411. https://doi.org/10.1056/NEJMoa2032994.

Carhart-Harris, R.L., Williams, T.M., Sessa, B., et al., 2011. The administration of psilocybin to healthy, hallucinogen-experienced volunteers in a mock-functional magnetic resonance imaging environment: a preliminary investigation of tolerability. J. Psychopharmacol. 25, 1562–1567. https://doi.org/10.1177/0269881110367445.

Carhart-Harris, R.L., Bolstridge, M., Rucker, J., et al., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3, 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7.

Center for Psychedelic & Consciousness Research, 2020. Center for Psychedelic & Consciousness Research. https://hopkinspsychedelic.org (accessed June 10, 2025).

ClinicalTrials.gov. National Library of Medicine (US). A Phase 3 Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Psilocybin in Adults with Major Depressive Disorder (MDD). https://clinicaltrials.gov/study/NCT06308653.

ClinicalTrials.gov. National Library of Medicine (US). A Phase III, Multicentre, Randomised, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, and Tolerability of COMP360 in Participants With Treatment-resistant Depression. https://www.clinicaltrials.gov/study/NCT05624268.

Dahmane, E., Hutson, P.R., Gobburu, J.V.S., 2021. Exposure-response analysis to assess the concentration-QTc relationship of psilocybin/psilocin. Clin. Pharmacol. Drug Dev. 10, 78–85. https://doi.org/10.1002/cpdd.796.

Davis, A.K., Barrett, F.S., May, D.G., et al., 2021. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 78, 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285.

Diagnostic and Statistical Manual of Mental Disorders, 2025. Psychiatry Online. DSM Library. https://doi.org/10.1176/appi.books.9780890425596 (accessed April 1, 2025).

Earleywine, M., De Leo, J., Bhayana, D., et al., 2024. Psilocybin without psychotherapy: a cart without a horse? AJP 181, 78–79. https://doi.org/10.1176/appi.ajp.20230572.

Espiard, M.-L., Lecardeur, L., Abadie, P., et al., 2005. Hallucinogen persisting perception disorder after psilocybin consumption: a case study. Eur. Psychiatry 20, 458–460. https://doi.org/10.1016/j.eurpsy.2005.04.008.

Flameling, L.J., Aday, J.S., van Elk, M., 2023. Expectancy effects cannot be neglected in MDMA-assisted therapy research. ACS Chem. Nerosci. 14, 4062–4063. https://doi.org/10.1021/acschemneuro.3c00692.

Freitas, R.R., Gotsis, E.S., Gallo, A.T., et al., 2025. The safety of psilocybin-assisted psychotherapy: a systematic review. Aust. N. Z. J. Psychiatry 59, 128–151. https://doi.org/10.1177/00048674241289024.

Goel, D.B., Zilate, S., 2025. Potential therapeutic effects of psilocybin: a systematic review. Cureus 14, e30214. https://doi.org/10.7759/cureus.30214.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., et al., 2022. Single-dose psilocybin for a treatment-resistant episode of major depression. N. Engl. J. Med. 387, 1637–1648. https://doi.org/10.1056/NEJMoa2206443.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., et al., 2023. Single-dose psilocybin for a treatment-resistant episode of major depression: impact on patient-reported depression severity, anxiety, function, and quality of life. J. Affect. Disord. 327, 120–127. https://doi.org/10.1016/j.jad.2023.01.108.

Griffiths, R.R., Richards, W.A., McCann, U., et al., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 187, 268–283 discussion 284–92.

Griffiths, R.R., Richards, W.A., Johnson, M.W., et al., 2008. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J. Psychopharmacol. 22, 621–632. https://doi.org/10.1177/0269881108094300.

Griffiths, R.R., Johnson, M.W., Richards, W.A., et al., 2011. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl) 218, 649–665. https://doi.org/10.1007/s00213-011-2358-5.

Griffiths, R.R., Johnson, M.W., Carducci, M.A., et al., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J. Psychopharmacol. 30, 1181–1197. https://doi.org/10.1177/0269881116675513.

Griffiths, R.R., Johnson, M.W., Richards, W.A., et al., 2018. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J. Psychopharmacol. 32, 49–69. https://doi.org/10.1177/0269881117731279.

Grob, C.S., Danforth, A.L., Chopra, G.S., et al., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch. Gen. Psychiatry 68, 71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116.

Guss, J., Krause, R., Sloshower, J., 2020. The Yale Manual for Psilocybin-Assisted Therapy of Depression (using Acceptance and Commitment Therapy as a Therapeutic Frame). https://doi.org/10.31234/osf.io/u6v9y.

Halpern, J.H., Pope, H.G., 2003. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend. 69, 109–119. https://doi.org/10.1016/s0376-8716(02)00306-x.

Hasler, F., Bourquin, D., Brenneisen, R., et al., 2002. Renal excretion profiles of psilocin following oral administration of psilocybin: a controlled study in man. J. Pharm. Biomed. Anal. 30, 331–339. https://doi.org/10.1016/s0731-7085(02)00278-9.

Hasler, F., Grimberg, U., Benz, M.A., et al., 2004. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. Psychopharmacology 172, 145–156. https://doi.org/10.1007/s00213-003-1640-6.

Health Canada. Notice to stakeholders: Health Canada''s expectations regarding risk-management measures for clinical trials involving psychedelic-assisted. psychotherapy.https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/expectations-risk-management-measures-clinical-trials-psychedelic-assisted-psychotherapy.html.

Heinzerling, K.G., Sergi, K., Linton, M., et al., 2023. Nature-themed video intervention may improve cardiovascular safety of psilocybin-assisted therapy for alcohol use disorder. Front. Psych. 14, 1215972. https://doi.org/10.3389/fpsyt.2023.1215972.

Hinkle, J.T., Graziosi, M., Nayak, S.M., et al., 2024. Adverse events in studies of classic psychedelics: a systematic review and Meta-analysis. JAMA Psychiatry 81, 1225–1235. https://doi.org/10.1001/jamapsychiatry.2024.2546.

Holze, F., Ley, L., Muller, F., et al., 2022. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology 47, 1180–1187. https://doi.org/10.1038/s41386-022-01297-2.

Husain, M.I., Blumberger, D.M., Castle, D.J., et al., 2023. Psilocybin for treatment-resistant depression without psychedelic effects: study protocol for a 4-week, double-blind, proof-of-concept randomised controlled trial. BJPsych Open 9, e134. https://doi.org/10.1192/bjo.2023.535.

Irizarry, R., Winczura, A., Dimassi, O., et al., 2025. Psilocybin as a treatment for psychiatric illness: a Meta-analysis. Cureus 14, e31796. https://doi.org/10.7759/cureus.31796.

Johnson, M.W., Richards, W.A., Griffiths, R.R., 2008. Human hallucinogen research: guidelines for safety. J. Psychopharmacol. 22, 603–620. https://doi.org/10.1177/0269881108093587.

Johnson, M.W., Garcia-Romeu, A., Cosimano, M.P., et al., 2014. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J. Psychopharmacol. 28, 983–992. https://doi.org/10.1177/0269881114548296.

Lewis, B.R., Garland, E.L., Byrne, K., et al., 2023. HOPE: a pilot study of psilocybin enhanced group psychotherapy in patients with Cancer. J. Pain Symptom Manage. 66, 258–269. https://doi.org/10.1016/j.jpainsymman.2023.06.006.

Ley, L., Holze, F., Arikci, D., et al., 2023. Comparative acute effects of mescaline, lysergic acid diethylamide, and psilocybin in a randomized, double-blind, placebo-controlled cross-over study in healthy participants. Neuropsychopharmacology 48, 1659–1667. https://doi.org/10.1038/s41386-023-01607-2.

Lindsay, B., 2022. Footage of therapists spooning and pinning down patient in B.C. trial for MDMA therapy prompts review. CBC News. https://www.cbc.ca/news/canada/british-columbia/bc-mdma-therapy-videos-1.6400256.

Lingjaerde, O., Ahlfors, U.G., Bech, P., et al., 1987. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr. Scand. Suppl. 334, 1–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x.

Ly, C., Greb, A.C., Cameron, L.P., et al., 2018. Psychedelics promote structural and functional neural plasticity. Cell Rep. 23, 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022.

Madsen, M.K., Petersen, A.S., Stenbaek, D.S., et al., 2024. CCH attack frequency reduction after psilocybin correlates with hypothalamic functional connectivity. Headache 64, 55–67. https://doi.org/10.1111/head.14656.

Marseille, E., Mitchell, J.M., Kahn, J.G., 2022. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: findings from a phase 3 trial. PloS One 17, e0263252. https://doi.org/10.1371/journal.pone.0263252.

Marseille, E., Stauffer, C.S., Agrawal, M., et al., 2023. Group psychedelic therapy: empirical estimates of cost-savings and improved access. Front. Psych. 14, 1293243. https://doi.org/10.3389/fpsyt.2023.1293243.

McGuinness, L.A., Higgins, J.P.T., 2021. Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. Res. Synth. Methods 12, 55–61. https://doi.org/10.1002/jrsm.1411.

van der Meer, P.B., Fuentes, J.J., Kaptein, A.A., et al., 2023. Therapeutic effect of psilocybin in addiction: a systematic review. Front. Psych. 14, 1134454. https://doi.org/10.3389/fpsyt.2023.1134454.

Moreno, F.A., Wiegand, C.B., Taitano, E.K., et al., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J. Clin. Psychiatry 67, 18864.

Muthukumaraswamy, S.D., Forsyth, A., Lumley, T., 2021. Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert. Rev. Clin. Pharmacol. 14, 1133–1152. https://doi.org/10.1080/17512433.2021.1933434.

Nutt, D., 2019. Psychedelic drugs—a new era in psychiatry? Dialogues Clin. Neurosci. 21, 139–147. https://doi.org/10.31887/DCNS.2019.21.2/dnutt.

Nutt, D., Erritzoe, D., Carhart-Harris, R., 2020. Psychedelic psychiatry's brave New World. Cell 181, 24–28. https://doi.org/10.1016/j.cell.2020.03.020.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.

Peck, S.K., Shao, S., Gruen, T., et al., 2023. Psilocybin therapy for females with anorexia nervosa: a phase 1, open-label feasibility study. Nat. Med. 29, 1947–1953. https://doi.org/10.1038/s41591-023-02455-9.

Peredy, T., Bradford, H., 2014. Mushroom, psilocybin. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, Third edition. Academic Press, Oxford, pp. 418–419. https://doi.org/10.1016/B978-0-12-386454-3.00759-4.

Perez, N., Langlest, F., Mallet, L., et al., 2023. Psilocybin-assisted therapy for depression: a systematic review and dose-response meta-analysis of human studies. Eur. Neuropsychopharmacol. 76, 61–76. https://doi.org/10.1016/j.euroneuro.2023.07.011.

Posner, K., Brown, G.K., Stanley, B., et al., 2011. The Columbia-suicide severity rating scale: initial validity and inter nal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168, 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704.

Raison, C.L., Sanacora, G., Woolley, J., et al., 2023. Single-dose psilocybin treatment for major depressive disorder: a randomized clinical trial. JAMA 330, 843–853. https://doi.org/10.1001/jama.2023.14530.

Romeo, B., Kervadec, E., Fauvel, B., et al., 2024. Safety and risk assessment of psychedelic psychotherapy: a meta-analysis and systematic review. Psychiatry Res. 335, 115880. https://doi.org/10.1016/j.psychres.2024.115880.

Roseman, L., Nutt, D.J., Carhart-Harris, R.L., 2017. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front. Pharmacol. 8, 974. https://doi.org/10.3389/fphar.2017.00974.

Rosenblat, J.D., Meshkat, S., Doyle, Z., et al., 2024. Psilocybin-assisted psychotherapy for treatment resistant depression: a randomized clinical trial evaluating repeated doses of psilocybin. Medicine, S2666634024000357. https://doi.org/10.1016/j.medj.2024.01.005.

Ross, S., Bossis, A., Guss, J., et al., 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J. Psychopharmacol. 30, 1165–1180. https://doi.org/10.1177/0269881116675512.

Rossi, G.N., Hallak, J.E.C., Bouso Saiz, J.C., et al., 2022. Safety issues of psilocybin and LSD as potential rapid acting antidepressants and potential challenges. Expert Opin. Drug Saf. 21, 761–776. https://doi.org/10.1080/14740338.2022.2066650.

von Rotz, R., Schindowski, E.M., Jungwirth, J., et al., 2023. Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine 56, 101809. https://doi.org/10.1016/j.eclinm.2022.101809.

Rucker, J.J., Marwood, L., Ajantaival, R.-L.J., et al., 2022. The effects of psilocybin on cognitive and emotional functions in healthy participants: results from a phase 1, randomised, placebo-controlled trial involving simultaneous psilocybin administration and preparation. J. Psychopharmacol. 36, 114–125. https://doi.org/10.1177/02698811211064720.

Salvetti, G., Saccenti, D., Moro, A.S., et al., 2024. Comparison between single-dose and two-dose psilocybin Administration in the Treatment of major depression: a systematic review and Meta-analysis of current clinical trials. Brain Sci. 14, 829. https://doi.org/10.3390/brainsci14080829.

Schindler, E.A.D., Sewell, R.A., Gottschalk, C.H., et al., 2021. Exploratory controlled study of the migraine-suppressing effects of psilocybin. Neurotherapeutics 18, 534–543. https://doi.org/10.1007/s13311-020-00962-y.

Schindler, E.A.D., Sewell, R.A., Gottschalk, C.H., et al., 2022. Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: results from a randomized, double-blind, placebo-controlled trial. Headache 62, 1383–1394. https://doi.org/10.1111/head.14420.

Schneier, F.R., Feusner, J., Wheaton, M.G., et al., 2023. Pilot study of single-dose psilocybin for serotonin reuptake inhibitor-resistant body dysmorphic disorder. J. Psychiatr. Res. 161, 364–370. https://doi.org/10.1016/j.jpsychires.2023.03.031.

Shapiro, H., Shodimu, V., Webb, N., 2024. SA109 quality assessment tools for single-arm studies: a rapid review. Value Health 27, S635–S636. https://doi.org/10.1016/j.jval.2024.10.3190.

Shnayder, S., Ameli, R., Sinaii, N., et al., 2023. Psilocybin-assisted therapy improves psycho-social-spiritual well-being in cancer patients. J. Affect. Disord. 323, 592–597. https://doi.org/10.1016/j.jad.2022.11.046.

Sloshower, J., Skosnik, P.D., Safi-Aghdam, H., et al., 2023. Psilocybin-assisted therapy for major depressive disorder: an exploratory placebo-controlled, fixed-order trial. J. Psychopharmacol. 37, 698–706. https://doi.org/10.1177/02698811231154852.

Smigielski, L., Kometer, M., Scheidegger, M., et al., 2019. Characterization and prediction of acute and sustained response to psychedelic psilocybin in a mindfulness group retreat. Sci. Rep. 9, 14914. https://doi.org/10.1038/s41598-019-50612-3.

Smith, F.L., Neill, J.C., Wainwright, V., 2022. An interpretative phenomenological analysis of the use of psilocybin by veterans with symptoms of trauma. Drug Sci. Policy Law 8. https://doi.org/10.1177/20503245221124117.

Sterne, J.A., Hernán, M.A., Reeves, B.C., et al., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919. https://doi.org/10.1136/bmj.i4919.

Sterne, J.A.C., Savović, J., Page, M.J., et al., 2019. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898. https://doi.org/10.1136/bmj.l4898.
Szigeti, B., Heifets, B.D., 2024. Expectancy effects in psychedelic trials. Biol. Psychiatry: Cognitive Neurosci. Neuroimag. 9, 512–521. https://doi.org/10.1016/j.bpsc.2024.02.004.
Wolfgang, A.S., Hoge, C.W., 2023. Psychedelic-assisted therapy in military and veterans healthcare systems: clinical, legal, and implementation considerations. Curr. Psychiatry Rep. 25, 513–532. https://doi.org/10.1007/s11920-023-01446-4.
Wsół, A., 2023. Cardiovascular safety of psychedelic medicine: current status and future directions. Pharmacol. Rep. 75, 1362. https://doi.org/10.1007/s43440-023-00539-4.
Yao, Y., Guo, D., Lu, T.-S., et al., 2024. Efficacy and safety of psychedelics for the treatment of mental disorders: a systematic review and meta-analysis. Psychiatry Res. 335, 115886. https://doi.org/10.1016/j.psychres.2024.115886.
Yerubandi, A., Thomas, J.E., Bhuiya, N.M.M.A., et al., 2024. Acute adverse effects of therapeutic doses of psilocybin: a systematic review and Meta-analysis. JAMA Netw. Open 7, e245960. https://doi.org/10.1001/jamanetworkopen.2024.5960.
Younger, J., Gandhi, V., Hubbard, E., et al., 2012. Development of the Stanford expectations of treatment scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. Clin. Trials 9, 767–776. https://doi.org/10.1177/1740774512465064.