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Review Article

Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis

Kwonmok Ko [a,*], Emma I. Kopra [a], Anthony J. Cleare [a,b,c], James J. Rucker [a,b,c]

[a] Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AF, UK
[b] National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, London SE5 8AF, UK
[c] South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham BR3 3BX, UK

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ABSTRACT

Background: Psychedelic therapy shows promise for Major Depressive Disorder, especially when treatment-resistant, as well as life-threatening illness distress. The objective of this systematic review, inclusive of meta-analysis, is to examine recent clinical research on the therapeutic effects of classic psychedelics on depressive symptoms.

Methods: Fourteen psychedelic therapy studies, utilising psilocybin, ayahuasca, or LSD, were systematically reviewed. For the meta-analysis, standardised mean differences were calculated for seven randomised controlled trials.

Results: The systematic review indicated significant short- and long-term reduction of depressive symptoms in all conditions studied after administration of psilocybin, ayahuasca, or LSD, with psychological support. In the meta-analysis, symptom reduction was significantly indicated in three timepoints out of four, including 1-day, 1-week, and 3–5 weeks, supporting the results of the systematic review, with the exception of the 6–8 weeks follow-up point which was less conclusive.

Limitations: The absence of required data for 2 studies necessitated the less precise use of graphical extraction and imputation. The small sample size in all but one study negatively affected the statistical power. None of the studies had long-term follow-up without also utilising the cross-over method, which did not allow for long-term results to be included in the meta-review.

Conclusions: This review indicates an association between psychedelic therapy and significant reduction of depressive symptoms at several time points. However, the small number of studies, and low sample sizes, calls for careful interpretation of results. This suggests the need for more randomised clinical trials of psychedelic therapy, with larger and more diverse samples.

1. Background

The administration of psychedelics for therapeutic use, or psychedelic therapy, is undergoing a renaissance in the mental health field. Classic psychedelics, which are all serotonin 2A receptor partial agonists, include psilocybin, lysergic acid diethylamide [LSD], *N, N*-dimethyltryptamine [DMT] and mescaline. While definitive clinical efficacy has not yet been determined, symptom reduction has been suggested by earlier reviews (Romeo et al., 2020; Wheeler and Dyer, 2020; Galvão-Coelho et al., 2021; Leger and Unterwald, 2021; Kisely et al., 2022; Schimmel et al., 2021).

This category of pharmaceuticals represents a putative new approach to the treatment of depressive disorder. Reviews have been conducted on the application of psychedelics for various psychological conditions, such as depression and anxiety (Muttoni et al., 2019), alcoholism and substance use disorder (DiVito and Leger, 2020), post-traumatic stress disorder [PTSD] (Krediet et al., 2020), and illness-related existential distress (Ross, 2018). All have demonstrated symptom reduction, although the trials themselves were not specifically designed or powered to investigate clinical efficacy definitively. Psychedelics for physical conditions are also being studied, including applications for chronic pain such as phantom limb pain and cluster headache, as reviewed by Castellanos et al. (2020). Research is currently ongoing in chronic, short-lasting unilateral neuralgiform headache attacks (Beckley Psytech

* Corresponding author at: IoPPN, KCL, 16 De Crespigny Park, London SE5 8AB, UK.
E-mail address: kwon.ko@kcl.ac.uk (K. Ko).

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Limited, 2021).

Psychedelic therapy shows promise for MDD, especially when treatment-resistant, as well as distress related to life-threatening diagnoses and terminal illness. Rucker et al. (2016) reviewed 21 early studies (1949–1973) that used psychedelic therapy as a clinical treatment for unipolar mood disorders; whilst acknowledging methodological deficits, the authors found that the majority of subjects showed clinical improvement, suggesting the value of re-examining the therapeutic potential of psychedelic substances. Specifically, analysis of the 19/21 studies with quantifiable outcome data, found that of a total of 423 subjects treated, 335 (79.2 %) experienced some clinician-assessed symptom reduction, more so when dosage was higher and/or models of psychological support were present.

Later reviews have focussed on more recent clinical studies (Romeo et al., 2020; Wheeler and Dyer, 2020; Galvão-Coelho et al., 2021; Leger and Unterwald, 2021; Kisely et al., 2022; Schimmel et al., 2021), and included studies examining the effects of classic psychedelics (psilocybin, LSD, and ayahuasca, dipropyltryptamine) and compounds with secondary psychedelic effects (ketamine and methylenedioxymethamphetamine [MDMA]) on healthy as well as mentally ill subjects. Conditions included obsessive compulsive disorder and mood disorders including distress, both existential and due to degenerative and/or life-threatening illness. In all reviews, significant clinical improvement was demonstrated. Schimmel et al. also included earlier studies in their review (1969–1973), all of which indicated clinical improvement, but were judged to be methodologically flawed, particularly in the absence of a control group. Galvão-Coelho et al. as well as Romeo et al. demonstrated efficacy in short-, medium-, and long-term outcomes; Leger and Unterwald looked at studies in which subjects received multiple doses. Wheeler and Dyer reviewed both qualitative and quantitative research, while Kisely et al. analysed exclusively randomised, double-blind, placebo-controlled trials.

While mechanisms for psychedelic therapy have not yet been determined, a number of possibilities have been identified. These include increased 'insight' (Carhart-Harris et al., 2018), enhanced social cognition and emotional processing (Vollenweider and Preller, 2020), psychological flexibility (Davis et al., 2020; Watts and Luoma, 2020), and mystical experience (Ko et al., 2022). Proposed biological mechanisms include increased neuroplasticity and fronto-limbic activation (Daws et al., 2022; Dos Santos and Hallak, 2020; Artin et al., 2021; De Vos et al., 2021).

Psychedelics seem to be relatively well tolerated, with primarily mild to moderate side effects rarely lasting longer than the acute drug effect; these include anxiety, nausea, mild hypertension and heart rate increase, and a post-dose tension headache (Muttoni et al., 2019). Psychedelics are given intermittently, which reduces the risk of treatment failure due to non-adherence. Additionally, complex psychological disorders that tend to be exacerbated by the social context (e.g., PTSD, substance use disorder, personality disorders) often respond inadequately to standard treatment approaches and may react better to novel therapies (Vargas et al., 2021; Zeifman and Wagner, 2020).

People with treatment-resistant depression [TRD] may benefit from this emerging category of pharmaceuticals (Roseman et al., 2018). There is no current consensus on the definition of TRD, but the most common criteria according to a review of 260 articles by Gaynes et al. (2020) are: 1) failure to respond to at least two antidepressants of different classes; 2) confirmation of adequate dosage; and, 3) a duration of treatment of >4 weeks for each antidepressant. Among those with Major Depressive Disorder [MDD], approximately 30 % are treatment-resistant (Voineskos et al., 2020).

The purpose of this review is to assess recent studies of classic psychedelics for their effects on depressive symptoms. Importantly, this review improves upon previous work by including both open-label studies and randomised controlled trials – and in particular, the largest RCT to date, a recently published large-scale phase 2b trial (Goodwin et al., 2022) – and by utilising a meta-analytic approach to outcome data.

2. Methods

2.1. Searches and study selection

The study protocol is registered at PROSPERO, number CRD42022318972, and follows the PRISMA guidelines (Liberati et al., 2009). The literature search was carried out in Embase, MEDLINE, PsychINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) to include publication dates from January 1990 to March 2022. Search string used was ("psychedelic*" OR "psilocybin" OR "LSD" OR "Lysergic acid diethylamide" OR "ayahuasca" OR "DMT" OR "hallucinogen*" OR "mescaline" OR "peyote" OR "3, 4, 5-trimethoxyphenethylamine") AND ("depress*" OR "distress*"). Study selection was performed by two independent researchers (KK and EK). Any discrepancies were resolved by discussion. The reference lists of selected studies and relevant systematic reviews that emerged from the searches were also reviewed for additional studies. Out of 1091 articles identified through the above searches, 13 were selected. Data from a further article (Goodwin et al., 2022), published after the initial search, was added subsequently to this analysis as it represents the largest clinical trial thus far in the field. For the meta-analysis, in order to reduce heterogeneity, only clinically similar randomised controlled trials were pooled, including comparable dosage and placebo rather than psychiatric medication as the control.

2.2. Inclusion and exclusion criteria

The studies included were selected according to the following criteria: 1) clinical trial in design, including randomised controlled and open-label; 2) adult subjects with depressive disorders and/or distress related to life-threatening diagnoses and terminal illness; 3) subjects received therapeutic clinical application of a classic psychedelic drug (e.g. psilocybin, mescaline, LSD, and DMT/ayahuasca); 4) assessment of treatment response (pre-/post-application) using standard, validated, and internationally recognised instruments such as Beck Depression Inventory or equivalent; and, 5) published in English in a peer-reviewed journal. Studies with healthy volunteers and application of micro-doses were excluded.

2.3. Quality assessment

Newcastle Ottawa Quality Modified Scale (Wells et al., 2000) was used to assess the qualities of open-label uncontrolled trials, and Revised Cochrane Risk of Bias Tool for Randomised Trials (Sterne et al., 2019) was used for randomised trials. Risk of bias [see Supplementary Tables S1, S2] was assessed independently by each of two reviewers according to the following characteristics: blinding, selective outcome reporting, randomisation sequence generation, completeness of outcome data, and other sources of bias. This assessment was performed by primary reviewer (KK) and verified by secondary reviewer (EK). First and second reviewers attempted to reach consensus; when not possible, an independent reviewer was consulted, and discrepancies were resolved by discussion.

2.4. Data extraction

The primary outcome of interest was the treatment effect on depressive symptoms, as indicated by pre-/post-scores of symptomatology using standard measures, as well as the statistical significance of results. Instruments used to measure treatment outcome and length of follow-up were also included. Data were collected regarding the treatment modality in terms of substance administered, dosage, number of dosing sessions, and model of support provided as well as demographic data including diagnosis, diagnostic manual used, and subject age. This extraction was performed by both reviewers. Any discrepancies were resolved by discussion.

For the meta-analysis, clinically similar randomised controlled trials in which the means and standard deviations of experimental and control groups for measures of depression were extracted. In Goodwin et al. (2022), the 'medium dose' group of 10 mg was not analysed as a medium dose was not included in any other of the studies. Corresponding authors were contacted for raw data when not available in the article [see Acknowledgements]. When researchers were not able to provide the data (Goodwin et al., 2022; Grob et al., 2011), means were obtained via graphical extraction utilising Plotdigitizer (pOrbital, 2022); standard deviations were imputed according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). For Goodwin et al. (2022), the formula used was, square root of N × (upper 95 % CI - lower 95 % CI) / 3.92. In the case of Grob et al. (2011), as upper and lower CIs were not available, the same value from other studies was applied for approximation according to the methodology of Furukawa et al. (2006).

2.5. Data analysis

To perform the meta-analysis, RevMan 5.4.1 (Cochrane, 2022) was utilised. Standardised mean differences [SMD] for depressive scores were utilised to determine effect size. Analyses were conducted with random-effect model. Pooled effect size was considered significant for a $<.05$ p-value. Heterogeneity was estimated with Q statistics and between study variance was estimated utilising Tau^2; cochrane's Q statistics tested whether this was different from 0. All I^2 values, proportions of total study variance attributable to between-study variance, were above 75 %, indicating marked heterogeneity between trials.

2.6. Ethical review

Review by an ethics board was not necessary, as this was an assessment of published studies.

3. Results

3.1. Study categorisation

A consort flow chart was developed to depict details of the study selection process, according to the PRISMA guidelines (Liberati et al., 2009) [see Fig. 1]. Fourteen studies were identified for systematic review based on the inclusion criteria, 10 of which were randomised (Carhart-Harris et al., 2021; Davis et al., 2021; Gukasyan et al., 2022; Goodwin et al., 2022; Palhano-Fontes et al., 2019; Ross et al., 2016; Agin-Liebes et al., 2020; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011) and the other 4 open-label (Carhart-Harris et al., 2016; Carhart-Harris et al., 2018; Sanches et al., 2016; Anderson et al., 2020). Seven of the randomised controlled trials were included in the meta-analysis (Davis et al., 2021; Goodwin et al., 2022; Palhano-Fontes et al., 2019; Ross et al., 2016; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011). Of the remaining three, two (Agin-Liebes et al., 2020; Gukasyan et al., 2022) were long-term follow-ups of already included studies, and the third (Carhart-Harris et al., 2021) was undertaken using an antidepressant control rather than placebo.

Of these 14 studies, 8 targeted Major Depressive Disorder (Carhart-Harris et al., 2021; Sanches et al., 2016; Davis et al., 2021; Gukasyan et al., 2022; Goodwin et al., 2022; Palhano-Fontes et al., 2019; Carhart-Harris et al., 2016; Carhart-Harris et al., 2018). Davis et al. and Gukasyan et al. utilised the same dataset with the latter a 12-month follow-up of patients included in the former. Treatment-resistance was the focus in Palhano-Fontes et al. (2019), Goodwin et al. (2022), Carhart-Harris et al. (2016), and Carhart-Harris et al. (2018). The latter two studies drew data from the same population, for which Carhart-Harris et al. (2018) conducted a 6-month follow-up.

The remaining 6 studied illness-related distress. Three trials (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016) recruited those with anxiety, depression, and/or adjustment disorder related to life-threatening cancer diagnosis; a long-term follow-up study of Ross et al. was conducted by Agin-Liebes et al. (2020). Gasser et al. (2014) included additional conditions such as coeliac disease, Parkinson's disease, and Bechterew's disease, among others. In a study of long-term AIDS survivors among homosexual males, Anderson et al. (2020), the focus was moderate-to-severe demoralization.

Three types of psychedelics were included, with 1 utilising LSD (Gasser et al., 2014), 2 ayahuasca (Sanches et al., 2016; Palhano-Fontes et al., 2019), and the remaining 11 psilocybin (Agin-Liebes et al., 2020; Anderson et al., 2020; Carhart-Harris et al., 2016; Carhart-Harris et al., 2018; Carhart-Harris et al., 2021; Davis et al., 2021; Griffiths et al., 2016; Grob et al., 2011; Goodwin et al., 2022; Gukasyan et al., 2022; Ross et al., 2016). Among the psilocybin studies, the majority dosed according to body mass, ranging from 0.2 mg/kg to 0.43 mg/kg [reported as 30 mg/70 kg], while Carhart-Harris et al. (2016), Carhart-Harris et al. (2018), Carhart-Harris et al. (2021), and Goodwin et al. (2022) administered 10 mg–25 mg, irrespective of body mass [see

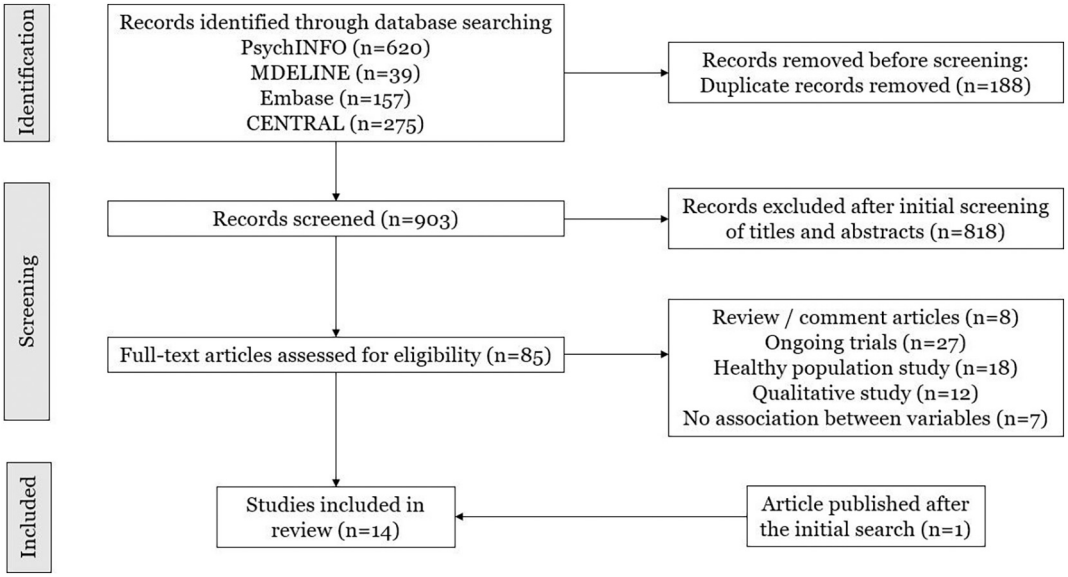

Fig. 1. Consort flow chart.

Tables 1, 2, 3 and 4].

Studies of psychedelic therapies must assess isolated efficacy, unaffected by prior use of other psychoactive medications. The reason, putatively, is that inhibition of SERT by antidepressants is likely, indirectly, to lead to down regulation of the 5HT2A receptor postsynaptically. If true, that would be likely to reduce the intensity of the subjective effect of psilocybin, given that this is almost entirely due to functionally selective partial agonism at 5HT2A. The washout period, to eliminate similar psychiatric medications from subjects' systems prior to trial, widely varied among the studies reviewed. While many used a 2-week cessation period, others included a reduction in half-life of the medication, an unspecified tapering off, or designated use of psychotropic medication as an exclusion criterion for the study.

Various models of support were provided pre-, during, and post-psychedelic therapy sessions. During the treatment, nondirective support was provided in every case. Various models of support, including formation of therapeutic rapport, eclectic and/or integrative therapies, were given pre- and post-treatment by a majority of trials, though some did not specify. [See Table 5.]

3.2. LSD study

In a randomised and double-blinded active placebo-control pilot study by Gasser et al. (2014), 12 participants with anxiety associated with life-threatening diagnoses were included for the purpose of examining safety and efficacy of LSD-assisted psychotherapy. The experimental group (n = 8) was administered 200 μg of LSD in 2 sessions with 2 to 3 weeks between the sessions, while the placebo group (n = 4) was administered 2 sessions of 20 μg with an open-label crossover to two sessions of 200 μg of LSD. Data from one active placebo participant was ultimately excluded from analysis due to misdiagnosis. At 2-month follow-up, the mean HADS-D score was reduced from 10.0 at baseline to 7.5 in the experimental group (n = 8), versus 9.3 to 8.7 in the placebo group (n = 3), which later dropped to 4.7 2-month post-crossover. At 12 months post full dose, crossover arm included, the mean HADS-D score was 7.6 (n = 9 due to drop-outs). No tests of significance were conducted since these measures were secondary outcomes.

3.3. Ayahuasca studies

Two studies utilised ayahuasca to investigate its effects on recurrent MDD (Sanches et al., 2016) and TRD (Palhano-Fontes et al., 2019). Sanches et al. conducted an open-label trial with 17 participants each of whom was administered a single dose of 120 to 200 mL of ayahuasca (2.2 mL/kg). Palhano-Fontes et al. conducted a parallel-arm, double-blind randomised placebo-controlled trial in 29 subjects with unipolar MDD with insufficient response to at least 2 antidepressants of different classes. Subjects were given a single dose of either 1 mL/kg of placebo (n = 15) or ayahuasca (n = 14) adjusted to contain 0.36 mg/kg of N, N-DMT.

Both studies demonstrated significant clinical effects of ayahuasca for symptomatic relief of depression. In Sanches et al. administration of ayahuasca resulted in significant decrease of both HAM-D and MADRS scores from day 1 to day 21 ($p < .001$). Specifically, mean baseline score of HAM-D scale was 19.24 (SD = 5.52), which dropped to 7.56 at day 21. Palhano-Fontes et al. found large between-group effect sizes in changes in HAM-D score at day 7 (Cohen's $d = 0.98$; 95 % CI 0.21 to 1.75) and MADRS score at day 1 (Cohen's $d = 0.84$; 95 % CI 0.05 to 1.62), 2 (Cohen's $d = 0.84$; 95 % CI 0.05 to 1.63), and 7 (Cohen's $d = 1.49$; 95 % CI 0.67 to 2.32). The response rate for HAM-D was 64 % in ayahuasca group and 27 % in placebo group ($p < .04$).

Table 2
Ayahuasca studies.

Study	Population	Design	Substance and dose	Main results
Sanches et al. (2016)	n = 17 Recurrent MDD - unresponsive to at least one antidepressant medication	Open-label	1 oral dose (2.2 mL/kg)	3-week (n = 17): Significant reduction of HAM-D (19.24 to 7.56) and MADRS (25.6 to <10[a]) scores ($p < .001$)
Palhano-Fontes et al. (2019)	n = 29 Moderate-to-severe MDD (HAM-D ≥ 17) including TRD (failure of 2 courses of medication / differing classes)	Parallel-arm double-blind randomised controlled trial	Treatment group (n = 14): 1 oral dose (1 mL/kg) Placebo group (n = 15): 1 oral dose of placebo (1 mL/kg)	7-day (treatment n = 14; placebo n = 15): Significantly large between-group effect size in changes of HAM-D (Cohen's d = 0.98; 95 % CI 0.21–1.75) and MADRS (Cohen's d = 1.49; 95 % CI 0.67–2.32) score

MDD: Major Depressive Disorder; TRD: Treatment-Resistant Depression; HAM-D: Hamilton Depression Rating Scale; MADRS: The Montgomery–Åsberg Depression Rating Scale.
[a] Specific value was unreported, but was indicated as <10 on a graph [Fig. 1 in original article].

3.4. Psilocybin studies

Eight clinical trials investigating the clinical efficacy of psilocybin were included in this review. Four were on MDD, including three randomised-controlled (Davis et al., 2021; Carhart-Harris et al., 2021; Goodwin et al., 2022) and one open-label (Carhart-Harris et al., 2016); two of these (Carhart-Harris et al., 2016; Goodwin et al.) had a TRD-specific focus. Two follow-up studies were also generated: Gukasyan et al. (2022) at 12 months following Davis et al. and Carhart-Harris et al. (2018) at 6 months following Carhart-Harris et al. (2016). The remaining 4 clinical trials targeted illness-related distress (Ross et al.,

Table 1
LSD study.

Study	Population	Design	Substance and dose	Main results
Gasser et al. (2014)	n = 12 Anxiety associated with life-threatening diseases (STAI >40 on either the state or trait subscale)	Double-blind, randomised, active placebo-controlled pilot study	Treatment group (n = 8): 2 oral doses (200 μg), 2–3 weeks apart Placebo group (n = 4): 2 oral doses (25 μg), 2–3 weeks apart	2-month (n = 11): HADS-D reduced from 10.0 at baseline to 7.5 at 2 months in the experimental group (n = 8), and from 9.3 to 8.7 in the control group (n = 3) 12-month (n = 9; cross-over arm included): Reduction of HADS-D sustained at 7.6 (no test of significance conducted[a])

STAI: The State-Trait Anxiety Inventory; HADS-D: Hospital Anxiety and Depression Scale.
[a] HADS-D used for secondary clinical outcome.

Table 3
Psilocybin studies on depressive disorders.

Study	Population	Design	Substance and dose	Main results
Carhart-Harris et al. (2021)	n = 59 MDD (17-item HAM-D ≥ 17; moderate-to-severe)	Double-blind randomised controlled trial	Psilocybin group (n = 30): Two (25 mg) sessions, 3 weeks apart, 6 weeks placebo + psychological support Escitalopram group (n = 29): Two low-dose psilocybin (1 mg) sessions, 3 weeks apart, 6 weeks daily oral escitalopram (10 mg) + psychological support	6-week: no significant between-group difference in mean change of QIDS SR-16 score for psilocybin (−8.0) and escitalopram (−6.0) group ($p = .017$) Significant difference in remission rates of QIDS for psilocybin (57 %) over escitalopram (28 %) group Secondary outcome favoured psilocybin generally for HAM-D, MADRS, and BDI-1A
Davis et al. (2021)*	n = 27 MDD (GRID-HAMD ≥17; moderate to severe)	Randomised, waiting list-controlled clinical trial	Treatment group (n = 15): Two sessions (20 and 30 mg/70 kg), 1.6 weeks apart on average Placebo group (n = 12): 8-week delay, followed by same intervention as treatment group	1-week (treatment n = 13; placebo n = 11): significant between-group difference ($p < .001$) in mean GRID-HAMD scores between treatment (8.0) and placebo (23.8) group 4-week (N = 24): significant GRID-HAMD scores difference maintained ($p < .001$) between treatment (8.5) and placebo (23.5) group; response and remission rate 71 % and 54 %
Gukasyan et al. (2022)*	As above	As above	As above	1-, 3-, 6-, and 12-month (n = 24; crossover arm included): large decrease in GRID-HAMD scores (Cohen's d = 2.3, 2.0, 2.6, and 2.4, respectively). 12-month: response and remission rate 75 % and 58 %.
Carhart-Harris et al. (2016)**	n = 12 MDD (21-item HAM-D ≥ 16; moderate-to-severe) including TRD (failure of 2 courses (minimum 6 weeks) of medication / differing classes)	Open-label	Two psilocybin sessions (10 mg and 25 mg), 7 days apart	1-week: marked reduction in QIDS at (Cohen's d = 2.2, $p < .001$) 5-week: marked reduction in QIDS (Cohen's d = 2.3, $p < .001$); response and remission rate at 45 % and 20 % 3-month (n = 12): reduction in QIDS remained positive (Cohen's $d = 1.5$, $p < .001$)
Carhart-Harris et al. (2018)**	n = 20 As above	As above	As above	6-month (n = 19): QIDS score reduction (Cohen's $d = 1.4$)
Goodwin et al. (2022)	n = 233 Single or recurrent MDD (clinical assessment, medical records, and MINI score) including TRD (failure of 2–4 antidepressant trials, with adequate dosage and duration)	Double-blind randomised controlled trial	Each group (1 mg, 10 mg, and 25 mg) received one session	3-week (n = 72 in each 1 mg, 10 mg, and 25 mg group): least-squares mean change of MADRS total score − 12.0 in 25 mg group, −7.9 in 10 mg group, and − 5.4 in 1 mg group, in which difference between 25 mg group and 1 mg group (−6.6) was significant ($p < .001$)

MDD: Major Depressive Disorder; HAM-D: Hamilton Depression Rating Scale; QIDS: Quick Inventory of Depressive Symptomatology; MADRS: Montgomery–Åsberg Depression Rating Scale; BDI: Beck Depression Inventory; GRID-HAMD: GRID-Hamilton Depression Rating Scale; TRD: Treatment-Resistant Depression; MINI: Mini International Neuropsychiatric Interview.

* Gukasyan et al. (2022) is a 12-month follow-up to Davis et al. (2021).

** Carhart-Harris et al. (2018) is a 6-months follow-up to Carhart-Harris et al. (2016).

2016; Griffiths et al., 2016; Grob et al., 2011; Anderson et al., 2020); in follow-up to Ross et al., Agin-Liebes et al. (2020) collected follow-up data within two ranges, 2.3–4.5 and 3.5–5.5 years.

All studies of MDD demonstrated positive results. Twelve TRD subjects were enrolled in an open-label feasibility study of psilocybin with psychological support (Carhart-Harris et al., 2016). Subjects had a diagnosis of MDD ranging from moderate-to-severe, and TRD was defined as failure of two courses (minimum 6 weeks) of antidepressants from differing classes. All participants were given increasing doses of 10 and 25 mg psilocybin, 7 days apart. Short-term results included significant reduction of QIDS-SR16 scores (mean; SD) at 1-week (7.4; 4.9) 2-week (6.3; 4.6]), 3-week (6.4; 5.1), 5-week (8.2; 5.4) and 3-month (10.0; 6.0) compared to baseline (19.2; 2.0) (all p-values<.005). Secondary outcome measures of BDI, MADRS, and HAM-D also showed significant decrease. Complete remission was met by 8 of the 12 participants at 1 week; at 3 months, 5 remained in complete remission while an additional 2 continued to show at least some response.

In a 6-month long-term follow-up study (Carhart-Harris et al., 2018), an additional 8 subjects were included and data from 19 who completed all assessments were reported. Marked reductions in QIDS-SR16 were observed at 1 week (Cohen's $d = 2.2$), and 5 week (Cohen's $d = 2.3$), which remained positive at 3 month (Cohen's $d = 1.5$), and 6 months (Cohen's $d = 1.4$) (all-p values<.001). Of 9 subjects who showed response at 5 weeks, 6 maintained response at 6 months.

The largest psilocybin clinical trial on TRD to date (Goodwin et al., 2022) was recently published, with participants recruited in 22 sites in 10 countries of Europe and North America. Two hundred and thirty-three subjects were randomised into 25 mg, 10 mg, and 1 mg psilocybin therapy arms in a 1:1:1 ratio. All received psychological support. After a single-dose session, they were followed up to 12 weeks. From baseline to 3-week, the least-squares mean change (95 % CI) of MADRS total score was −12.0 (−14.6 to −9.3) in the 25 mg group, compared to −7.9 (−10.6 to −5.2) in the 10 mg and − 5.4 (−8.1 to −2.7) in the 1 mg groups, in which the difference between 25 mg and 1 mg group was significant (−6.6 (−10.2 to −2.9); $p < .001$). However, the difference between the 10 mg and 1 mg group was not significant (−2.5 (−6.2 to 1.2); $p < .184$). Response and remission rates for the 25 mg group was 36.7 % and 29.1 %, for the 10 mg group 18.7 % and 9.3 %, and for the 1 mg group 17.7 % and 7.6 %, respectively. Results were sustained in the 25 mg group up to 12-weeks, at which point the response rate was 20.3 % (OR, 2.2 [95 % CI, 0.9–5.4]).

Carhart-Harris et al. (2021) conducted a double-blinded randomised controlled trial comparing the clinical efficacy of psilocybin and escitalopram, a selective serotonin-reuptake inhibitor [SSRI]. Fifty-nine participants with chronic moderate-to-severe MDD were randomly assigned to either psilocybin (n = 30) or escitalopram (n = 29) groups.

Table 4
Psilocybin studies on illness related distress.

Study	Population	Design	Substance and dose	Main results
Grob et al. (2011)	n = 12 Patients with advanced-stage anxiety	Double-blind, randomised, placebo-controlled, cross over trial study	Treatment group (n = 6): 1 dose of psilocybin (0.2 mg/kg), and then niacin (250 mg) second session, after several weeks Placebo group (n = 6): 1 dose of niacin (250 mg), and then psilocybin (0.2 mg/kg) second session, after several weeks	2-week (treatment n = 6; placebo n = 6): no appreciable change in placebo group; in treatment group, reduction of BDI (10.0) from baseline (16.1) observed (no test of significance indicated) 1-month (n = 11, including cross-over arm): "almost 30 %" drop in BDI compared to baseline ($p = .05$) 6-month (n = 8, including cross-over arm): reduction of BDI score sustained ($p < .03$)
Griffiths et al. (2016)	n = 51 Patients with life-threatening cancer and depression and/or anxiety	Double-blind, randomised, active placebo-controlled crossover trial	Treatment group (n = 26): 1 oral dose (22 or 30 mg/70 kg), and 1 oral low-dose (1 or 3 mg/70 kg), 7 weeks apart Placebo group (n = 25): 1 oral low-dose (1 or 3 mg/70 kg), and 1 oral dose (22 or 30 mg/70 kg), 7 weeks apart	5-week (treatment n = 26; placebo n = 25): compared to baseline, treatment group with significantly lowered score of GRID-HAMD-17 (Cohen's $d = 1.30$, $p < .001$) and HAM-A (Cohen's $d = 1.23$, $p < .001$) than placebo 6-month (n = 48; crossover arm included): sustained significant reduction of GRID-HAMD-17 (Cohen's $d = 2.98$, $p < .001$) and HAM-A (Cohen's $d = 3.40$, $p < .001$) scores
Anderson et al. (2020)	n = 18 Older long-term AIDS survivor gay men with demoralization (Demoralization Scale-II ≥ 8; moderate-to-severe)	Open-label	1 oral dose (0.3 mg/kg) cohort 1; 1 oral dose (0.36 mg/kg), cohorts 2 and 3	3-week (n = 18): significant reduction of CESD-R score compared to baseline (mean reduction = −8.94 [SD = 14.73]; Cohen's $d = 0.74$) 3-month (n = 18): sustained reduction of CESD-R score (mean reduction = −8.89 [SD = 12.02]; Cohen's $d = 0.71$)
Ross et al. (2016)*	n = 29 Patients with life-threatening cancer and anxiety or depression (HADS ≥8)	Double-blind, randomised, placebo-controlled, cross-over trial	Treatment group (n = 14): 1 oral psilocybin dose (0.3 mg/kg), and then 1 oral niacin dose (250 mg), 7 weeks apart Placebo group (n = 15): 1 oral niacin dose (250 mg), and then 1 oral psilocybin dose (0.3 mg/kg), 7 weeks apart	7-week (treatment n = 14; placebo n = 15): significant reduction ($p < .05$) of HADS T, HADS A, HADS D, BDI, STAI S, STAI T score for treatment group, compared to placebo; BDI response rate 83 % in treatment group vs 14 % in placebo group
Agin-Liebes et al. (2020)*	n = 16 (avg 3.2 years); n = 14 (avg 4.5 years) As above	As above	As above	At all timepoints (n = 16, avg. 3.2 years; n = 14, avg. 4.5 years): sustained significant reduction ($p < .05$) of HADS T, HADS A, HADS D, BDI, STAI S, and STAI T; response and remission rates for BDI 57 % and 50 %, and for HADS-D 79 % and 79 %, respectively

BDI: Beck Depression Inventory; GRID-HAMD: GRID-Hamilton Depression Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; CESD-R: Center for Epidemiological Studies Depression Scale-Revised; HADS: Hospital Anxiety and Depression Scale; STAI: The State-Trait Anxiety Inventory.
* Agin-Liebes et al. (2020) is a long-term follow up of Ross et al. (2016).

The former group was administered two doses of 25 mg of psilocybin 3 weeks apart, followed by a daily placebo for 6 weeks; the latter group received 1 mg of psilocybin 3 weeks apart, and a 10 mg of daily oral escitalopram for 6 weeks. The mean change in QIDS-SR-16 at 6 weeks compared to baseline score was −8.0 in psilocybin group, compared to −6.0 in escitalopram group; no significant between-group difference was detected ($p = .17$). However, the secondary outcome measures at 6 weeks compared to baseline generally favoured psilocybin over escitalopram (HAM-D-17: −10.5 vs −5.1, 95 % CI = −8.2 to −2.4; MADRS: −14.4 vs −7.2, 95 % CI = −12.1 to −2.4; BDI-1A: −18.4 vs −10.8, 95 % CI = −13.3 to −1.8; all values psilocybin and escitalopram, respectively). However, the confidence intervals for these between-group differences were unadjusted for multiple comparisons; hence, no definitive conclusion can be drawn.

Davis et al. (2021) also conducted a randomised psilocybin trial for moderate-to-severe MDD, which was controlled by waitlist. A total of 27 subjects were randomly assigned to either immediate (n = 15) or delayed treatment condition (n = 12). The former group was given two psilocybin sessions approximately 2 weeks apart (20 mg and 30 mg per 70 kg, respectively). The delayed treatment group was given the same treatment 8 weeks later. Intervention and post-session assessments were completed by 24 participants. A significant between-group difference ($p < .001$) was detected between the mean and standard deviation of GRID-HAMD scores for immediate treatment group (n = 13) at weeks 1 (8.0; 7.1) and 4 (8.5; 5.7), compared to scores of delayed treatment group (N = 11) at corresponding weeks of 5 (23.8; 5.4) and 8 (23.5; 6.0). Large effect sizes were detected at weeks 5 (Cohen's $d = 2.5$; 95 % CI, 1.4 to 3.5; $p < .001$) and 8 (Cohen's $d = 2.6$; 95 % CI, 1.5 to 3.7; $p < .001$). A limitation to this study design is the nocebo effect of waitlist which tends to artificially increase effect sizes. A 12-month follow-up analysis was conducted by Gukasyan et al. (2022), with 100 % participation of subjects in all follow-up visits. Compared to baseline, a large decrease in GRID-HAMD scores was detected at 1-, 3-, 6-, and 12-month follow-up (Cohen $d = 2.3$, 2.0, 2.6, and 2.4, respectively). Response and remission rates were 71 % and 54 % at 1 month (Davis et al., 2021), and 75 % and 58 % at 12 months, respectively (Gukasyan et al., 2022).

Illness-related distress and the effects of psilocybin assisted therapy was investigated in clinical trials by Ross et al. (2016), Griffiths et al. (2016), Grob et al. (2011), and Anderson et al. (2020), while Agin-Liebes et al. (2020) conducted a long-term follow-up to Ross et al.; all yielded generally positive results. One of the earliest modern pilot trials of this kind was conducted by Grob et al. to explore the safety and efficacy of psilocybin. Twelve subjects were selected who had a diagnosis of advanced-stage cancer plus at least one of the following: anxiety disorder due to cancer, generalised anxiety disorder, adjustment disorder with anxiety, and/or acute stress disorder. They were randomised into treatment (n = 6) and placebo (n = 6) groups; the former received psilocybin (0.2 mg/kg) in the first session and niacin (250 mg) in the second while the latter received the same dose of both but in opposite order, with "several weeks" [undefined by researchers] between sessions. The treatment group saw a reduction of BDI score from 16.1 at baseline to 10.0 at 2 weeks. At 1 month, nearly 30 % drop in BDI score

Table 5
Accompanying models of support.

Study	Therapy content		
	Pre-treatment	Treatment	Post-treatment
Anderson et al. (2020)	Therapeutic relationship and Supportive Expressive Group Therapy (3 group and 1 individual therapy sessions)	Nondirective Support	4–6 group and 1 individual therapy sessions
Agin-Liebes et al. (2020)	(Follow-up to Ross et al., 2016)		
Carhart-Harris et al. (2016)	Therapeutic relationship (1 preparation visit)	Nondirective support	Integrative (2 sessions in person (one day and one week post dosing; second session optional))
Carhart-Harris et al. (2018)	(Follow-up to Carhart-Harris et al., 2016)		
Carhart-Harris et al. (2021)	Therapeutic relationship (1 preparation visit)	Nondirective support	Integrative (3 in-person sessions (one day after each dosing and three weeks after second dosing); and 6 optional integration telephone/video calls)
Davis et al. (2021)	8 h of preparation meetings	Nondirective support	8 × 1-2 h in-person integration/follow up sessions, 4 of which before primary outcome (1 day & 1 week after each dosing), and rest at subsequent follow ups (1, 3, 6, 12 month)
Gasser et al. (2014)	2 preparatory psychotherapy sessions	Nondirective support (Brief support, focus on inward exploration, 2 investigators, private practice setting)	Integrative (3 × 60-90 min sessions)
Griffiths et al. (2016)	Therapeutic relationship (2 or more pre-dosing meetings (mean = 3))	Nondirective support (2 therapists)	2 or more meetings between dosing (mean = 2.7); 2 or more meetings after second dosing (mean = 2.5)
Grob et al. (2011)	Therapeutic relationship (amount not specified)	Nondirective support (Brief support, focus on inward exploration, therapy team present, in a hospital clinical research unit)	(Follow-up meetings mentioned, amount not specified)
Goodwin et al. (2022)	Minimum of 3 preparation visits	Nondirective support	Safety assessment on dosing day and two integration sessions, Day 2 and Week 1
Gukasyan et al. (2022)	(Follow-up to Davis et al., 2021)		
Palhano-Fontes et al. (2019)	No formal preparation meetings besides clinical evaluation at screening including 'anamneses'	Nondirective support	No formal integration meetings besides 'debriefing' once psychedelic effects ceased on dosing day
Ross et al. (2016)	Eclectic	Nondirective support (Psychotherapy, emphasis on meaning making, 2 therapists, comfortable room with a couch and music available)	Eclectic
Sanches et al. (2016)	No formal preparation except for 'detailed information regarding the effects of ayahuasca' provided prior dosing	Nondirective support	No formal integration

was observed ($p = .05$), which was sustained at 6 months ($p = .03$).

A clinically similar crossover randomised controlled trial was conducted by Ross et al. (2016), in which 29 subjects with cancer-related anxiety and depression were randomised into psilocybin-then-niacin (n = 14) and niacin-then-psilocybin (n = 15) groups. Dosage was 0.3 mg/kg for psilocybin and 250 mg for niacin, with a 7-week interval. At 7 weeks, prior to second dosage, the treatment group showed 83 % response rate according to BDI, compared to 14 % in placebo group. Agin-Liebes et al. (2020) conducted a long-term follow-up at two timepoints, which averaged 3.2 (n = 16) and 4.5 years (n = 14) post-trial (Ross et al.). Significant reduction of HADS A, HADS D, HADS Total, STAI State Anxiety, STAI Trait Anxiety, BDI was maintained (all p-values < .05), over the course of all follow-up timepoints. The response and remission rates for BDI were 57 % and 50 %, and for HADS-D were 79 % and 79 %, respectively.

Griffiths et al. (2016) conducted a randomised, double-blind, crossover trial of 51 patients with life-threatening cancer diagnosis who had anxiety and depression symptoms. Participants were divided into two groups, immediate-treatment (n = 26; initial high dose of 22 or 30 mg/70 kg and 5-week very low dose of 1 or 3 mg/70 kg) and delayed-treatment (n = 25; administered same doses in the reverse sequence). At 5 weeks, prior to crossover, the immediate-treatment group had a significantly lower score of GRID-HAMD-17 (Cohen's $d = 1.30$, $p < .001$) and HAM-A (Cohen's $d = 1.23$, $p < .001$). Secondary measures were congruent (BDI: Cohen's $d = 0.81$, $p < .01$; HADS-D: Cohen's $d = 0.56$, $p < .05$; STAI-Trait Anxiety: Cohen's $d = 0.60$, $p < .05$). The response and remission rates, respectively, in the immediate-treatment group were 92 % and 60 % compared to 32 % and 16 % in the delayed-treatment group. Of the 48 participants who were included in the 6-month follow-up, reduction of GRID-HAMD-17 (Cohen's $d = 2.98$, $p < .001$) and HAM-A (Cohen's $d = 3.40$, $p < .001$) scores remained significant. The response and remission rates were 68 % and 65 %, respectively.

An open-label study of psilocybin-assisted group therapy for long-term AIDS survivors with moderate-to-severe demoralization was undertaken by Anderson et al. (2020). The study included eighteen males (mean age = 59.2 years) who were provided with 8–10 group therapy sessions and one session of psilocybin (0·3–0·36 mg/kg) administration. While the primary clinical measure for this study was demoralization, viewed as a form of distress based on life-threatening illness, for the nature of this review, the secondary measure of depression (Center for Epidemiological Studies Depression Scale-Revised [CESD-R]) is meaningful. Compared to baseline (2.06 [SD = 13.79]), there was a significant reduction of the score at both post-treatment (mean reduction = −8.94 [SD = 14.73]; Cohen's $d = 0.74$; 95 % CI = 0.12 to 1.41) and 3-month follow-up (mean reduction = −8.89 [SD = 12.02]; Cohen's $d = 0.71$; 95 % CI = 0.21 to 1.27).

3.5. Meta-analysis

Standardised mean differences were calculated at day 1 (n = 4 studies; SMD = −1.36, 95 % CI: −2.50 to −0.22; $p = .02$), week 1 (n = 3; SMD = −1.37, 95 % CI: −2.41 to −0.34; $p = .009$), weeks 3–5 (n = 3; SMD = −3.12, 95 % CI: −6.19 to −0.04; $p = .05$), and weeks 6–8 (n = 3; SMD = −1.52, 95 % CI: −3.55 to 0.51; $p = .14$), demonstrating a significant reduction of depressive symptoms at all timepoints with the exception of weeks 6–8 [see Figs. 2 and 3].

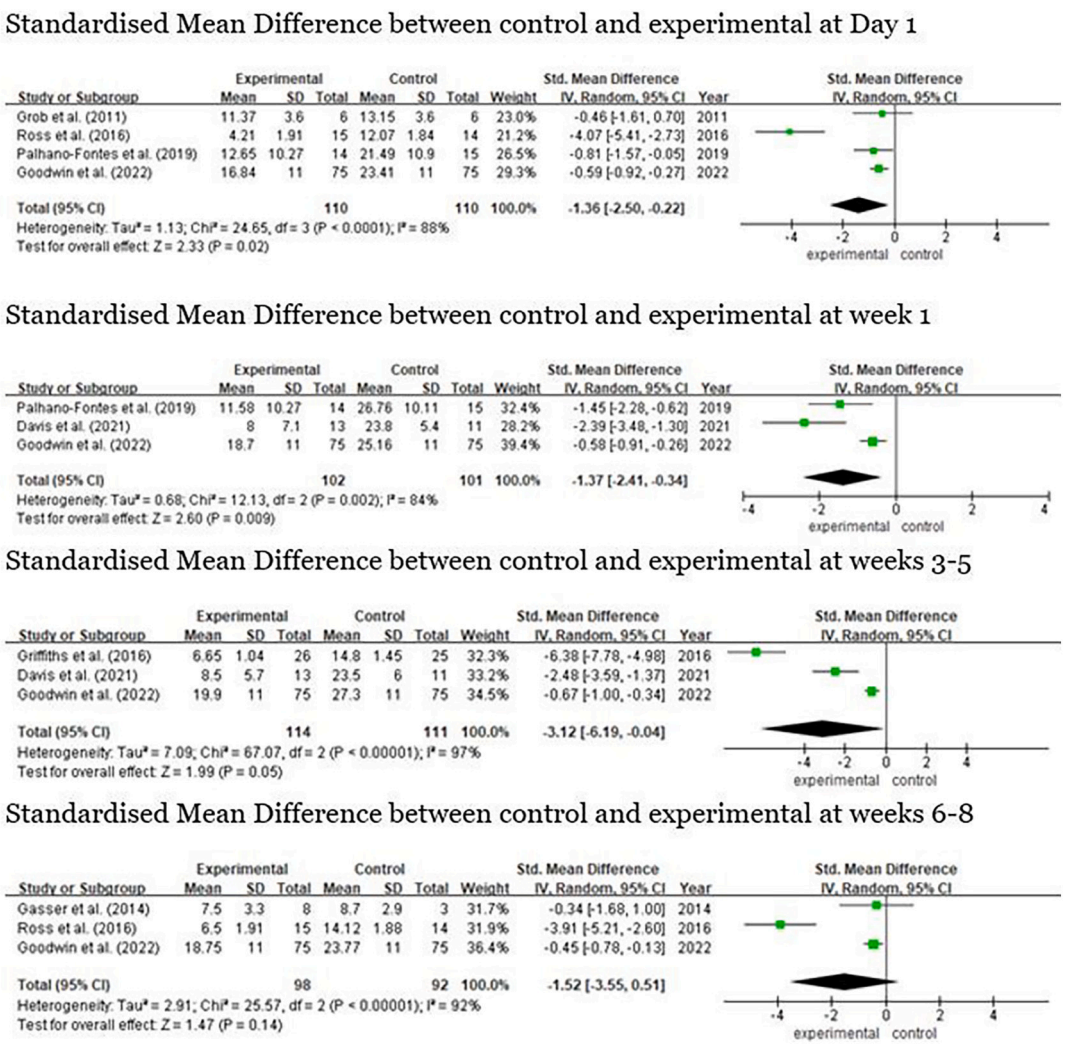

Fig. 2. Standardised mean differences between experimental and control at day 1, week 1, weeks 3–5, and weeks 6–8.

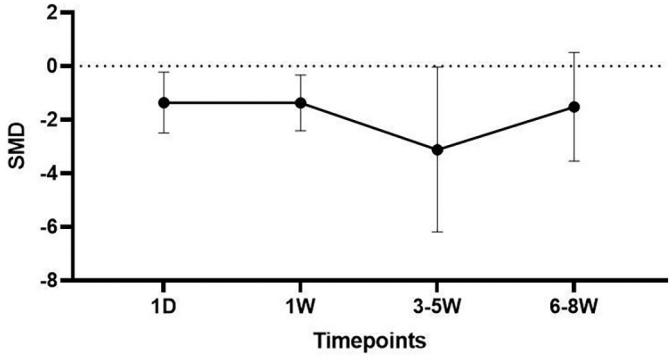

Fig. 3. Overall standardised mean differences between experimental and control at each time point of depressive score.

4. Discussion

The objective of this systematic review, inclusive of meta-analysis, was to analyse studies on the use of psychedelic therapies for the reduction of depressive symptoms. A total of 14 studies were analysed, which included 11 clinical trials and 3 long-term follow-ups; seven randomised controlled trials were included for the meta-analysis. The trials administered classic psychedelic substances to an adult population with depressive disorders, including treatment-resistant depression, and/or distress related to life-threatening diagnoses and terminal illness.

Overall, the results of the 14 studies included in the systematic review indicated significant short- and long-term reduction of depressive symptoms in all conditions studied after administration of psilocybin, ayahuasca, or LSD, with psychological support. In the meta-analysis of 7 randomised controlled trials, symptom reduction was significantly indicated in three timepoints out of four, including 1-day, 1-week, and 3–5 weeks, supporting the results of the systematic review, with the exception of the 6–8 weeks follow-up point which was less conclusive.

As the resurgence of psychedelic research is still in its infancy, there is a lack of long-term follow-up on double-blind randomised controlled trials. Of the three long-term follow-up trials (Agin-Liebes et al., 2020; Carhart-Harris et al., 2018; Gukasyan et al., 2022) in this review, Agin-Liebes et al. showed the longest results to date, with two follow-up time points at an average of 3.2 and 4.5 years. The results at both time points indicated sustained efficacy of psilocybin treatment.

Definitive clinical efficacy of psychedelic therapy for depressive symptoms has not yet been demonstrated, despite the fact that it is referenced in a number of studies. Most studies to date are small-scale and tend to have blinding and other issues of bias, including drug versus control expectancy effects. Nevertheless, our meta-analysis suggests robust symptom reduction in the short- to medium-term, and early indications are that this effect may persist into the longer-term.

This review has several key strengths. It is the first meta-analysis in a

systematic review of psychedelic therapy trials for depressive symptoms which includes a large-scale RCT (Goodwin et al., 2022), thereby considerably adding to the evidence base. Analysis at multiple time-points also contributes to the value of this analysis demonstrating results from acute to medium-term. While this is not a definitive demonstration of clinical efficacy, it strengthens the accumulating evidence base.

These results are significant for several reasons. Psychedelic therapy can generally be administered intermittently, while standard antidepressants often require a longer-term course of treatment. In Carhart-Harris et al. (2021), for example, psilocybin was administered for 2 doses only, while escitalopram was administered for 42 doses (daily for 6 weeks) with similar results. Additionally, potential side-effects for psychedelics are well tolerated, and generally occur immediately following treatment while the patient is still under the more intensive care of the therapy team. Conversely, standard antidepressants are most often self-administered and the patient is not under the same level of care. The intermittent nature of psychedelic therapy and minimal side-effects may potentially increase patient compliance in some groups who are dissatisfied with traditional antidepressant therapy, and may decrease medical system burden.

Health economic analyses of psilocybin therapy are ongoing. However, it can be projected that, if approved, the cost of psychedelic therapy relative to antidepressants will be expensive due to the requirement for supervised delivery and many hours of therapist supervision before, during and after drug administration. Within publicly funded healthcare systems, this could lead to ethical challenges if psychedelic therapy is deemed too expensive to deliver, leaving those able to pay for private therapy the sole recipients. Nevertheless, for those who have failed to respond to multiple standard treatments, the case for psychedelic therapy may become more compelling as more studies are undertaken and further results accumulate.

4.1. Limitations

An inherent weakness of this meta-analysis lies in the absence of required data for 2 studies (Goodwin et al., 2022; Grob et al., 2011), which necessitated the less precise use of graphical extraction and imputation. The small sample size in all included studies, with the exception of Goodwin et al. (2022), negatively affects the statistical power. None of the studies had long-term follow-up without also utilising the cross-over method; while the strength of the cross-over process is apparent, it does not allow for long-term results to be included in the meta-review.

The systematic review overall is limited by the exclusion criteria in all the underlying studies for those who are at significant risk of suicide. While this pertains to the ethical principle of non-malfeasance, it limits the generalisability of the findings by potentially not including those with more severe depressive conditions. A commonly identified limitation in studies of this nature, which also applies here, is the lack of ethnic, cultural, gender, and socioeconomic diversity among subjects. This represents a further limitation of this review in that the results also reflect a relatively homogenous population. Additionally, the fact that the reviewers do not know how many people were excluded presents a limitation in terms of sample representation; this is true of all clinical trials, but the selection criteria may be different for psilocybin trials. The washout period widely varies, presenting a further limitation; the importance or necessity of SSRI cessation prior to trial, and whether that interferes with therapeutic effect, is not well understood at this time.

Several other limitations were noted in the studies themselves. Among the included open-label trials, there were no control groups, which increases the susceptibility of the results to both researcher and participant bias: any changes in symptomatology cannot definitively be attributed to the intervention. In the randomised trials, a common limitation is the difficulty of achieving true blinding, as both participants and researchers can usually guess allocation by subject response. This issue was addressed by several methods, to include using low-dose psychedelics as a comparator (Carhart-Harris et al., 2021; Gasser et al., 2014; Goodwin et al., 2022; Griffiths et al., 2016); using placebo that mimics some aspects of the acute psychedelic reaction (Grob et al., 2011; Palhano-Fontes et al., 2019; Ross et al., 2016); and, requiring that most subjects be naïve to psychedelic substances (Gasser et al., 2014; Goodwin et al., 2022; Grob et al., 2011). Another common limitation in randomised-controlled trials is the use of cross-over design; once the crossover has occurred, period and carryover effects contaminate the comparison between experimental and control groups. This also affected the meta-review of longer-term outcomes as previously mentioned.

Psychedelics are generally given with psychological support before, during and after the dosing session [see Table 5]. This makes it difficult to assess the isolated effect of psychedelic substances, although the recent paper by Goodwin et al. does suggest a putative effect for 25 mg of psilocybin versus 1 mg in subjects receiving the same psychological support. However, the impact of expectancy effects due to unblinding cannot be accounted for, nor for the potential synergy between the drug and the therapy provided. Ultimately, these issues may not be of much clinical relevance, and they pose sufficient methodological and logistical challenges to potentially render further study economically unfeasible.

Other limitations as identified could be addressed in future studies. The small sample size has been partly compensated for by Goodwin et al., 2022; however, studies of this size need to be replicated by others, and even larger scale trials are required for licensing of psychedelic therapy. One concern is that the participant burden, in administration of multiple instruments and visits required for psychedelic research, may be prohibitive to many; a streamlining of the process may be considered. The lack of diversity among subjects as mentioned must continue to be addressed; wider public awareness about this type of research may attract a broader pool of potential subjects. Additionally, more diverse recruitment methods could be considered, such as the use of social media platforms or recruiting through social welfare programmes.

5. Conclusion

The aim of this article was to review the most recent trials of psychedelic therapies and specifically their effects on depressive symptoms. Our review and meta-analysis suggests that administration of psychedelics results in a significant reduction of depressive symptoms at several time points, most notably at short- and medium-term follow-up, but with some suggestions of the maintenance of benefits into the longer term. However, the small number of studies, and low sample sizes (with the exception of one recent large study), calls for careful interpretation of results. This suggests the need for more randomised clinical trials of psychedelic therapy, with larger and more diverse samples, and increased attention to blinding.

Contributors

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

KK and EIK are both PhD students and members of Psychoactive Trials Group [PTG] at King's College London [KCL]. KCL receives grant funding from COMPASS Pathways PLC and Beckley PsyTech to undertake phase 1 and phase 2 trials with psychedelics, including psilocybin.

JJR is an honorary consultant psychiatrist at The South London & Maudsley NHS Foundation Trust [SLaM, NHS UK], a consultant

psychiatrist at Sapphire Medical Clinics and an NIHR Clinician Scientist Fellow at the Centre for Affective Disorders at King's College London. JR leads PTG at KCL, with the same potential conflict of interest as above; COMPASS Pathways PLC has paid for JJR to attend trial related meetings and conferences to present the results of research using psilocybin. JJR has undertaken paid consultancy work for Beckley PsyTech, Delica Therapeutics and Clerkenwell Health.

AJC is employed by KCL and is an honorary consultant for SLaM (NHS UK). He has recently received honoraria for presentations and/or serving on advisory boards from the following pharmaceutical companies: Janssen, Lundbeck, Allergan, and Livanova. Additionally, he is supported by the NIHR Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Data availability

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.09.168.

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