European Neuropsychopharmacology 101 (2025) 41–55

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Efficacy, all-cause discontinuation, and safety of serotonergic psychedelics and MDMA to treat mental disorders: A living systematic review with meta-analysis

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https://doi.org/10.1016/j.euroneuro.2025.09.011
Received 17 April 2025; Received in revised form 22 September 2025; Accepted 24 September 2025
Available online 7 November 2025

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ARTICLE INFO

Keywords:
Psychedelics
Psilocybin
Lysergic acid diethylamide
Ayahuasca
N-methyl-3,4-methylenedioxyamphetamine
Meta-analysis

ABSTRACT

Serotonergic psychedelics and 3,4-methylendioxtmethamphetamine (MDMA) are promising treatments for mental disorders with a continuously evolving evidence base. We searched Pubmed/Scopus/clinical trial registries up to 08july2025 for double-blind randomized controlled trials (RCTs) testing MDMA or serotonergic psychedelics in patients with mental disorders. Primary outcomes were change in disease-specific symptoms and all-cause discontinuation. Standardized mean differences (SMD) and relative risk (RR) were estimated using random-effects meta-analysis. Risk of bias (RoB) was assessed with Cochrane's RoB-tool version 2 and certainty of evidence with GRADE. The review is maintained as living systematic review (https://ebipsyche-database.org/). We included 30 RCTs (1480 participants; female=45.8 %; with psychological support=83.3 %; high RoB=83.3 %). In post-traumatic stress disorder (PTSD), MDMA reduced PTSD symptoms compared to any control (k = 11; SMD=-0.85 [-1.09; -0.60]; I^2=0 %; GRADE=low). In major depressive disorder (MDD), psilocybin/ayahuasca/LSD reduced depressive symptoms (k = 8; SMD=-0.62 [-0.97; -0.28]; I^2=55 %; GRADE=very low). In anxiety disorders, both MDMA and serotonergic psychedelics reduced anxiety symptoms (SMD_{MDMA}=-1.18 [-2.04; -0.32]; I^2=0 %; k = 2; GRADE=low and $SMD_{serotonergic}$=-0.88 [-1.70; -0.06]; I^2=54 %;k = 5; GRADE=very low). In alcohol use disorder, neither psilocybin nor LSD reduced abstinence rates (k = 6; RR=1.42 [0.89; 2.26]; I^2=7 %; GRADE=very low). In attention-deficit hyperactivity disorder (ADHD), LSD did not reduce ADHD symptoms (k = 1; SMD=0.22 [-0.32; 0.76]; GRADE=very low). Moderate certainty in evidence was only found for MDMA on PTSD symptoms when compared to placebo. MDMA/serotonergic psychedelics were not associated with higher risk of all-cause discontinuation (RR_{MDMA}=0.74 [0.32; 1.72]; $RR_{serotonergic}$=0.81 [0.56; 1.15]). Overall, MDMA/serotonergic psychedelics are promising for the treatment of PTSD, MDD, and anxiety disorders with moderate to large effect sizes. Pragmatic trials, long-term, head-to-head trials exploring the role of psychological support, aiming to identify predictors of response, and accounting for expectancy and functional unblinding are needed. Studies addressing these limitations will likely be required for regulatory approval of psychedelic drugs.

1. Introduction

Suboptimal treatment response in major depressive disorder (MDD), anxiety disorders, and post-traumatic stress disorder (PTSD) is common, varying from 20 % to 60 % in clinical practice (Bystritsky, 2006; Howes et al., 2022). Moreover, only 35–54 % of individuals with substance use disorder (SUD) achieve remission with current treatment options (Fleury et al., 2016). The progress over the last few decades in the development of novel psychopharmacological agents and psychotherapeutic interventions to treat mental disorders has been slow, with limited impact on improving outcomes for people with mental and substance use disorders (Correll et al., 2023; Schenberg, 2018). There has been a resurgence of interest in repurposing serotonergic psychedelics agents, such as Lysergic Acid Diethylamide (LSD), 4-phosphoryloxy-N,N-dimethyltryptamine (psilocybin), and N, N-dimethyltryptamine (DMT/ayahuasca), as well as 3, 4-methylenedioxymethamphetamine (MDMA), as novel and alternative therapeutic options for treatment resistant mental disorders (Andersen et al., 2021; Carhart-Harris and Goodwin, 2017; National Institute on Drug Abuse, 2023). Serotonergic psychedelics and MDMA are not currently approved for routine clinical use, largely due to regulatory and safety considerations. According to the National Institute on Drug Abuse (2023), these substances are classified as Schedule I drugs under the Controlled Substances Act, indicating that they are considered to have a high potential for abuse and no accepted medical use. Furthermore, potential short-term side-effects (e.g., increased blood pressure and heart rate, seizures, amnesia, panic attacks, illusions, and psychosis-like symptoms) and long-term side-effects (e.g., persistent psychosis, addiction, memory loss, depression and suicidal thoughts) call for firm evidence regarding their safety and efficacy (Schlag et al., 2022).

An increasing number of studies have demonstrated promising moderate to large beneficial effects of psychedelics in the existential anxiety of terminally ill patients (Ross, 2018), treatment-resistant PTSD (Smith et al., 2022), social anxiety disorder in individuals with autism spectrum disorder (ASD) (Danforth et al., 2018), obsessive-compulsive

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disorder (Moreno et al., 2006), and MDD (Carhart-Harris et al., 2021; Davis et al., 2021). Furthermore, in individuals with alcohol use disorder (AUD), researchers have reported that patients administered LSD or psilocybin showed significant reduction in the number of drinks, general health scores, and total abstinence compared to controls (Bogenschutz et al., 2022, 2015; Denson and Sydiaha, 1970; Pahnke et al., 1970; Savage and McCabe, 1973; Tomsovic and Edwards, 1970), despite some negative results (Bowen et al., 1970; Johnson, 1969; Ludwig et al., 1969). Thus far, meta-analyses have been conducted to investigate the effect of psychedelics on suicidality (Zeifman et al., 2022), depressive symptoms (Galvão-Coelho et al., 2021; Haikazian et al., 2023; Metaxa and Clarke, 2024; Romeo et al., 2020), PTSD (Illingworth et al., 2021; Smith et al., 2022), and the effect of LSD on mental disorders (Fuentes et al., 2020; Krebs and Johansen, 2012). To comprehend the therapeutic efficacy of psychedelics from a broader perspective, Luoma et al. (2020) calculated the pooled effect size (ES) of psychedelic-assisted psychotherapy (PAP) for different mental disorders, and found a significant mean ES (Hedges' g) of 1.21 with PAP compared to control groups at the primary endpoint. However, there are important limitations to their meta-analysis: they investigated the pooled effect of psychedelics and not of each agent separately, did not focus on both disease-specific and non-disease specific symptoms, and included only nine randomized controlled trials (RCTs) (Luoma et al., 2020). Other previous meta-analyses in this area have focused on individual psychedelic agents, individual psychiatric disorders, or included both single-blinded and unblinded studies. Specifically, these previous meta-analyses have focused on psilocybin for anxiety and depressive disorders (Goldberg et al., 2020; Vargas et al., 2020), psilocybin for depression (Haikazian et al., 2023; Li et al., 2022; Metaxa and Clarke, 2024; Perez et al., 2023; Yu et al., 2022), psilocybin for addiction (van der Meer et al., 2023), psilocybin for anxiety in life-threatening disorders (Yu et al., 2021), psilocybin for mental disorders (Bahji et al., 2023; Irizarry et al., 2022), psychedelics for anxiety and depression (Leger and Unterwald, 2022; Sicignano et al., 2023), psilocybin and MDMA for mental disorders (Kisely et al., 2023), psychedelics for mood disorders (Galvão-Coelho et al., 2021; Haikazian et al., 2023; Metaxa and Clarke, 2024; Romeo et al., 2020), psychedelics for suicide (Zeifman et al., 2022), MDMA for PTSD (Bahji et al., 2020; Hoskins et al., 2021; Illingworth et al., 2021; Tedesco et al., 2021), LSD and other psychedelics for AUD (Krebs and Johansen, 2012; Sicignano et al., 2024); and included both single-blinded and unblinded studies (Dos Santos et al., 2018; Maia et al., 2022), or did not investigate disease-specific or non-disease specific symptoms (Luoma et al., 2020).

The proliferation of meta-analyses suggests the need of a comprehensive evidence synthesis project on the clinical effects of serotonergic psychedelics and MDMA for mental disorders. According to international guidance, a living-systematic review is needed when 1) the recommendations are a high priority for clinical and policy decision-making; 2) new evidence is likely to change (in this case, create the base for) recommendations; and 3) new evidence is expected to emerge (Iannizzi et al., 2023). All these criteria are met for serotonergic psychedelics and MDMA. Therefore, we conducted a living-systematic review and meta-analysis of double-blind RCTs to evaluate efficacy, all-cause discontinuation and safety (i.e., severe adverse events (SAEs), treatment-emergent adverse events (TEAEs), and the total number of adverse events (AEs)) of serotonergic psychedelics and MDMA in the treatment of any mental disorder.

Our aims were to: i) evaluate the clinical effect of serotonergic psychedelics and MDMA on disease-specific symptoms (e.g., depressive symptoms in depressive disorder) and non-disease specific symptoms (e.g., anxiety symptoms in depressive disorder), and ii) assess all-cause discontinuation and safety of serotonergic psychedelics and MDMA in the treatment of people with mental disorders.

2. Experimental procedures

This living systematic review (LSR) with meta-analysis is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 (checklists as sTable 1+2) (Page et al., 2021). The protocol is publicly available at https://osf.io/ahrt8/ (See also Appendix 1).

2.1. Living systematic review

The need for a LSR has been verified adhering to available guidance including that from the Australian Living Evidence Collaboration (2022). Briefly, the LSR will be maintained by revising the search strategy (e.g., to include new molecules) and searching relevant databases every three months. These searches will be conducted by the first and last authors and a rotating subgroup of co-authors will then screen and summarize any newly identified studies. Updates to the review will be published when sufficient evidence emerges to warrant new conclusions, ensuring that each update provides meaningful contribution. The LSR will be transitioned out of the living mode (entirely or for selected agents, conditions, or outcome combinations) when certainty in evidence reaches moderate to high or when new evidence ceases to appear. Further methodological details are available in the protocol.

2.2. Literature search strategy

We searched Medline, Scopus, and the Cochrane Central Trial register from inception to July 8th, 2025 using following search terms: [(random* or trial or RCT) AND (psychedel* OR psilocyb* OR psilocyn OR cybin OR MDMA OR ecstasy OR mescaline OR allylescaline OR escaline OR methallylescaline OR proscaline OR 2C-series OR 2C-B or 2C-C OR 2C-D OR 2C-E OR 2C-H OR 2C-I OR 2C-P 2C-TFM OR 2C-T* OR tryptamine* OR lyserg* OR LSD OR ayahuasca OR salvia divinorum OR *NBOMe* OR *NBOH* OR 5-MeO* OR ibogaine OR peyote OR tryptamine* OR entheogen*)] (Detailed search strategy in Appendix 2). We also manually searched reference lists of identified studies and of previous reviews and meta-analyses on psychedelics.

2.3. Eligibility criteria

We included published and unpublished studies that (1) were double-blind RCTs; (2) administered any serotonergic psychedelics or MDMA, either alone or in combination with psychological support; (3) involved participants of any age with any mental disorder among those listed in any version of the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM); (4) diagnosed according to a questionnaire with a severity threshold, clinical diagnosis, DSM or ICD criteria; (5) had a comparison intervention including pharmacotherapy, placebo, active placebo (low dose psychedelics), or psychotherapy. Trials that were not randomized, non-double blind, or without a control group were excluded. Review papers, opinion pieces or comments, letters or editorials, case reports or case series, conference abstracts, posters, and book chapters were also excluded.

2.4. Data extraction and risk of bias assessment

Minimum two authors (HYK, BK, SW, NF, and JZ) independently screened the titles and abstracts according to inclusion and exclusion criteria. Full reports of all records that seemed relevant to any of the reviewers were obtained. Thereafter, the full texts of selected reports were independently assessed by minimum two authors (MH, HYK, BK, SW, NF, JZ). Disagreements were resolved through consensus with a third author (MSo). We extracted the trial identifier, first author, publication year, study design, sample size, patient age and sex, diagnosis, intervention (including dose and control group), follow-up duration (weeks), scales for efficacy domain, primary and secondary efficacy

outcome scale baseline/endpoint/change values in both groups, the number of completers in both groups, and SAEs, TEAEs, and AEs. Outcomes were extracted at the primary RCT endpoint as defined by the authors.

Methodological quality of RCTs was evaluated using the Cochrane risk-of-bias tool for randomized trials, version 2 (Sterne et al., 2019). The risk of bias (RoB) judgment was rated as high risk of bias, some concern, or low risk of bias. HYK, BK, and MH assessed the methodological quality of RCTs. Discrepancies were discussed until a consensus was reached.

2.5. Certainty of evidence

We classified evidence from the meta-analysis of the included studies as high, moderate, low, or very low based on the GRADE approach (Guyatt et al., 2008). The level of evidence was determined by (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. The specific criteria used for down- and upgrading in this review was based on previous applications to grading of RCTs (Solmi et al., 2023) and are described in sMethods.

2.6. Statistical analysis

We conducted meta-analyses within specific mental disorders, for serotonergic psychedelics and MDMA, as well as for individual agents.

For continuous outcomes (e.g., studies reporting change in symptom scores such as depressive symptoms), we calculated standardized mean differences (SMDs) with 95 % confidence intervals (CIs) in change from baseline to primary endpoint using random-effects models. When studies did not report results for change from baseline to end of treatment/follow-up, we calculated mean change by subtracting end of treatment/follow-up scores from baseline values. The metaConvert functions were used for conversion from other effect size measures to SMDs (Gosling et al., 2025). ES were categorized according to Cohen as small=0.2, moderate=0.5, and large=0.8 (Cohen, 1988).

For dichotomous outcomes (e.g., abstinence, drop-out, or adverse events), we calculated relative risk (RR) with 95 %CIs.

We synthesized data in a random-effects meta-analysis for each outcome separately using the inverse variance approach, since we expected studies to be methodologically and clinically heterogeneous. In both cases, the between-study heterogeneity was estimated using the restricted maximum likelihood estimator (Veroniki et al., 2016). We also calculated the percentage of variability that can be due to heterogeneity rather than chance using the I^2 statistic (Higgins et al., 2003). To be conservative, we calculated CIs for the overall estimate using the Hartung-Knapp-Sidik-Jonkman method (Cochrane Statistical Methods Group, 2022) when the number of trials were less than 10 and the estimated heterogeneity was positive; otherwise CIs were calculated using the traditional Wald type CIs (Jackson et al., 2017). We supplemented 95 % CIs with the calculation of prediction intervals (PIs) for the overall effect when at least three studies were available to capture the interval within which a true intervention effect of a future study is expected to lie (Riley et al., 2011).

The association between treatment effect and potential effect modifiers (i.e., mean age, male sex proportion, sample size, publication year, study and psychotherapy duration) was explored using mixed-effects meta-regression models for outcomes with ≥10 studies.

We conducted several subgroup analyses to explore the impact of potential effect modifiers, i.e., by: (1) control group (active placebo/microdose vs. inactive placebo), (2) adjunctive psychotherapy (yes vs. no), (3) risk of bias (low/some concerns vs. high), (4) diagnostic criteria (DSM/ICD vs. other), and (5) small sample size (<20 vs. ≥20 participants). Post-hoc, we conducted two additional sensitivity analyses: (1) excluding one arm of the Mithoefer, 2018-study (Mithoefer et al., 2018) because of an extremely large value for effect of MDMA on PTSD symptoms (SMD of −3.95), and (2) excluding studies conducted before 1990 in the analyses of psychedelics on abstinence rates due to concerns of comparable methodology in relation to newer trials.

Potential publication bias for outcomes with ≥10 studies was explored in three ways: by (1) Harbord's test, (2) comparing the agreement between estimates obtained in a random-effect and a fixed-effect model, and (3) examining contour-enhanced funnel plots. *A priori*, we planned to conduct additional analyses using the Copas' method in case of evidence of publication bias according to the Harbord's test (p-values <0.1), but this was not relevant.

All analyses were conducted using R (version 4.4.3) and the *meta*-package (Schwarzer et al., 2015).

2.7. Patient and public involvement

Two persons with lived experience of psychedelic use and living experience of mental disorders were involved in the outcome selection, online platform design, and interpretation of findings as part of the work group (RR, TW). The LSR results are available on an online portal (ebipsyche-database.org). Lay language summary will be used in the dissemination of the results.

3. Results

Altogether, 14,549 records were detected from databases, registers, and citation searching (Fig. 1). We assessed the eligibility of 143 studies based on full-text screening (see sTable 3 for the reasons for the exclusion of studies after full-text assessment). Ultimately, 33 studies, reporting on 30 RCTs, involving 1480 participants with a mental disorder were included (45.8 % female; Table 1). Altogether, 819 participants were enrolled in the active arms from eleven RCTs of MDMA (n = 197) (Bouso et al., 2008; Brewerton et al., 2022; Danforth et al., 2018; Mitchell et al., 2023, 2021; Mithoefer et al., 2018, 2011; NCT01689740, 2008; NCT01958593, 2022; Nicholas et al., 2022; Oehen et al., 2013; Ot'alora G et al., 2018; van der Kolk et al., 2024; Wolfson et al., 2020), seven RCTs of LSD (n = 187) (Gasser et al., 2014; Hollister et al., 1969; Holze et al., 2023; Mueller et al., 2025; Müller et al., 2025; Smart et al., 1966; Tomsovic and Edwards, 1970), ten RCTs of psilocybin (n = 409) (Back et al., 2024; Bogenschutz et al., 2022; Carhart-Harris et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Luquiens et al., 2025; Raison et al., 2023; Rieser et al., 2025; Ross et al., 2016; Von Rotz et al., 2023), and two RCTs of ayahuasca (n = 26) (Dos Santos et al., 2021; Palhano-Fontes et al., 2019) (Table 1). Overall, 661 participants were included in the control arms, consisting of inactive placebo (n = 328), active placebo (n = 137), low-dose psychedelics (n = 167), or selective serotonin reuptake inhibitors (n = 29). Importantly, when psychological support was delivered in intervention arms, all control arms had the same protocol. Efficacy of psychedelics was investigated in PTSD (k = 9; n = 303), MDD (k = 7; n = 569), anxiety disorders (k = 7; n = 188), AUD (k = 6; n = 367), and attention-deficit hyperactivity disorder (k = 1; n = 53). Overall, 23 RCTs (76.7 %) used DSM/ICD criteria to define mental disorders. The average duration of observation (primary endpoint) after the last experimental session was 8.9 weeks (standard deviation [SD]: 7.5; range=355 min-28 weeks). Except for five RCTs (Dos Santos et al., 2021; Hollister et al., 1969; Mueller et al., 2025; Palhano-Fontes et al., 2019; Tomsovic and Edwards, 1970), psychedelics were used in association with psychological support in all other studies. The mean number of non-drug preparatory psychotherapy sessions and post-drug integrative psychotherapy sessions were 2.6 (SD=0.8) and 5.0 (SD=2.4), respectively. The mean duration of sessions for non-drug preparatory psychotherapy was 241 ± 94 min (range=60–480) and for the sessions of post-drug integrative psychotherapy was 428 ± 209 min (range=180–810). Psychedelics were administered 2.0 ± 1.9 times (range=1–12). The average proportion of participants with prior use of psychedelic substances was 24.3 % (k = 20; range=0–56 %; sTable 4).

The level of risk of bias across the included studies varied, with the highest being for deviation from the intended intervention and bias in

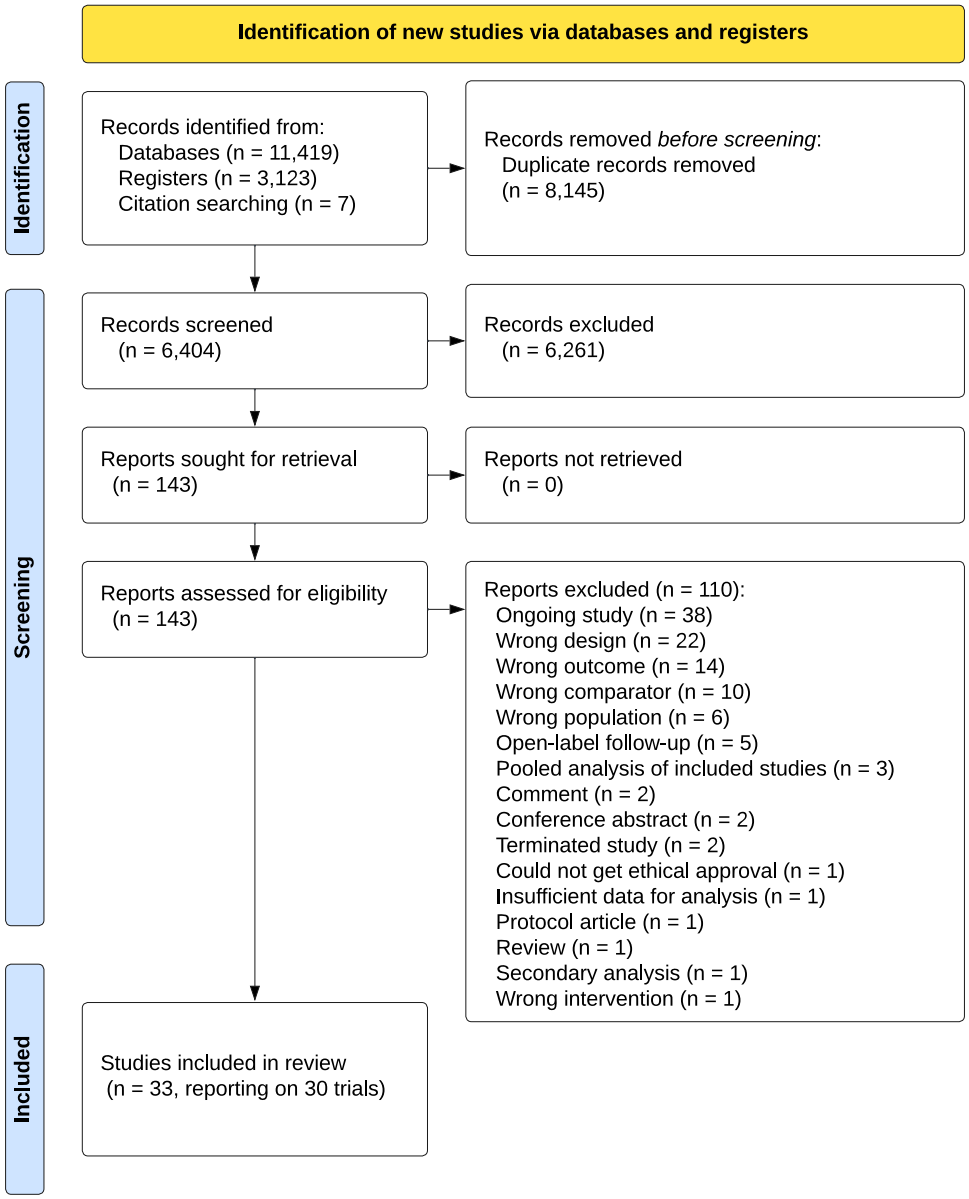


Fig. 1. PRISMA flow diagram of study selection.

measurement of the outcome (sFigure1). Regarding the overall risk of bias, 25 RCTs were judged as having high risk of bias (83.3 %), three as having some concerns (10.0 %), and two as having low risk for bias (6.7 %). In studies of LSD and ayahuasca no study was judged to have low risk of bias. In studies of psilocybin one of ten studies was judged as having low risk of bias, while two had some concerns, and seven high risk of bias. In studies of MDMA only one study was judged as having low risk of bias, while the remaining ten were judged as having high risk of bias. The average proportion of participants/therapists who guessed whether they were on the active substance and/or the comparator was 85.1 % (k = 19; range=46–100 %; sTable 4).

3.1. Efficacy of MDMA in post-traumatic stress disorder

In PTSD, all studies examined MDMA. A large ES was found for MDMA on PTSD symptoms (k = 11; SMD −0.85 [−1.09; −0.60]) with no heterogeneity (I^2=0 %) and zero not included in the prediction interval (Fig. 2 and sFig. 2a). Overall, certainty in evidence for MDMA on PTSD symptoms was rated "low" (sTable 5), although the certainty in evidence was rated "moderate" for MDMA on PTSD symptoms when compared to placebo (sTable 6).

A large ES was found for MDMA on sleep quality in PTSD (k = 5; SMD −0.82 [−1.42; −0.22]; sFig. 2b); while a moderate ES was seen for depressive symptoms (k = 7; SMD −0.73 [−1.19; −0.27]; sFig. 2c); and a small ES for functional impairment (k = 2; SMD −0.43 [−0.72; −0.15]; sFig. 2d). MDMA was not effective in reducing dissociative symptoms, reducing anxiety symptoms, nor improving functioning in PTSD (Fig. 2 and sFig. 2e-g). Certainty in the evidence for secondary outcomes ranged from "low" for the MDMA effect on functioning, sleep quality, depressive symptoms, and functional impairment to "very low" for dissociative symptoms and anxiety symptoms (sTable 5).

3.2. Efficacy of serotonergic psychedelics in major depressive disorder

In MDD, studies examined ayahuasca, LSD, and psilocybin. A moderate ES was seen for serotonergic psychedelics on depressive symptoms (k = 8; SMD −0.62 [−0.97; −0.28]), but with moderate heterogeneity (I^2=55 %) and zero included in the prediction interval (Fig. 2 and sFigure 3a). Overall, certainty in evidence for psychedelics on depressive symptoms was rated "very low" (sTable 5), although the certainty in

Table 1
Study characteristics.

Author, year (trial ID)	Condition	Intervention	Control	Duration
Studies included in meta-analysis				
Back et al., 2024 (NCT05163496)	Major depressive disorder (MADRS≥21)	Psilocybin 25 mg ($N = 15$) + PSY (2 × 60–90 min preparatory sessions + 1 × 7 h experimental session + 3 × 60–90 mins integrative sessions)	Niacin 100 mg ($N = 15$) + PSY (identical to the intervention group)	4 weeks
Bogenschutz et al., 2022 (NCT02061293)	Alcohol use disorder (DSM-IV)	Psilocybin 25–40mg/70 kg ($N = 49$) + PSY (4 × 60mins preparatory sessions + 2 × 8 h experimental sessions + 8 × 60mins integrative sessions)	Diphenhydramine 50–100 mg ($N = 46$) + PSY (identical to the intervention group)	28 weeks
Bouso et al., 2008 (NA)	PTSD (DSM-IV)	MDMA 50–150 mg ($N = 4$) + PSY (3 × 90mins preparatory sessions + 1 × 6 h experimental session w/therapy + 3 × 90mins integrative sessions)	Placebo ($N = 2$) + PSY (identical to the intervention group)	4 weeks
Carhart-Harris et al., 2021 (NCT03429075)	Major depressive disorder (Clinical diagnosis)	Psilocybin 25 mg ($N = 30$) + PSY (3 × 60mins preparatory sessions + 2 experimental sessions + 6 × 60mins integrative sessions)	Psilocybin 1 mg + escitalopram 10–20 mg ($N = 29$) + PSY (identical to the intervention group)	6 weeks
Danforth et al., 2018 (NCT02008396)	Autism spectrum disorder and social anxiety disorder (DSM-IV)	MDMA 75–125 mg ($N = 8$) + PSY (3 × 60–90mins preparatory sessions + 2 experimental sessions + 6 × 60–90mins integrative sessions)	Placebo ($N = 4$) + PSY (identical to the intervention group)	8 weeks
Dos Santos et al., 2021 (NA)	Social anxiety disorder (DSM-V)	Ayahuasca 2ml/kg ($N = 9$)	Placebo ($N = 8$)	1 day
Gasser et al., 2014 (NCT00920387)	Anxiety in life-threatening conditions (STAI>40)	LSD 200 mcg ($N = 8$) + PSY (2 preparatory sessions + 2 experimental sessions + 6 × 60–90mins follow-up sessions)	LSD 20 mcg ($N = 4$) + PSY (identical to the intervention group)	8 weeks
Goodwin et al., 2022 (NCT03775200)	Treatment-resistant major depressive disorder (DSM-V)	Psilocybin 10 ($N = 75$) or 25 mg ($N = 79$) + PSY (3 preparatory sessions + 1 experimental session + 2 × 90mins follow-up sessions)	Psilocybin 1 mg ($N = 79$) + PSY (identical to the intervention group)	3 weeks
Griffiths et al., 2016 (NCT00465595)	Adjustment disorder with anxiety, adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, generalized anxiety disorder, major depressive disorder and cancer (DSM-IV)	Psilocybin 22–33mg/70 kg ($N = 29$) + PSY (3 preparatory sessions + 1 experimental session + min 2 follow-up sessions)	Psilocybin 1–3mg/70 kg ($N = 27$) + PSY (identical to the intervention group)	5 weeks
Hollister et al., 1969 (NA)	Alcohol use disorder (Clinical diagnosis)	LSD 600 pg ($N = 29$)	Dextroamphetamine 60 mg ($N = 23$)	24 weeks
Holze et al., 2023 (NCT03153579)	Anxiety with or without life-threatening conditions (STAI>40)	LSD 200 mcg ($N = 20$) + PSY (1 preparatory session + 2 experimental sessions + 4 integrative sessions)	Placebo ($N = 22$) + PSY (identical to the intervention group)	24 weeks
Kotler et al., 2008 (NCT01689740, 2008) (MP-9)	PTSD (DSM-IV)	MDMA 125 mg ($N = 5$) + PSY (3 preparatory sessions + 2 experimental sessions each followed by 3 integrative sessions)	MDMA 25 mg ($N = 3$) + PSY (identical to the intervention group)	4 weeks
Luquiens et al., 2025 (NCT06235411)	AUD (DSM-V)	PSI 25 mg ($N = 20$) + PSY (2 preparatory sessions + 2 experimental sessions each followed by 1 integrative session)	PSI 1 mg ($N = 10$) + PSY (identical to the intervention group)	12 weeks
Mitchell et al., 2021 (NCT03537014)	PTSD (DSM-V)	MDMA 80–180 mg ($N = 46$) + PSY (3 × 90mins preparatory sessions + 3 experimental sessions each followed by 3 × 90mins integrative sessions)	Placebo ($N = 44$) + PSY (identical to the intervention group)	8 weeks
Mitchell et al., 2023 (NCT04077437)	PTSD (DSM-V)	MDMA 120–180 mg ($N = 53$) + PSY (3 × 90mins preparatory sessions + 3 × 8hours experimental sessions each followed by 3 × 90mins integrative sessions)	Placebo ($N = 51$) + PSY (identical to the intervention group)	12 weeks
Mithoefer et al., 2011 (NCT00090064)	PTSD (DSM-IV-R)	MDMA 125 mg ($N = 15$) + PSY (2 × 90mins preparatory sessions + 2 experimental sessions each followed by 4 × 90mins integrative sessions)	Placebo ($N = 8$) + PSY (identical to the intervention group)	8 weeks
Mithoefer et al., 2018 (NCT01211405)	PTSD (DSM-IV)	MDMA 75 mg ($N = 7$) or 125 mg ($N = 12$) + PSY (3 × 90mins preparatory sessions + 2 experimental sessions each followed by 3 × 90mins integrative sessions)	MDMA 30 mg ($N = 7$) + PSY (identical to the intervention group)	4 weeks
Müller et al., 2025 (NCT03866252)	MDD (DSM-V)	LSD 100–200 mcg ($N = 29$) + PSY (2 preparatory sessions + 2 experimental sessions followed by a total of 5 integratory sessions)	LSD 25 mcg ($N = 28$) + PSY (identical to the intervention group)	9 weeks
Mueller et al., 2025 (NCT05200936)	ADHD (DSM-IV/-V) with AISRS-score ≥26	LSD 20mcg two times weekly for 6 weeks ($N = 27$)	Placebo ($N = 26$)	6 weeks
Oehen et al., 2013 (NCT00353938)	PTSD (DSM-IV-R)	MDMA 125 mg ($N = 8$) + PSY (3 × 90mins preparatory sessions + 3 experimental sessions each followed by 3 × 90mins integrative sessions)	MDMA 25 mg ($N = 4$) + PSY (identical to the intervention group)	9 weeks
Ot'alora et al., 2018 (NCT01793610)	PTSD (DSM-IV)	MDMA 100 mg ($N = 9$) or 125 mg ($N = 13$) + PSY (3 × 90mins preparatory sessions + 2 experimental sessions each followed by 3 × 90mins integrative sessions)	MDMA 40 mg ($N = 6$) + PSY (identical to the intervention group)	4 weeks

(*continued on next page*)

Table 1 (*continued*)

Author, year (trial ID)	Condition	Intervention	Control	Duration
Pacey et al., 2022 (NCT01958593, 2022)	PTSD (DSM-IV)	MDMA 125 mg ($N = 4$) + PSY (3 preparatory sessions + 2 experimental sessions each followed by 3 integrative sessions)	Placebo ($N = 2$) + PSY (identical to the intervention group)	12 weeks
Palhano-Fontes et al., 2019 (NCT02914769)	Treatment-resistant major depressive disorder (DSM-IV)	Ayahuasca 1ml/kg ($N = 17$)	Placebo ($N = 18$)	1 week
Raison et al., 2023 (NCT03866174)	Major depressive disorder (DSM-V)	Psilocybin 25 mg ($N = 51$) + PSY (6–8 h preparatory sessions + 1 × 7–10 h experimental session + 4 h integrative sessions)	Niacin 100 mg ($N = 53$) + PSY (identical to the intervention group)	6 weeks
Rieser et al., 2025 (NCT04141501)	Alcohol use disorder (DSM-V)	Psilocybin 25 mg ($N = 19$) + PSY (2 preparatory sessions + 1 experimental session + 3 integrative sessions)	Placebo ($N = 21$) + PSY (identical to the intervention group)	4 weeks
Ross et al., 2016 (NCT00957359)	Adjustment disorder with anxiety or anxiety disorder in life-threatening conditions (DSM-IV)	Psilocybin 0.3 mg/kg ($N = 16$) + PSY (3 preparatory sessions + 1 experimental session + 3 integrative sessions)	Niacin 250 mg ($N = 15$) + PSY (identical to the intervention group)	7 weeks
Smart et al., 1966 (NA)	Alcohol use disorder (Clinical diagnosis)	LSD 800 mcg ($N = 10$) + PSY (1 experimental session + group therapy, unspecified duration)	Ephedrine 60 mg ($N = 20$) + PSY (identical to the intervention group)	24 weeks
Tomsovic and Edwards, 1970 (NA)	Alcohol use disorder (± schizophrenia) (Clinical diagnosis)	LSD 500 mcg ($N = 64$)	Placebo ($N = 56$)	24 weeks
Von Rotz et al., 2023 (NCT03715127)	Major depressive disorder (DSM-IV)	Psilocybin 0.215 mg/kg ($N = 26$) + PSY (2 × 60mins preparatory sessions + 1 × 6hours experimental sessions + 3 × 60mins integrative sessions)	Placebo ($N = 26$) + PSY (identical to the intervention group)	2 weeks
Wolfson et al., 2020 (NCT02427568)	Anxiety disorders in life-threatening conditions (STAI-$T > 45$)	MDMA 125 mg ($N = 13$) + PSY (3 × 60–90mins preparatory sessions + 2 experimental sessions + 6 × 90mins integrative sessions)	Placebo ($N = 5$) + PSY (identical to the intervention group)	4 weeks
Studies not included in meta-analysis*				
Brewerton et al., 2022 (NCT03537014)	PTSD (DSM-V)	MDMA 80–180 mg ($N = 46$) + PSY (3 × 90mins preparatory sessions + 3 experimental sessions each followed by 3 × 90mins integrative sessions)	Placebo ($N = 43$) + PSY (identical to the intervention group)	8 weeks
Nicholas et al., 2022 (NCT03537014)	PTSD, with or without alcohol and cannabis use disorder (DSM-V)	MDMA 80–180 mg ($N = 46$) + PSY (3 × 90mins preparatory sessions + 3 experimental sessions each followed by 3 × 90mins integrative sessions)	Placebo ($N = 44$) + PSY (identical to the intervention group)	8 weeks
Van Der Kolk et al., 2024 (NCT03537014)	PTSD (DSM-V)	MDMA 80–180 mg ($N = 46$) + PSY (3 × 90mins preparatory sessions + 3 experimental sessions each followed by 3 × 90mins integrative sessions)	Placebo ($N = 44$) + PSY (identical to the intervention group)	8 weeks

Legend: ADHD, attention-deficit hyperactivity disorder; AISRS, Adult Investigator Symptom Rating Scale; DSM, Diagnostic and Statistical Manual; LSD, lysergic acid diethylamide; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDMA, 3,4-methylenedioxymethamphetamine; N, number; NA, not applicable; PTSD, post-traumatic stress disorder; PSY, psychotherapy; STAI-T, Spielberger State-Trait Anxiety Inventory – Trait; TRD, treatment-resistant depression.

Notes: *All three studies listed under this subsection were secondary analyses of the study by Mitchell et al. 2021 included in the main analysis.

evidence was rated "low" for psilocybin on depressive symptoms when compared to active control (sTable 6).

Results for individual psychedelic agents demonstrated that psilocybin ($k = 6$; SMD −0.52 [−0.80; −0.24]), ayahuasca ($k = 1$; SMD −1.73 [−2.52; −0.94]), and LSD ($k = 1$; SMD −0.63 [−1.17; −0.09]) improved depressive symptoms, with medium to large ESs (sFigure 3a).

A moderate ES was seen for functional impairment ($k = 2$; SMD −0.70 [−1.02; −0.39]; sFigure 3b) and anxiety symptoms ($k = 3$; SMD −0.69 [−0.97; −0.42]; sFigure 3c), while no significant reduction was seen for suicidal ideation (sFigure 3d). Certainty in the evidence for secondary outcomes ranged from "low" for functional impairment and anxiety symptoms (both with I^2=0 %) to "very low" for the effect on suicidal ideation (sTable 5–6).

3.3. Efficacy of MDMA and serotonergic psychedelics for anxiety disorders

In anxiety disorders, studies examined both MDMA and serotonergic psychedelics (ayahuasca, LSD, and psilocybin).

A large ES was seen for the effect of serotonergic psychedelics on anxiety symptoms ($k = 5$; SMD −0.88 [−1.70; −0.06]), but with moderate heterogeneity (I^2=54 %) and zero included in the prediction interval (Fig. 2 and sFigure 4a). Among the individual molecules, psilocybin ($k = 2$; SMD −0.95 [−1.60; −0.29]) improved anxiety symptoms, whereas ayahuasca and LSD did not (sFigure 4a). Certainty in evidence for the effect of serotonergic psychedelics on anxiety symptoms was rated "very low". For the individual serotonergic psychedelics, the certainty in evidence was also rated "very low" (sTable 5 and 6).

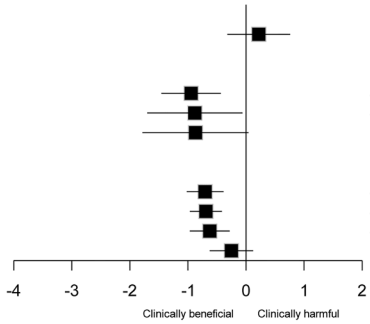
Similarly, a large ES was seen for the effect MDMA on anxiety symptoms ($k = 2$; SMD −1.18 [−2.04; −0.32]) with no heterogeneity (I^2=0 %), but with zero included in the prediction interval (Fig. 2 and sFigure 4b). Certainty in evidence for the effect of MDMA on anxiety symptoms was rated "low" (sTable 5 and 6).

Serotonergic psychedelics demonstrated a large effect on improvement in quality of life ($k = 2$; SMD 0.95 [0.43; 1.46]; sFigure 4c), while no difference emerged for depressive symptoms ($k = 4$; SMD −0.87 [−1.78; 0.04]; sFigure 4d). The certainty in the evidence was rated "low" to "very low" for the effect on all secondary outcomes, overall and for each comparison (sTable 5–6).

MDMA was not effective in reducing depressive symptoms, improving sleep quality, or improving functioning (sFigure 4e-g) with certainty in evidence rated "low" depressive symptoms and "very low" for sleep quality and functioning (sTable 5–6).

A: Serotonergic psychedelics (Ayahuasca, LSD, and psilocybin)

Disorder/domain	N studies	N participants	SMD (95% CI)	p-value	I²	95% PI	Harbords test p-value	GRADE
Attention-deficit hyperactivity disorder								
ADHD symptoms	1	53	0.22 (-0.32; 0.76)	0.43	NA	NA	NC	Very low
Anxiety disorders								
Quality of life	2	68	-0.95 (-1.46; -0.43)	<0.001	0	-2.37;4.26	NC	Low
Anxiety symptoms	5	158	-0.88 (-1.70; -0.06)	0.041	54	-2.05;0.29	NC	Very low
Depressive symptoms	4	141	-0.87 (-1.78; 0.04)	0.056	60	-2.61;0.86	NC	Very low
Major depressive disorder								
Functional impairment	2	163	-0.70 (-1.02; -0.39)	<0.001	0	-2.76;1.35	NC	Low
Anxiety symptoms	3	215	-0.69 (-0.97; -0.42)	<0.001	0	-1.3;-0.09	NC	Low
Depressive symptoms	8	569	-0.62 (-0.97; -0.28)	0.0035	55	-1.32;0.07	NC	Very low
Suicidal ideation	2	111	-0.25 (-0.63; 0.12)	0.19	0	-2.68;2.17	NC	Very low



B: MDMA

Disorder/domain	N studies	N participants	SMD (95% CI)	p-value	I²	95% PI	Harbords test p-value	GRADE
Anxiety disorder								
Anxiety symptoms	2	30	-1.18 (-2.04; -0.32)	0.0071	0	-6.76;4.39	NC	Low
Sleep quality	1	18	-0.69 (-1.75; 0.38)	0.21	NA	NA	NC	Very low
Functioning	1	18	-0.33 (-1.37; 0.71)	0.54	NA	NA	NC	Very low
Depressive symptoms	2	30	-0.16 (-0.95; 0.63)	0.69	0	-5.27;4.95	NC	Low
Post-traumatic stress disorder								
Dissociative symptoms	4	55	-1.81 (-5.16; 1.54)	0.18	70	-7.68;4.06	NC	Very low
Functioning	3	35	-1.75 (-3.79; 0.29)	0.066	3	-0.44;3.94	NC	Low
Anxiety symptoms	1	6	-0.88 (-2.76; 1.00)	0.36	NA	NA	NC	Very low
PTSD symptoms	11	303	-0.85 (-1.09; -0.60)	<0.001	0	-1.13;-0.57	0.32	Low
Sleep quality	5	63	-0.82 (-1.42; -0.22)	0.0077	0	-1.67;0.03	NC	Low
Depressive symptoms	7	159	-0.73 (-1.19; -0.27)	0.0083	13	-1.16;-0.3	NC	Low
Functional impairment	2	194	-0.43 (-0.72; -0.15)	0.0028	0	-2.28;1.41	NC	Low

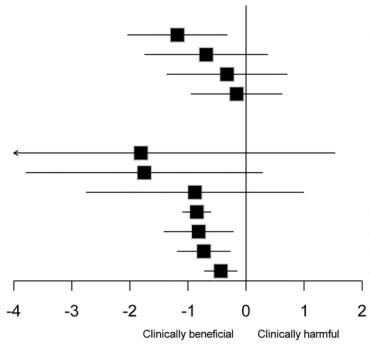


Fig. 2. Effect of serotonergic psychedelics (A) and MDMA (B) on mental health symptoms in various mental disorders. Legend: ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; N, number; NA, not applicable; NC, not calculated; PI, prediction interval; PTSD, post-traumatic stress disorder; SMD, standardized mean difference. Harbord's test was only conducted for outcomes with ≥10 studies. Improvement in functioning and sleep quality is presented as negative numbers in this figure to allow comparison with other outcomes, although the SMDs might be positive (see sFigures 2–5 for actual values).

3.4. Efficacy of serotonergic psychedelics on attention-deficit hyperactivity disorder

In patients with attention-deficit hyperactivity disorder (ADHD), microdosing LSD was not found effective in reducing ADHD symptoms ($k = 1$; SMD 0.22 [−0.32; 0.76]; Fig. 2 and sFigure 5). Certainty in the evidence was rated "very low".

3.5. Efficacy of serotonergic psychedelics on alcohol use disorders

In AUD, studies examined LSD and psilocybin. In patients with AUD, no significantly beneficial effect of serotonergic psychedelics emerged compared to control groups on abstinence ($k = 6$; RR 1.42 [0.89; 2.26]; I^2=7 %; sFigure 6). Neither psilocybin ($k = 3$; RR 1.75 [0.51; 5.95]) nor LSD ($k = 3$; RR 1.11 [0.50; 2.49]; sFigure 6) was effective for abstinence in AUD. Overall, certainty in the evidence was rated "very low". Considering psychedelic agents separately, within homogeneous populations, interventions, comparators, and outcomes, no result was supported by at least moderate GRADE (sTable 6).

3.6. Exploratory meta-regression of moderator variables on disease-specific symptoms

We found no association of PTSD symptoms with age, sex, sample size, publication year, study duration, and duration of psychotherapy in PTSD (i.e. the only disorder with ≥10 studies reporting potential moderators; Table 2).

Table 2
Results of exploratory meta-regression of moderator variables of psychedelic effects on disease-specific symptoms in post-traumatic stress disorder.

Domain	k	Coefficient (95 % CI)	p-value	I^2	τ^2
PTSD symptoms					
Mean age	10	0.058 (−0.082; 0.198)	0.42	0	0
% Male	11	−0.018 (−0.040; 0.003)	0.09	0	0
Sample size	11	0.002 (−0.004; 0.009)	0.51	0	0
Publication year	11	0.018 (−0.047; 0.082)	0.59	0	0
Study duration (weeks)	11	0.076 (−0.022; 0.174)	0.13	0	0
Therapy duration (hours)	10	0.008 (−0.101; 0.118)	0.88	0	0

Legend: CI, confidence interval; k, number of studies/arms reporting the moderator; PTSD, post-traumatic stress disorder.
Notes: A meta-regression analysis was only conducted for outcomes reported in ≥10 studies. Positive coefficients represent increasing effect with increasing mean age, increasing proportion of males, increasing sample size, more recent publication year, or increasing study duration in the samples.

3.7. All-cause discontinuation

Drop-out rates at the primary endpoint did not differ significantly between intervention and control groups for either class of compounds. Specifically, among participants receiving serotonergic psychedelics, the drop-out rate was 8.7 % versus 11.6 % in control groups (RR 0.81 [0.56; 1.15]; sFigure 7a+8a). Similarly, for MDMA, drop-out rates were

comparable between intervention and control groups (6.1 %vs. 9.6 %, RR 0.74 [0.32; 1.72]; sFigure 7b+8b). Furthermore, no difference emerged regarding drop-out rates in individual disorders and psychedelic compounds (sFigure 7–8).

3.8. Safety

Common side effects (reported by ≥20 % in the intervention group) are listed in Table 3 for each molecule (all reported side effects by molecule can be found in sTable 7). No molecule was associated with an increased risk of serious adverse events. Use of ayahuasca was associated with increased risk of nausea (53.8 %vs. 15.4 %; RR 2.98) and vomiting (42.3 %vs. 0 %; RR 10.7) compared to the control groups. Use of LSD was associated with increased risk of illusions (40.8 %vs. 3.1 %; RR 5.14) compared to the control groups. Use of MDMA was associated with increased risk of muscle strain (56.9 %vs. 15.5 %; RR 2.98), jaw clenching (45.3 %vs. 11.5 %; RR 2.70), lack of appetite (40.4 %vs. 14.8 %; RR 2.25), nausea (31.0 %vs. 15.4 %; RR 2.07), and hyperhidrosis (29.2 %vs. 6.3 %; RR 3.21) compared to the control groups. Use of psilocybin was associated with increased risk of headache (39.9 %vs. 9.8 %; RR 4.48), emotional distress (32.1 %vs. 12.5 %; RR 2.57), illusions (23.2 %vs. 3.1 %; RR 6.80), and nausea (20.3 %vs. 6.1 %; RR 2.89) compared to control conditions.

Table 3
Relative risk of common side-effects (experienced by ≥20 % of participants in the intervention group) by molecule.

Adverse event	N studies	Intervention n/N (%)	Control n/N (%)	RR (95 % CI)	p-value	I^2
Ayahusca						
Nausea	2	14/26 (53.8)	4/26 (15.4)	2.98 (1.21; 7.32)	**0.018**	0
Vomiting	2	11/26 (42.3)	0/26 (0)	10.69 (1.48; 77.15)	**0.019**	0
Restlessness	1	7/17 (41.2)	3/18 (16.7)	2.47 (0.76; 8.03)	0.13	NA
Anxiety	1	7/17 (41.2)	11/18 (61.1)	0.67 (0.34; 1.33)	0.25	NA
Tension headache	2	8/26 (30.8)	8/26 (30.8)	1.06 (0.30; 3.72)	0.93	21
Sedation	1	2/9 (22.2)	0/8 (0)	4.47 (0.25; 80.65)	0.31	NA
LSD						
Feeling cold	1	12/22 (54.5)	0/6 (0)	7.22 (0.49; 106.25)	0.15	NA
Emotional distress	1	10/22 (45.5)	2/6 (33.3)	1.36 (0.40; 4.62)	0.62	NA
Illusions	2	20/49 (40.8)	1/32 (3.1)	5.14 (1.11; 23.84)	**0.036**	0
Dizziness	2	17/49 (34.7)	11/50 (22)	1.42 (0.29; 6.87)	0.66	79
Headache	3	26/76 (34.2)	38/76 (50)	0.73 (0.31; 1.77)	0.49	78
Gait disturbance	1	7/22 (31.8)	0/6 (0)	4.33 (0.28; 66.21)	0.29	NA
Nausea	3	19/76 (25)	14/76 (18.4)	1.24 (0.20; 7.70)	0.82	70
Feeling abnormal	2	12/49 (24.5)	2/32 (6.2)	1.63 (0.53; 5.06)	0.39	0
MDMA						
Treatment emergent AE	1	53/53 (100)	49/51 (96.1)	1.04 (0.98; 1.10)	0.16	NA
Any AE	11	120/141 (85.1)	75/97 (77.3)	1.00 (0.96; 1.04)	0.88	21
Muscle strain	4	41/72 (56.9)	9/58 (15.5)	2.50 (1.05; 5.95)	**0.038**	33
Astehnia	1	2/4 (50)	0/2 (0)	2.78 (0.20; 37.90)	0.44	NA
Muscle thightness	3	17/34 (50)	9/22 (40.9)	1.19 (0.67; 2.10)	0.56	0
Headache	4	22/47 (46.8)	11/27 (40.7)	1.04 (0.68; 1.61)	0.85	0
Jaw clenching	7	48/106 (45.3)	6/52 (11.5)	2.70 (1.37; 5.35)	**0.0043**	0
Fatigue	5	27/62 (43.5)	15/35 (42.9)	1.00 (0.67; 1.50)	0.98	0
Increased need for sleep	2	12/28 (42.9)	2/13 (15.4)	2.31 (0.78; 6.83)	0.13	NA
Lack of appetite	7	74/183 (40.4)	20/135 (14.8)	2.25 (1.34; 3.78)	**0.0021**	25
Anxiety	11	69/176 (39.2)	35/112 (31.2)	1.31 (0.96; 1.79)	0.086	0
Thirst	3	24/65 (36.9)	2/26 (7.7)	2.63 (0.92; 7.50)	0.07	2
Insomnia	6	46/127 (36.2)	22/82 (26.8)	1.30 (0.85; 1.98)	0.23	0
Gait disturbance	1	12/37 (32.4)	3/13 (23.1)	1.41 (0.47; 4.21)	0.54	NA
Nausea	6	52/168 (31)	19/123 (15.4)	2.07 (1.32; 3.25)	**0.0016**	0
Asthenia	5	23/78 (29.5)	6/35 (17.1)	1.45 (0.70; 3.03)	0.32	0
Hyperhidrosis	6	49/168 (29.2)	8/127 (6.3)	3.21 (1.44; 7.15)	**0.0043**	11
Tension headache	7	24/90 (26.7)	10/41 (24.4)	0.96 (0.54; 1.70)	0.88	0
Depersonalization	1	1/4 (25)	0/2 (0)	1.67 (0.10; 27.47)	0.72	NA
Migraine	1	1/4 (25)	0/2 (0)	1.67 (0.10; 27.47)	0.72	NA
Photosensitivity	1	1/4 (25)	0/2 (0)	1.67 (0.10; 27.47)	0.72	NA
Feeling cold	6	42/170 (24.7)	15/130 (11.5)	1.66 (0.89; 3.07)	0.11	19
Restlessness	6	38/170 (22.4)	10/130 (7.7)	2.12 (0.64; 7.05)	0.22	62
Drowsiness	2	6/28 (21.4)	1/13 (7.7)	2.31 (0.36; 14.66)	0.38	NA
Diarrhea	2	4/19 (21.1)	2/10 (20)	0.95 (0.24; 3.75)	0.95	0
Suicidal ideation	8	33/161 (20.5)	29/130 (22.3)	0.89 (0.58; 1.36)	0.59	0
Ororpharyngeal pain	1	1/5 (20)	0/3 (0)	1.91 (0.10; 34.92)	0.66	NA
Dizziness	5	24/120 (20)	8/77 (10.4)	1.43 (0.63; 3.27)	0.39	0
Bronchitis	1	1/5 (20)	3/3 (100)	0.27 (0.07; 1.07)	0.062	NA
Psilocybin						
Any AE	7	254/357 (71.1)	203/360 (56.4)	1.21 (1.08; 1.35)	**<0.001**	39
Treatment emergent AE	2	49/77 (63.6)	27/79 (34.2)	1.82 (1.33; 2.50)	**<0.001**	0
Headache	5	65/163 (39.9)	15/153 (9.8)	4.48 (1.90; 10.54)	**<0.001**	8
Emotional distress	1	18/56 (32.1)	7/56 (12.5)	2.57 (1.17; 5.67)	**0.019**	NA
Tension headache	5	70/256 (27.3)	55/258 (21.3)	1.22 (0.93; 1.62)	0.16	19
Illusions	2	23/99 (23.2)	3/98 (3.1)	6.80 (2.32; 19.93)	**<0.001**	0
Nausea	10	85/419 (20.3)	25/411 (6.1)	2.89 (1.51; 5.53)	**0.0013**	43

Legend: CI, confidence interval; n, events; N, number of subjects in group; NA, not applicable; RR, risk ratio.
Notes: Complete set of results for adverse events can be found in sTable 7.

3.9. Subgroup and sensitivity analyses

For disease-specific outcomes, the effect of psychedelics did not differ by control group, risk of bias, diagnostic criteria, or sample size (sFigure 9–13). Although in one study, depressive symptoms were found to improved more in a study without adjunctive psychological support than in studies with adjunctive psychological support (SMD −1.73 vs. −0.54; $p < 0.01$; sFigure 14). Excluding the 75 mg MDMA-arm from Mithoefer et al., 2018, did not negate the observed significant effect of MDMA on PTSD symptoms, depressive symptoms, and sleep quality (sTable 8). Sensitivity analysis excluding pre-1990 LSD studies found no effect of serotonergic psychedelics on abstinence in AUD (RR 1.75 [0.51–5.95]; sFigure 6).

3.10. Publication bias

The Harbord's test results suggested no evidence of publication bias ($p > 0.1$ in all analyses) (Fig. 2). Regarding anxiety symptoms, depressive symptoms, and PTSD symptoms, results between effect sizes from random-effects and fixed-effects models were also comparable (sFig. 2a, 3a, 4a and 4b). Moreover, funnel plots did not reveal apparent asymmetry (sFigure 14–17).

4. Discussion

This systematic review and meta-analysis of RCTs provides a comprehensive and evidence-based overview of serotonergic psychedelics and MDMA in the treatment of mental disorders, including data from double-blind RCTs only. Serotonergic psychedelics demonstrated a large therapeutic effect on anxiety symptoms and quality of life in anxiety disorders; and a moderate effect on anxiety symptoms, depressive symptoms, and functional impairment in MDD. MDMA showed a large therapeutic effect on anxiety symptoms in anxiety disorders, on PTSD symptoms and sleep quality in PTSD; as well as a moderate effect on depressive symptoms and functional impairment in PTSD. Regarding individual agents, MDMA, LSD, psilocybin, and ayahuasca had antidepressant effects; while MDMA, LSD, and psilocybin improved anxiety symptoms. Both MDMA and psilocybin also significantly reduced functional impairment compared to control conditions. However, serotonergic psychedelics were not effective in reducing ADHD symptoms or improving abstinence rates in AUD. Several quantitative and qualitative limitations emerged from the current evidence and should be considered in future research, regulatory decisions, and clinical guidance, as discussed below.

In sensitivity analyses, consistent with previous reports (Bahji et al., 2020; Illingworth et al., 2021; Tedesco et al., 2021) among patients with PTSD, MDMA had a greater effect on improving PTSD symptoms, sleep problems, depressive symptoms, and functional impairment compared to controls. Studies were qualitatively homogeneous. We also found a large ES on dissociative symptoms, but variability across the studies was significantly large, and the result was not statistically significant. Importantly, comorbid depression in PTSD predict decreased response to available treatments, and having a treatment that targets both depressive and PTSD symptoms is promising (Kline et al., 2021). Furthermore, sleep problems that are associated with exacerbated daytime symptoms, poor clinical outcomes, increased depression and suicidality, and poor quality of life and functioning are usually refractory, despite treatment among patients with PTSD (Starke and Stein, 2017). Our findings suggested that MDMA-assisted psychotherapy can be an effective treatment option for PTSD by reducing PTSD core symptoms, depressive symptoms, sleep problems, and improving functioning, without more frequent all-cause discontinuation than in control groups. However, importantly, we could not disentangle the role of psychotherapy from MDMA's direct drug effect, given that no trial administered MDMA without psychotherapy (Madero and Alvarez, 2023). Unblinding of both patient and therapist further has the possibility of differentially impacting the nature and quality of the therapy delivered across groups.

This meta-analysis showed that serotonergic psychedelics, especially psilocybin and ayahuasca, had a medium ES on depressive symptoms, anxiety symptoms, and functioning among patients with treatment-resistant MDD and moderate to severe MDD compared to control groups. The mean duration until the primary end-point of the studies was only 9 weeks. We detected no significant variability in the effect among the included RCTs. Patients with anxious depression show less clinical remission and greater side effect burden with antidepressants compared with those without anxiety symptoms (Fava et al., 2008). Moreover, a recent meta-analysis (Kamenov et al., 2017) reported that the mean effect of currently available pharmacotherapy on functioning among patients with MDD is small ($g = 0.35$). Considering the rapid onset and moderate efficacy on depressive symptoms, anxiety symptoms and functioning, serotonergic psychedelics might be considered as a treatment option for both moderate to severe depression and treatment-resistant depression, pending additional evidence on long-term safety and once clarified the role of psychological support (Carhart-Harris and Goodwin, 2017; Zeifman and Maia, 2024).

Among the included RCTs, the efficacy of psychedelics on anxiety disorders was investigated in social anxiety disorder (Danforth et al., 2018; Dos Santos et al., 2021) and anxiety in life-threatening cancer (Gasser et al., 2014; Griffiths et al., 2016; Ross et al., 2016; Wolfson et al., 2020). At least one-third to one-half of the patients with social anxiety disorder remain unresponsive to currently available first-line treatments (Nemeroff, 2012). Our results showed that compared to controls, serotonergic psychedelics or MDMA were effective in reducing anxiety symptoms (especially psilocybin and MDMA) and improved quality of life among patients with anxiety disorders. These results were homogeneous. Therefore, serotonergic psychedelics show a promising therapeutic potential for anxiety disorders, that however needs to be further explored. Same happens with other potential indications, for which there is practically no evidence yet, such as eating disorders (Calder et al., 2023) or bipolar depression (Aaronson et al., 2024).

In contrast to earlier meta-analyses (Fuentes et al., 2020; Krebs and Johansen, 2012), this meta-analysis did not demonstrate any significant improvement in abstinence rates for LSD or psilocybin compared to the comparison group over 6 months among patients with AUD. This discrepancy may reflect our stricter inclusion criteria. Despite including only controlled trials, five of the six RCTs were rated at high risk of bias, and the remaining study raised some concerns; moreover, only three of the six studies were conducted after 1970. This negative result is in line with the more conservative estimates of this meta-analysis compared with previous evidence synthesis reports, reflecting both stricter inclusion criteria and more robust statistical analyses.

No significant results emerged in subgroup or sensitivity analyses investigating the effect of different comparison groups (i.e., active vs. inactive placebo groups), risk of bias, diagnostic criteria (DSM/ICD vs. non-DSM/ICD), and sample size. The results of subgroup analyses investigating the effect of psychotherapy should be considered exploratory and were not likely reliable since only one study for different comparison groups was available for the analysis. Moreover, age, sex, sample size, publication year, study duration, and therapy duration did not indicate a significant moderator effect. Since this is a living systematic review, we will be able to update the search strategy, expand the number of eligible trials, and to iteratively update moderator analyses.

Adverse events were not systematically assessed in most studies, with various classifications or detail in their reporting. Available results showed that the occurrence of SAEs and TEAEs were similar between the psychedelic and control groups. Patients in the psychedelic groups experienced more AEs than controls. There was significant variability among the RCTs in terms of TEAEs and the total number of AEs. Consistent with a recent meta-analysis (Breeksema et al., 2022), our results showed that all compounds acutely induce transient headache, nausea, and anxiety. Considering that there was no difference in serious

adverse events, psychedelics administered in RCT settings to pre-selected patient populations seem to be safe in the short term, despite tolerability issues.

The generalizability of these results is subject to certain limitations. Notably, our risk of bias assessment found that almost all meta-analyzed studies were at high risk of bias, despite filtering out single-blinded trials. Several study samples have been enriched for those with past use and high interest in psychedelics, which could select for those with positive past experiences and high allegiance/interest (Mitchell et al., 2023, 2021). Blinding and expectancy have been noted to be important sources of bias in studies of psychedelics, with blinding often being unsuccessful or not reported, and few studies exploring participant beliefs regarding which arm they were randomized to (Hovmand et al., 2023). The impact of this may be undercaptured by risk of bias tools, especially when the integrity of the blind is not assessed. For example, 94 % of participants reported correctly that they had received MDMA and 75 % that they had received placebo in the study by Mitchell et al. (2023). Assessment of the integrity of the blind was a strength of this study and lacking in other studies although was limited to participants and did not include therapists or outcome assessors. The actual integrity of the blind might have been affected by the psychedelic agents' immediate mind-altering effects, which could bias away from the null hypothesis, particularly for the subjective outcomes used in these studies (Savović et al., 2012). Furthermore, the included trials did not compare the effect of psychedelics to current first-line therapies (e.g., SSRIs) or standard of care in other forms in these disorders. Future studies are recommended to ensure adequate reporting of statistics, all outcome data, and reasons for missing data. Such studies are also encouraged to prioritize blinding through study design such as through use of comparators with immediate mind-altering effects, even considering use of deception if needed to do so (Hovmand et al., 2023). Despite this limitation, subgroup analyses showed no significantly differences in the results between RCTs with low risk of bias/some concerns and those with high risk of bias. Moreover, this meta-analysis was also limited by the small sample size of the included RCTs, differences in methodology, comparison groups, psychedelic substances and doses, primary end-points, the application of different psychological support practices/protocols, and the limited ability to investigate moderators of treatment effects, yet we did conduct sensitivity, subgroup, and meta-regression analyses. The limitations of psychedelic research were underscored by the U.S. Food and Drug Administration's scientific advisory committee vote against supporting MDMA for PTSD (Reardon, 2024).

Despite these limitations, this study offers a broad perspective on both the efficacy and short-term safety of MDMA and serotonergic psychedelics for disease-specific and non-disease-specific psychiatric symptoms, based on the best available trials. Including only double-blind randomized studies, conducting more conservative analyses showing that previously reported unusually high effect sizes are probably inflated, measuring the certainty of evidence, and investigating the role of moderators in subgroup, sensitivity and meta-regression analyses are strengths of this study. Since we included more than three times (30 vs. 9) the number of double-blind RCTs than the previously largest meta-analysis (Ko et al., 2023), the current meta-analysis is the most comprehensive meta-analysis conducted to date and as the first living systematic review can be updated to what is likely to be a rapidly changing literature.

In conclusion, the current living meta-analysis provided evidence for the therapeutic potential of serotonergic psychedelics in anxiety disorders by reducing anxiety symptoms and improving quality of life; for serotonergic psychedelics in MDD by reducing depressive and anxiety symptoms and improving functioning; for MDMA in anxiety disorders by reducing anxiety symptoms; and for MDMA in PTSD by reducing PTSD core symptoms, sleep problems, depressive symptoms, and improving functioning. Although there was no significant benefit of serotonergic psychedelics on abstinence among patients with AUD, these studies had major methodological limitations. Results from this meta-analysis also showed that MDMA and serotonergic psychedelics were overall safe, at least, in pre-selected samples and in the short-term, yet tolerability issues emerged. The only molecule superior to control interventions and with evidence with at least moderate GRADE was MDMA in PTSD. However, these promising results should be supported by future and more robust research to establish a solid evidence base for the use of MDMA and serotonergic psychedelics in mental disorders, accounting for real-world safety data, longer-term follow-up, exploring the role of adjunctive psychotherapy, designs to mitigate and account for functional unblinding and expectancy bias, comparing psychedelics to current first-line therapies; and conducting additional RCTs in conditions where results are preliminary, conflicting, or likely inflated.

Role of funding source

Funding for this study was provided by CIHR (Project Grant, PJT – 195881); the CIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. MS is supported by Clinical Research Chair in Evidence-Based Mental Health, from the Faculty of Medicine, University of Ottawa, Canada.

Samuele Cortese, NIHR Research Professor (NIHR303122) is funded by the NIHR for this research project. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH-2022-DISEASE-07-03 from the European Research Executive Agency

Contributors

MS, MH, VAA, HYK conceptualized the study; HYK, BK, JZ, SW, and MH extracted the data and conducted quality assessment of the individual studies; MH conducted the statistical analyses with methodological guidance from VAA; HYK, MH, and MS drafted the original manuscript and all authors critically revised the manuscript and approved the final version for publication; MH, HYK, and MS are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interest statement

M Højlund has received honoraria/has been a consultant for Lundbeck and Otsuka.

P Fusar-Poli is supported by #NEXTGENERATIONEU (NGEU), funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

CU Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Sage, Supernus, Tolmar and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option

holder of Cardio Diagnostics, Mindpax, LB Pharma, Kuleon Biosciences and Quantic.

M Solmi has received honoraria/has been a consultant for AbbVie, Angelini, Bausch Health, Boehringer Ingelheim, Lundbeck, Otsuka, and Teva.

S Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian ADHD Alliance Resource, the British Association of Psychopharmacology, Healthcare Convention and CCM Group team for educational activity on ADHD, and has received honoraria from Medice.

MI Husain has led contracted research for COMPASS Pathfinder Ltd., and provided consultancy to Mindset Pharma Inc., Psyhed Therapeutics, and Wake Network Inc.

JD Rosenblat has received industry funding for speaker/consultation/research fees from iGan, Boehringer Ingelheim, Janssen, Braxia Health, Braxia Scientific, Allergan, Lundbeck, Sunovion and COMPASS.

L Yatham has been a consultant and/or advisor to or has received honoraria from Allergan, Abbvie, Merck, Sanofi, Sumitomo Pharma, Sunovion, GSK, Gedeon Richter, Intracellular Therapies, Otsuka, Lundbeck, JAMA Pharma, received grant funding from Abbvie and Sumitomo Pharma and served on the Data Monitoring Board for Allergan and Alkermes.

A Cipriani has received honoraria for lectures from Angelini Pharma and Lundbeck Pharma. AC is investigator of an early phase trial about seltorexant in adolescent depression (payment to my institution).

D Moher is a member of the BMJ North American advisory committee.

E Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Alcediag, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work.

M Solmi has received honoraria/has been a consultant for AbbVie, Angelini, Bausch Health, Boehringer Ingelheim, Lundbeck, Otsuka, and Teva.

Other authors have no conflicts of interest to disclose.

Acknowledgements

We thank Gyselle de Geus (Ottawa Hospital Research Institute) for valuable help with literature search and screening.

This work was supported in part by an Academic Scholars Award to MI Husain from the Department of Psychiatry, University of Toronto. MI Husain receives salary support from a Canadian Institutes of Health Research Canada Research Chair.

M Berk is supported by a NHMRC Senior Principal Research Fellowship and Leadership 3 Investigator grant (1156072 and 2017131).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.09.011.

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