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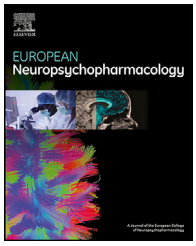

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REVIEW

Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies

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Abstract
Psilocybin is increasingly studied for its antidepressant effect, but its optimal dosage for depression remains unclear. We conducted a systematic review and a dose-response meta-analysis to find the optimal dosage of psilocybin to reduce depression scores.
Following our protocol (CRD 42022220190) multiple electronic databases were searched from their inception until February 2023, to identify double-blind randomized placebo-controlled (RCTs) fixed-dose trials evaluating the use of psilocybin for adult patients with primary or secondary depression. A one-stage dose-response meta-analysis with restricted cubic splines was used. Cochrane risk of bias was used to assess risk of bias.
Our analysis included seven studies with a total of 489 participants. Among these, four studies focused on primary depression ($N = 366$), including one study with patients suffering from treatment-resistant depression. The remaining three studies examined secondary depression ($N = 123$). The determined 95% effective doses per day (ED95) were 8.92, 24.68, and 36.08 mg/70 kg for patients with secondary depression, primary depression, and both subgroups, respectively. We observed significant dose-response associations for all curves, each plateauing at different levels, except for the bell-shaped curve observed in the case of secondary depression. Additionally, we found significant dose-response associations for various side effects, including physical discomfort, blood pressure increase, nausea/vomiting, headache/migraine, and the risk of prolonged psychosis.
In conclusion, we discovered specific ED95 values for different populations, indicating higher ED95 values for treatment-resistant depression, primary depression, and secondary depression groups. Further RCTs are necessary for each population to determine the optimal dosage, allowing for maximum efficacy while minimizing side effects.

1. Introduction

Depression is a prevalent mental disorder, affecting more than 300 million people worldwide (WHO, 2017). It is one of the most debilitating illnesses with the most significant impact on quality of life. The lifetime prevalence of major depressive disorder (MDD) is between 10% and 20% (Lim et al., 2018), with an onset in a third of patients by 25 years old, an median age at onset at 30 years old (M. Solmi et al., 2021). A third of people suffering from an MDD will experience more than one depressive episode in their lifetime (Richards, 2011), and approximately half of patients with depressive disorder lack adherence to antidepressants as soon as 6 months after initiation of treatment, with a further increase of non-adherence with complex treatments regimens (Solmi et al., 2021). While most prescribed antidepressants are superior to placebo in adults (Cipriani et al., 2018a) - but not in children and adolescents - and are reasonably safe in the long term (Correll et al., 2021), they do have a small effect size, can have limited tolerability, with associated discontinuation and high relapse rates (Anagha et al., 2021; Locher et al., 2017; Solmi et al., 2021). Hence, novel treatments for depression are needed, in particular for those that do not respond to available antidepressants. As such, renewed interest in psychedelic-assisted therapy has emerged in recent years after being demonized in the early 1960s despite initial promising research (Hofmann, 1980). This resurgence of psychedelics started as therapeutic tools for resistant-depression, mainly with lysergic acid diethylamide (LSD) and psilocybin (Solmi et al., 2022). Both substances are classified as classics psychedelics, also called serotonergic psychedelics (De Gregorio et al., 2021), typically produce perceptual distortions and mind-altering effects, mainly by agonistic action at the serotonin (5-HT) 2A brain receptor, with potential antidepressant properties (Kwan et al., 2022).

Although the exact physiopathology of MDD has not been fully understood, it is widely accepted that dysregulation of the monoaminergic system, of which serotonin is a part, contributes to affective symptoms (Otte et al., 2016). Considering that both conventional antidepressants and psilocybin act by modulating the serotonergic neurotransmission system, this opens a door for the use of the latter in the treatment of MDD.

Over the past decade, several RCTs have shown promising effects of psilocybin use in the treatment of mood disorders by reducing symptoms of anxiety and depression. However, only one RCT has directly compared psilocybin-assisted therapy with escitalopram (Carhart-Harris et al., 2021).

Animal studies have indicated that psilocybin has a low addiction and physical dependence potential (Johnson et al., 2018), and national surveys report low rates of abuse (European Monitoring centre for Drugs and Drug Addiction). In RCTs conditions, psilocybin appears to be well-tolerated in the long term (Roland R Griffiths et al., 2016; Studerus et al., 2011).

A recent meta-analysis conducted by Li and colleagues focused on the clinical effects of classic psychedelics on depressive symptoms (Li et al., 2022). The analysis revealed that psilocybin had a small effect size on both acute and

long-term reduction of depressive symptoms in patients dealing with MDD and secondary anxiety and depression related to cancer following psilocybin administration. Furthermore, a sub-group meta-analysis investigating the dose-effects of psilocybin on MDD and depression associated with cancer indicated that the optimal therapeutic effect of psilocybin is achieved at a dose of 30–35 mg/70 kg (Galvão-Coelho et al., 2021).

Considering the increase research and use of psilocybin, and the crucial aspect of the dose-relationship concerning efficacy and potential side-effects, we decided to perform a dose-response meta-analysis of RCTs on psilocybin to determine the near maximum effective doses of psilocybin on both primary and secondary depression, and the relative risks of adverse events.

2. Methods

2.1. Registration

This systematic review was conducted according to the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) (Supplementary Information 1). The review protocol was registered on PROSPERO in December 2022 (CRD 42022220190). The database was updated in February 2023.

2.2. Search strategy

We conducted a systematic search for randomized controlled trials (RCTs) comparing all serotoninergic psychedelics in Embase, the Cochrane Database of Systematic Reviews and PsycInfo. A combination of search terms and MeSH terms that can be found in the published protocol were used, such as 'psilocibine', 'psilocybin' and 'hallucinogens'. Subsequently, we retrieved RCTs focusing on psilocybin for the treatment of primary or secondary depression. The results were limited to the adult population (18–65 years) without any language or time restrictions. Two reviewers (NP, FL) independently reviewed titles and abstracts using Rayyan, a research collaboration web platform for systematic reviews. In case of disagreement, full texts were analyzed until both reviewers reached a consensus.

2.3. Inclusion criteria and study selection

We included all double-blind RCTs and cross-over trials with a minimum duration of one-week, comparing any fixed dose of psilocybin in any form of administration with placebo in patients diagnosed with primary or secondary depression (e.g.; cancer patients representing secondary depressive disorder). Diagnoses were based on versions of the DSM or the SCID (e.g.; DSM-IV, DSM-V, and SCID-5) (APA, 2022; First et al., 2016). Case-control studies, case reports, reviews and uncontrolled clinical trials were excluded. We excluded case-control studies, case reports, reviews, and uncontrolled clinical trials. Primary depression is defined as MDD occurring in the absence of comorbid psychiatric disorders, except for anxiety disorder. In contrast, secondary depression occurs in the presence of an incapacitating or life-threatening medical illness that precedes and parallels the symptoms of depression (Florita and Barbini, 2005).

2.4. Outcomes measures and data extraction

The primary aim of our study was to establish the dose-response profile of the effect of psilocybin on depressive symptoms for patients diagnosed with primary or secondary depression. In order to determine the near maximum effective dose of psilocybin needed to achieve a reduction of depressive symptoms, we considered the mean changes from each study by extracting the baseline and endpoint score (mean±SD) of each study using the Hamilton Depression Rating Scale (Hamilton, 1960), the Montgomery-Åsberg Depression Rating Scale (Montgomery and Asberg, 1979), or any other suitable scale to assess changes in depressive symptoms. Missing standard deviations were estimated from p-values or by using the mean standard deviation from other included studies with validated imputation methods (Furukawa et al., 2005). Furthermore, considering the phenomenological overlap between depression and anxiety, we also extracted the mean change on anxiety score using the Beck Anxiety Inventory (Beck et al., 1988).

The secondary aim of the study was to determine if possible, psilocybin side-effects were dose-dependent, and to assess tolerability by examining the relative risk of adverse effects.

2.5. Risk of bias assessment

The risk of bias was assessed independently by two reviewers (MS and NP) using the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). RoB 2 evaluates risk of bias in five different domains: generation of allocation sequence, allocation concealment, masking of study personnel and participants, masking of outcome assessor, attrition, and selective outcome reporting. We classified studies as having low risk of bias if none of these domains was rated as high risk of bias and three or fewer were rated as unclear risk; moderate if four or more were rated as unclear risk; and all other cases were assumed to have high risk of bias.

2.6. Statistical analysis

We used the one stage dose-response meta-analysis package 'doresmeta' published by Crippa & Orsini (Crippa et al., 2019). For our primary outcome, the objective was to examine the relationship between the dose of psilocybin (independent variable) and the effect on depressive symptoms (dependent variable). We included all RCTs with fixed doses of psilocybin. We converted dose to total dose in mg/70 kg for all studies (e.g.; 0.2 mg/kg= total of 14 mg/70 kg of psilocybin ingested). As a measure of effect size, the standardized mean difference (Cohen's d) was used. We used a random-effects model with the standardized mean difference (SMD) to account for between-study variability

(Higgins et al., 2003). In dose-response models, the null hypothesis states that there is no dose-response relationship, meaning that the outcome does not vary significantly with different doses of the intervention or exposure (flat curve). If the p-value is below a pre-defined significance level (e.g., 0.05), the null hypothesis is rejected, leading to a significant dose-response relationship.

The dose-response relationship was characterized using a restricted cubic spline model (nonlinear model) knot at the 25th, 50th, and 75th percentiles (Crippa et al., 2018; Hamza et al., 2021). Estimations of 50% (ED50) and 95% (ED95) effective doses were extracted from the estimated dose-response curves. The ED50 was the mean dose at which half of the possible psilocybin antidepressant effect would occur.

Furthermore, for the secondary outcome regarding psilocybin side effects, we estimated the association between the dose and the logarithm of risk ratio (RR) for physical (physical discomfort, blood pressure increase, tachycardia, nausea or vomiting, headache, or migraine) or psychological adverse events (psychological distress, prolonged psychosis) across studies.

We further conducted separate analysis regarding the diagnosis of primary and secondary depression. We quantified heterogeneity using the variance partition coefficient (VPC), a multivariate extension of the I^2 value. The VPC can be defined as the ratio of the between-studies component by the total residual. All analyses were conducted using R statistical software v4.2.2 (metafor and dosresmeta packages) (Crippa et al., 2019; R Core Team, 2019; Viechtbauer, 2010). Moreover, if suitable we will conduct a subgroup analysis and leave-one-out analysis to explore residual heterogeneity.

3. Results

3.1. Search results

The systematic search yielded 5196 references. We searched for additional articles by conducting a snowball search in identified reviews. Following our protocol, we retained 260 clinical trials on psilocybin that were screened for eligibility (Supplementary Fig 1). Overall, 7 studies were included in the final dataset (Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016; von Rotz et al., 2023). Studies including healthy participants or without control groups were excluded (Becker et al., 2022; Carhart-Harris et al., 2016; Rucker et al., 2022).

Follow-ups of various length (up to 33 weeks, mean 14.14 weeks) was present for several studies (Table 1). When considering all studies, 53.2% of included patients were women. Furthermore, all studies reported the age albeit one study (Grob et al., 2011), and thus the mean age was of 44.1(±12.8) years, and of 39.2(±11.6) and 56.3(±5.3) years for the primary and secondary depression subgroups respectively.

Although some patients presented treatment-resistant depression, all patients were considered as stable outpatients. Of the 7 studies included, four studies included patients with MDD (Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022; von Rotz et al., 2023), with one study including patients with treatment-resistant depression comparing different doses of psilocybin (Goodwin et al., 2022). In most studies, treatment resistant episode was defined by lack of response to two to four antidepressant trials at sufficient dose of $\geq$ 8 weeks duration. One study included both patients with MDD (30% of patients) and patients with depression and anxiety disorders secondary to cancer (dysthymic disorder, adjustment disorder with anxiety and depressed mood, other anxiety disorder) (Griffiths et al., 2016). One study included patients with anxiety disorder secondary to cancer (acute stress disorder, generalized anxiety disorder, adjustment disorder with anxiety) (Grob et al., 2011). One study included patients with adjustment disorder (90%) and generalized anxiety disorder (10%) secondary to cancer (Ross et al., 2016). For studies including patients with MDD, 2 studies delivered 2 doses, and 2 studies delivered one of psilocybin (Table 1). For the 3 studies focusing on secondary depression (and anxiety) to cancer, one study delivered two doses, and 2 studies delivered 2 doses.

In all included studies, psilocybin was manufactured by pharmaceutical companies and administered orally in capsules. The mean dose used in studies that delivered a unique dose of psilocybin was 16.5 mg/70 kg, and for studies with 2 doses, of 31.5 mg/70 kg.

Prior hallucinogen use was reported in all studies, with a prevalence of 26.3% of patients having already experienced the use of psychedelics at least once in their life. However, almost no studies provided information on the years since last psychedelic use, except for one study that reported a mean length of 30 years since last psychedelic use (Griffiths et al., 2016).

In all studies, participants had not been taking antidepressants for at least 2 weeks prior to psilocybin intake. The substance intake involved only one patient at a time, in an individual psychedelic-assisted psychotherapy setting (IPAP) (Ponomarenko et al., 2023).

Furthermore, all studies delivered non-directive supportive psychotherapy, albeit one study delivered a psychedelic psychotherapy training program (Ross et al., 2016).

3.2. Dose-response curve of the psilocybin effect on depressive symptom

A total of 7 RCTs ($N = 489$) examined the effect of psilocybin on depression, with doses between 1.5 mg and 50 mg/70 kg. These studies were conducted between 2011 and 2023. Study durations greatly differed considering that follow-up was up to a year after inclusion, however the mean length between first and second dose of psilocybin was 3.54 weeks (range 2 to 8 weeks). A detail of all results for primary outcome is reported in Table 2.

A significant dose-response association was found ($p<0.0001$) (Fig. 1). The visual inspection of the curve shows an ascending curve that starts to plateau at the highest examined dose in presence of a considerable heterogeneity (I^2=85%) (Supplementary Table S1.a). The ED95 was reached at the dose of 41.14 mg/70 kg (95%IC 26.37–47.80), and the ED50 was 10.13 mg/70kg(95%IC 6.6–14.5). These results sug-

Table 1 Characteristics of included studies.

Study (country)	Methods, aim of the study	Population characteristic	Inclusions (Female gender%) Mean age (mean ± SD)		Dose range of psilocybin (Psi[a]) (mg/70 kg) / Dose of placebo	Prior experience with psychedelics	Sessions design and psychological support	Adverse physical or psychological effects
Primary depression								
1- Davis et al., 2021	8 weeks waiting-list randomized controlled trial (RCT) with 1 month follow up. Two doses of psilocybin delivered.	Outpatients with moderate to severe major depressive disorder episode (SCID-5 criteria); no use of ketamine or classic hallucinogens during the past 6 months; no current pharmacotherapy for depression. ($n = 27$; 21-75)	Intervention group Waiting-list group	9(69%) 43.6 ± 13 7(64%) 35.2 ± 9.9	Psi 20 mg (1st dose) Psi 30 mg (2nd dose)	4(44%) 7 (100%)	*2-3 h of meeting after each session * One day session with non-directive supportive psychotherapy *Participants were instructed to lie on a couch in a living room-like environment with eyeshades and headphones and were encouraged by facilitators to focus their attention inward and stay with any experience that arose	* The most common adverse event was mild-to-moderate headache and challenging emotions that were limited to the time of sessions
2- Carhart-Harris et al., 2021	6 weeks RCT, with no follow up, comparing psilocybin with escitalopram. Two doses of psilocybin delivered.	Oupatients with moderate-to-severe major depressive disorder assessed by a score ≥17 on the HAM-D-17[b], with no current use of psychotropic medication nor psychotherapy (DSM-IV criteria). 73% of subjects were psilocybin naïve. ($n = 59$;21-64)	Intervention group Control group	11(37%) 43.3 ± 11.7 9(31%) 39.1 ± 9.7	Two separate dose of Psi 25 mg, or Psi 1 mg Escitalopram 10 mg for 3 weeks, then escitalopram 20 mg daily	8 (27%) 9 (28%)	*2 sessions of unknown duration *Psychological support during sessions consisted of caring for the physical and psychological well-being of subjects and responding to signs of discomfort during and immediately after the administration	*The most common adverse event was transient headache within 24 h after the psilocybin session

(*continued on next page*)

Table 1 (*continued*)

Study (country)	Methods, aim of the study	Population characteristic	Inclusions (Female gender%) Mean age (mean ± SD)		Dose range of psilocybin (Psi[a]) (mg/70 kg) / Dose of placebo	Prior experience with psychedelics	Sessions design and psychological support	Adverse physical or psychological effects
3- Goodwin et al., 2022	3 weeks phase 2, dose-finding RCT, that assess of the safety and efficacy of various doses of synthetic psilocybin, with 12 weeks follow up. Unique dose of psilocybin (1, 10 or 25 mg)	Outpatients with treatment-resistant depression (DSM-V criteria). Treatment resistance is defined by no response after two to four adequate trials ≥ 8 weeks duration. Drugs affecting the central nervous system were discontinued two weeks before psilocybin administration. ($n = 233$; 36-58)	High dose group Low dose group Control group	44(56%) 40.2 ± 12.2 41(55%) 40.6 ± 12.8 36(46%) 38.7 ± 11.7	Psi 25 mg Psi 10 mg Psi 1 mg (Placebo)	5 (6%) 5 (7%) 4 (5%)	*6-8 h session * Subjects were in a quiet room and listened to music wearing eyeshades, and returned home once the psychedelic experience fully dissipated *3 meetings with a therapist before the psilocybin session to build trust and to prepare for the psychedelic experience *2 integration sessions after the psilocybin experience to integrate the psychedelic experience	* Adverse events occurred in 77% of subjects (headache, nausea and dizziness) in particular in the high dose group, as for the severe adverse event such as suicidal ideation, behavior or self-injury
4- Von Rotz et al. 2023	3 weeks RCT. Unique dose of psilocybin.	Outpatients diagnosed with major depressive disorder (DSM-V) and no unstable somatic conditions were allocated to receive either a single, moderate dose (0.215 mg/kg body weight) of psilocybin or placebo in conjunction with psychological support. Prior experience with psychedelics. ($n = 52$; 20-60)	Psilocybin Group Control group	26 (61.5%) 37.6 ± 10.9 26 (65.4%) 35.9 ± 9.80	Psi 15.05 mg Pure mannitol	5 (19.02%) 11(42.3%)	*6-8 h session * Subjects were instructed to immerse themselves in an introspective focus. A standardized playlist with music was played via headphones or speakers. One trained therapist was present in the room throughout the administration day to respond to the participants' needs. * One integration session after the psilocybin experience	*Of a total of eight adverse events, the most frequently reported was mild headache (11%) which resolved completely within two days after drug administration

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Table 1 (*continued*)

Study (country)	Methods, aim of the study	Population characteristic	Inclusions (Female gender%) Mean age (mean ± SD)		Dose range of psilocybin (Psi[a]) (mg/70 kg) / Dose of placebo	Prior experience with psychedelics	Sessions design and psychological support	Adverse physical or psychological effects
Secondary depression								
5-Grob et al., 2011 **(USA)**	2 weeks RCT and 6 months follow-up. Unique dose of psilocybin	Outpatients with secondary depression (acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety; DSM-IV criteria). ($n = 12$; 36-58)	Intervention group Control group	6(91.7%) n.a. 6(100%) n.a.	Psi 10-15 mg Niacin 250 mg	4 (66.6%) 4(66.6%)	*6 h session *Subjects were encouraged to lie in bed wearing eye shades and were able to listen to preselected music. A debriefing was proposed after the session	*Safe physiological and psychological responses
6- Griffiths et al., 2016 **(USA)**	5 weeks crossover study with 6 months follow-up. Two doses delivered.	Outpatients with secondary depression (dysthymic disorder, or adjustment disorder with anxiety and depressed mood, chronic) or anxiety disorders using DSM-IV criteria. Participants were not taking antidepressants. Almost all participants were hallucinogens naïve. ($n = 51$; 29-62)	Intervention group Waiting-list group	25(48%) 56.1 ± 2.3 26(50%) 56.5 ± 1.8	Psi 22-30 mg Psi 1-3 mg	23 (45%) 23 (45%)	*7 h sessions *Subjects were encouraged to lie in bed wearing eye shades and were able to listen to music. A debriefing was proposed after the session.	*Safe physiological and psychological responses
7-Ross et al., 2016 **(USA)**	7 weeks RCT with a crossover design, and with a follow-up at 33 weeks. Unique dose of psilocybin	Outpatients of which the majority meeting criteria for an adjustment disorder (90%) and the rest for generalized anxiety disorder (10%) DSM-IV criteria. 55% prior hallucinogens use. All participants were hallucinogens naïve. ($n = 29$; 22-75)	Intervention group Waiting-list group	15(62%) 56.3 ± 7.3 16(62%) 56.3 ± 9.5	Psi 21 mg Niacin 250 mg	7 (50%) 9 (60%)	* 4 h session * Subjects were encouraged to lie in bed wearing eye shades and were able to listen to music. A debriefing was proposed after the session. * Stanislas Grof method of preparatory psychotherapy, and post—dosing integrative psychotherapy	*Most common psychiatric AEs were transient anxiety (17%) and transient psychotic-like symptoms (7%)

Abbreviations.
n.a.: not available.
[a] Psi: Psilocybin.
[b] HAM-D-17: Hamilton depression rating scale (17 items).

Table 2 Results for the primary outcome: psilocybin effect on depressive and anxiety symptoms.

Psilocybin effect on	Results	Primary and secondary depression	Primary depression	Secondary depression
Depressive symptoms	Inclusions	$n = 7$, $N = 489$	$n = 4$, $N = 366$	$n = 3$, $N = 123$
	ED50	10.13 mg/70kg	8.23 mg/70kg	3.20 mg/70kg
	ED95	36.08 mg/70kg	24.68 mg/70kg	8.92 mg/70kg
	Curve shape	Plateau	Plateau	Bell-shape
	Significancy; I^2	$p<0.0001$; $I^2=85\%$	$p< 0.0001$; $I^2= 80\%$	$p = 0.07$; $I^2= 80\%$
Anxiety symptoms	Inclusions	$n = 6$; $N = 258$	$n = 3$; $N = 135$	$n = 3$; $N = 123$
	ED50	7.58 mg/70kg	11.94 mg/70kg	4.08 mg/70kg
	ED95	22.78 mg/70kg	24.68 mg/70kg	8.86 mg/70kg
	Curve shape	Plateau	Plateau	Plateau
	Significancy; I^2	$p<0.0001$; $I^2=85\%$	$p<0.0001$; $I^2=85\%$	$p<0.0001$; $I^2=85\%$

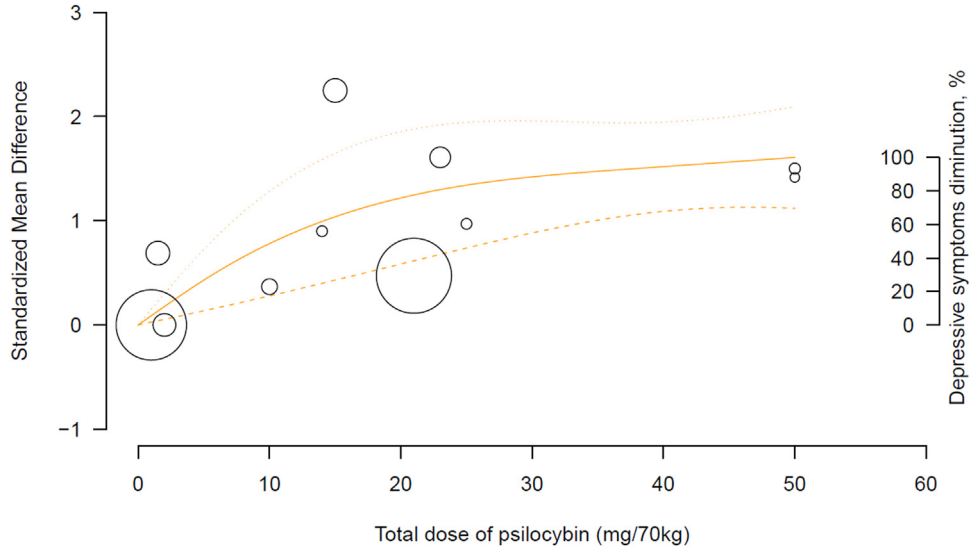

Fig. 1 Dose-response curve of psilocybin for patients with both primary and secondary depression (X2= 31.56 (df = 2), $p< 0.0001$, $I^2= 85\%$). The maximum reduction of depressive symptoms (ED95%) was reached for the dose of 41.14 mg/70 kg (95CI%: 26.37-47.80), $n = 7$, $N = 489$; mean duration of 3.71 weeks. ED50 was reached at 10.13 mg/70 kg. Each circle represents one study, and the size of a circle is proportional to the number of patients that have received a single dose of psilocybin. The dose-response curve represents the standardized mean differences reduction of depressive symptoms for the treatments arm compared to the placebo arm. Y-axis represents the standardized mean differences of reduction of depressive symptoms for the dose-response curve. X-axis represents doses (total mg/70 kg received). The dotted lines are 95% confidence intervals. We used knot locations at the 25th, 50th, and 75th percentiles to anchor the curves.

gested that higher dose that the ED95 might not be more efficient on depressive scores reduction.

We performed a sensitivity analysis, excluding studies with that presented an overall risk different than low risk (Supplementary Table 2). Only the Grob et al. (2011) study was excluded. The dose-response association did not significantly change ($p<0.0001$), the ED50 was 10.13 and the ED95 was 36.08 mg/70 kg.

Furthermore, we excluded the Goodwin et al. (2022) that administered only one dose of psilocybin to patients with treatment-resistant depression. Results were unchanged ($p<0.0001$) (Supplementary Fig S2), however both lowest ED50 and ED95 were reached at 8.23 and 24.05 mg/70 kg respectively. We complemented our sensitivity analysis with a leave-one-out analysis, which found no significant modification of results with range of ED50 from 8 to 14 mg/70 kg and range of ED95 from 24 to 45 mg/70 kg (Supplementary Table 3).

3.3. Subgroup analysis for patients with primary and secondary depression

Considering the heterogeneity of included population among retained studies we conducted a subgroup analysis to distinguish the effects of psilocybin for patients with MDD and patients' depression secondary to cancer (Fig. 2).

For primary depression ($n = 4$; $N = 366$), a significant dose-response association was found ($p< 0.0001$), in pres-

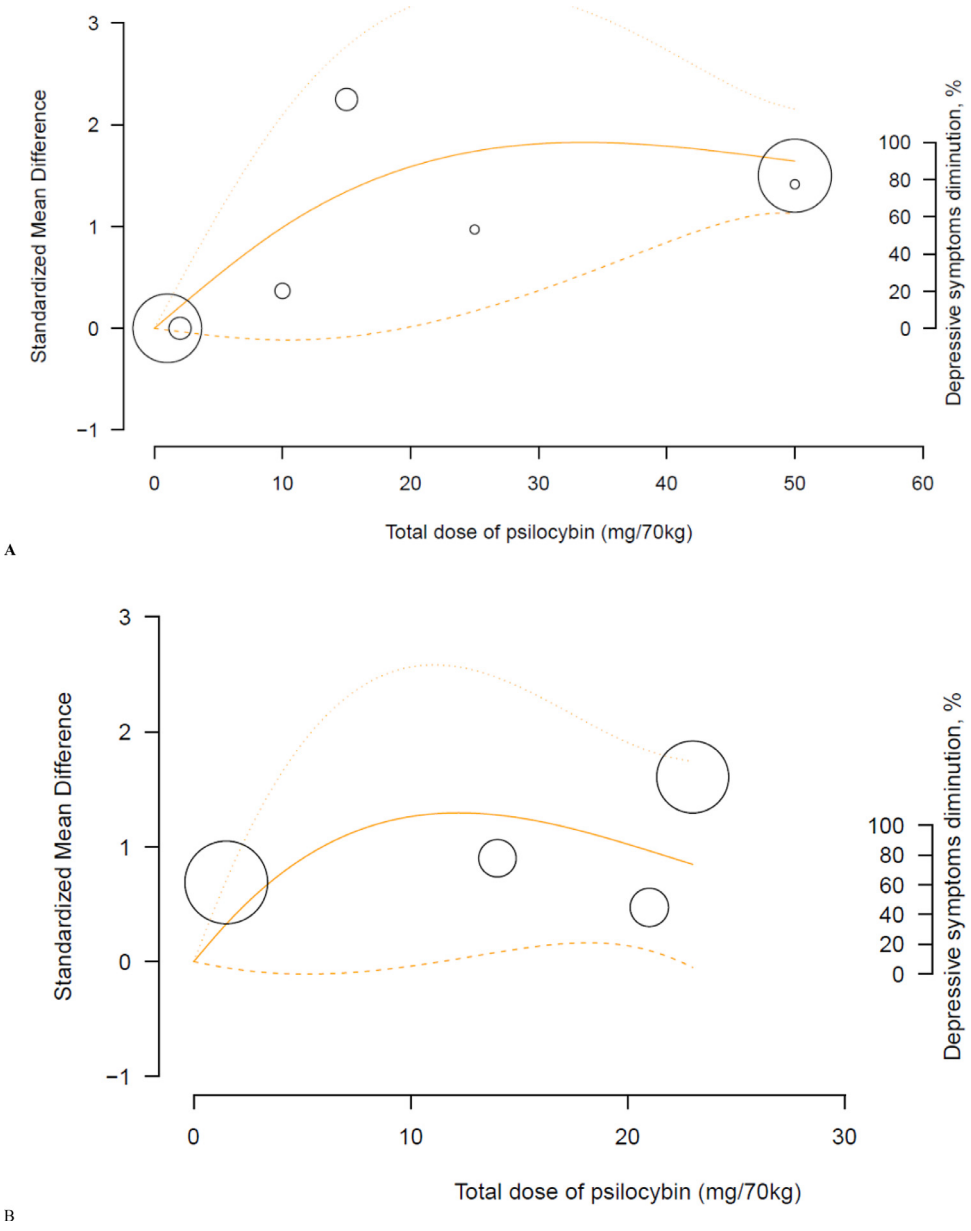

Fig. 2 Subgroup analysis with dose-response curve of psilocybin for depressive symptoms, when considering patients with only primary depression (A) and only with secondary depression (B) without distinction of the number of sessions. For primary depression, the maximum reduction of depressive symptoms (ED95%) was reached for the dose of 24.68 mg/70 kg (95CI%: 19.29–48.73), $n = 4$, $N = 366$; mean duration of 3 weeks. The effect size at the maximum dose reaches a 95% CI of 1.62 ([1.15, 1.8]. For secondary depression, the maximum reduction of depressive symptoms (ED95%) was reached for the dose of 8.92 mg/70 kg (95CI%: 7.15-22.42), $n = 3$, $N = 123$; mean duration of 4.6 weeks. The effect size at the maximum dose reaches a 95% CI of 1.0 ([0.85, 1.25].

ence of a considerable heterogeneity ($I^2 = 80\%$) (Supplementary Table S1). The curve plateaued at the ED95 of 24.68 mg/70kg(95%IC 19.29–48.73).

For the subgroup focusing only on secondary depression to cancer ($n = 3$; $N = 123$), the dose-response association was not statistically significant ($p = 0.07$), and these results were found in presence of a considerable heterogeneity ($I^2 = 80\%$) (Supplementary Table S1). Nevertheless, the visual inspection revealed a bell-shape curve, suggesting that higher dose than the ED95 of 8.92 mg/70kg(95%IC 7.15–22.42), was no more beneficial on depressive symptoms. For both subgroup analysis, a visual inspection of VPC curves suggested that heterogeneity was essentially found for the highest dose of psilocybin.

3.4. Dose-response curve of the psilocybin effect on anxiety symptoms

All studies, albeit one study (Goodwin et al., 2022) reported anxiety symptoms change using the BDI scale total of ($n = 6$ RCTs; $N = 258$), with doses between 1.5

to 50 mg/70 kg. When considering both primary and secondary depression, a significant dose-response association was found ($p<0.0001$) with a curve that plateaued (Supplementary Fig S3.A.B.C). Highest doses were associated with a considerable heterogeneity ($I^2=85\%$). The ED95 was reached at the dose of 22.78 mg/70kg(95%IC 15.82–47.2) and the ED50 at 7.58 mg/70kg(95%IC 3.3–11.7). The subgroup of primary and secondary depression revealed that although both curve that plateaued also present significant dose-response association in favor of a decrease of anxiety, ED50 and ED95 were very different. The ED95 was of 24.68 mg/70kg(95%IC 17.09–47.47), and 11.94 mg/70kg(95%IC 2.91–22.42), and the ED50 of 8.86 mg/70 kg and 4.08 mg/70 kg, for primary and secondary depression respectively in presence of considerable heterogeneity ($I^2=80$–85%).

3.5. Secondary outcome: relative risks of adverse events

We examined the relationship between psilocybin dose and the occurrence of physical or psychological adverse events using linear model of binary sample data with the one-stage random-effects meta-analysis and the covariance approximation of Greenland & Longnecker (Greenland and Longnecker, 1992). All results are reported in Fig. 3.

For somatic adverse events, we found a significant dose-association for physical discomfort ($p = 0.023$), with a curve that continues to increase. On the exponential scale, the relative risk was +2.35% suggesting that the risk of physical discomfort event increase by 1.0235 times (exp(0.0235)=1.0235), or increase by +2.35% with each 1 mg/70Kg of psilocybin ingested. We also found a similar curve for the relative risk of blood pressure increase ($p = 0.042$), with a relative risk of +1.04%.

For tachycardia, although the visual inspection of the curve suggested that a dose-response association similar to the two previous one described was present, this association was not significant ($p = 0.09$), with the presence of a major uncertainty. The relative risk was +2.02%.

Furthermore, for nausea and vomiting, as for headache and migraine, two bell shaped curves were obtained, with significant dose-response associations ($p<0.001$ and $p<0.05$), with relative risk of +1.25% and +1.42% respectively. Of importance, vomiting and migraine where only reported in a few cases, with mostly nausea and headache occurring.

Regarding psychiatric adverse events, for the combined risk of prolonged psychosis (>24 h) and the risk of hallucinogen persisting perception disorder (HPPD), we obtained a significant dose-response relation with a curve that plateaued ($p = 0.001$), although in presence of a considerable heterogeneity. The relative risk was +2.51% suggesting that the risk of such adverse event increase by 1.025, times with each additional 1 mg/70 kg dose of psilocybin is ingested. However, the occurrence of such events was relatively rare, and the author's consideration of psychotic symptoms varies between studies ($N = 12$ cases on a total of 465 subjects) (Supplementary Table S4).

Of importance, it should be noted that the definitions of different outcomes varied between studies. For instance, the threshold at which blood pressure increase was considered an adverse event differed across studies. Furthermore, certain adverse events, such as 'psychological distress,' were not consistently retained due to ambiguous definitions between studies and highly variable rates of events, particularly in the placebo groups.

4. Discussion

To the best of our knowledge, this is the first dose-response meta-analysis conducted for psilocybin and depression. Our analysis included 7 RCTs with a total of 489 participants, and the findings revealed that psilocybin significantly reduced depressive symptoms in both primary and secondary depression. For primary depression, the dose-response curve plateaued, while for secondary depression, a bell-shaped curve was observed. Notably, the near maximal effective dose was much lower for secondary depression than for primary depression.

Furthermore, the analysis also yielded significant results for anxiety scores, and specific dose-response associations were identified regarding somatic and psychological adverse events. These findings provide valuable insights into the therapeutic potential of psilocybin for depression and its associated effects, enhancing our understanding of its efficacy and safety profile.

4.1. Dose response association of the antidepressant effect of psilocybin

Our results are somewhat different from those of a recent meta-analysis studying the dose effects of psilocybin on primary and secondary depression (Li et al., 2022), which pointed out that the antidepressive effect of psilocybin decline from a dose of 10–15 mg/70 kg to 20–25 mg/70 kg, before increasing at the dose of 30–35 mg/70 kg, being the optimal therapeutic dose. This meta-analysis included fewer studies and does not use a dose-response model. When considering both primary and secondary depression, we found that half of psilocybin antidepressant effect occurs at doses of 10.13 mg/70 kg, and 95% of the antidepressant effect occurs at doses of 41.14 mg/70 kg, achieving the optimal therapeutic effect. However, these results must be interpreted with caution, as with the exclusion of the only study including treatment-resistant patients (Goodwin et al., 2022), the ED95 for depressive symptoms reduction dropped to 24.05 mg/70 kg, suggesting that resistant patients mostly respond to higher dose of psilocybin (40 mg/kg).

Furthermore, the bell-shaped curve obtained for patients with secondary depression, with a low E95% (24.68 mg/kg) also points out the importance of the type of population considered. Among the pool of patients with secondary depression, only 16% of patients presented MDD as a 'primary' diagnosis, other patients presenting adjustment and anxiety disorders. We hypothesize that patients with comorbid, or with 'primary' anxiety disorders will be more likely to only respond to a lower dose of psilocybin, at least in the first psilocybin sessions. Similarly, the results regarding the decrease of BDI score, and the different ED50 and ED95 values between both subgroups of patients point out that patients with comorbid anxiety symptoms seem

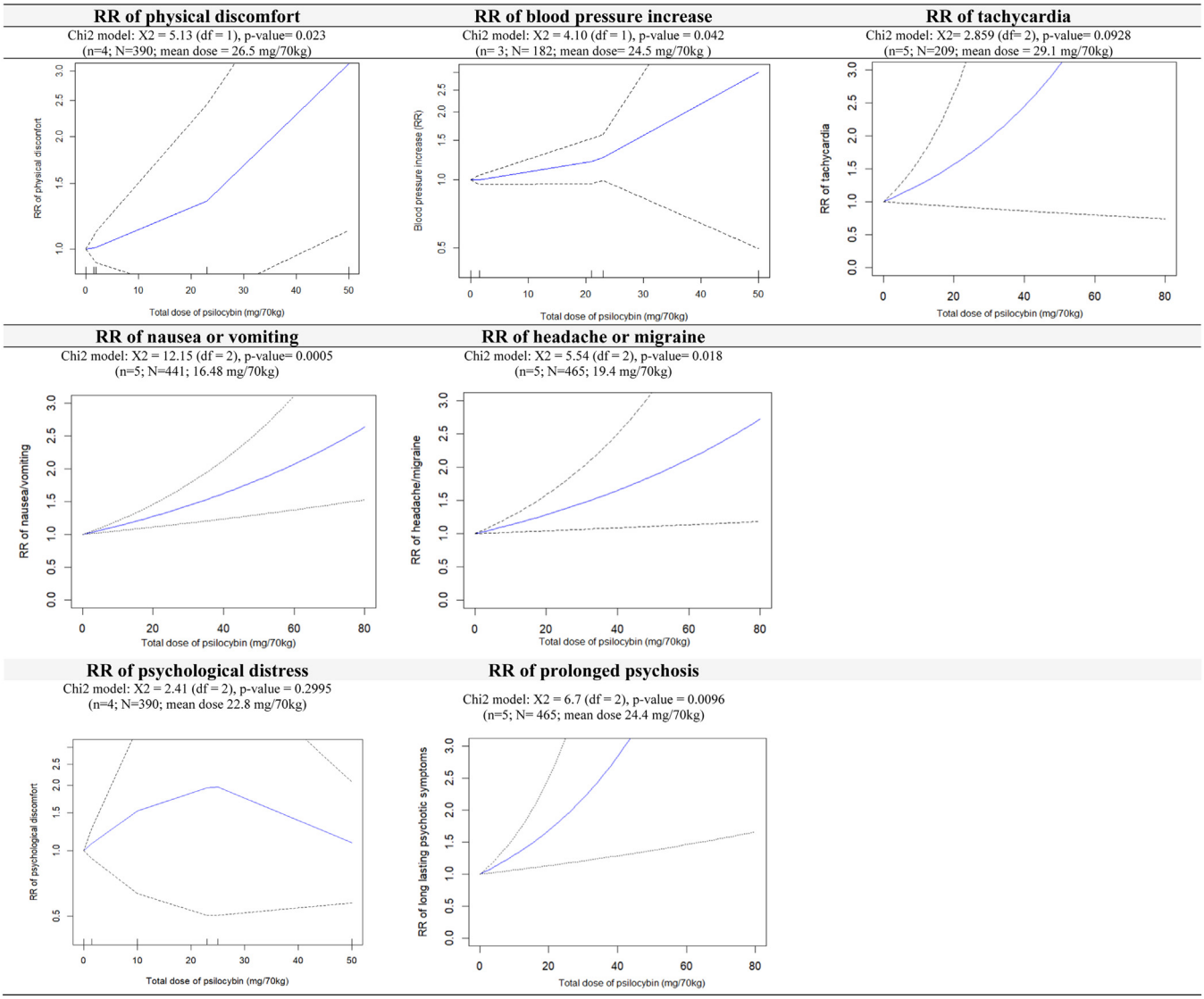

Fig. 3 Dose-response association for adverse events reported with psilocybin RR=risk ratio. Each tick on the x-axis represents the dose examined in a treatment group. The dotted lines represent 95% CIs.

to benefit from lower doses (almost half dose) of psilocybin than when considering patients with primary depression. For such patients presenting a proneness of anxiety, or even for patients with a proneness for psychotic symptoms, we could assume that higher doses might mitigate response due to subsume dysphoric mood states such as anxiety and fearful delusions, arising mainly from ego-disintegration and loss of self-control phenomena (Stoliker et al., 2022; Studerus et al., 2011).

Indeed, it is important to remind the frequent paradoxical effect of serotonergic psychedelics to increase feelings of anxiety (Carhart-Harris et al., 2016), and the very nature of psychedelics trips with dose-dependent effect for ego dissolution that can be associated with a sense of loss of control with subsequent levels of anxiety or even short-term psychosis-like symptoms (Hirschfeld and Schmidt, 2021).

On the neurobiological level, 5-HT_{2A}R stimulation has been associated with both positive and negative facets of the acute psychedelic state (e.g., positive mood but also anxiety and psychotic symptoms). Cahart-Harris and colleagues propose the notion of 'increased cognitive entropy' ('entropic brain' hypothesis) to explain the possible occurrence of such paradoxical psychological effects (Carhart-Harris et al., 2014; Rankaduwa and Owen, 2023). In opposite, oceanic boundlessness, usually associated with positive emotional states is an indirect measure of derealization and depersonalization, which might be difficult to apprehend for such patients (Preller and Vollenweider, 2018).

Considering these unforeseen reactions caused by serotoninergic psychedelics, we can only stipulate that for first sessions, patients prone to anxiety or psychotic symptoms are very likely to reach the ED95% for depressive symptoms reduction at lower dose, as indicated by our results. The optimal dose of psilocybin for depression therefore clearly varies between the subgroup of patient considered. By extension, caution regarding the dose of psilocybin used should be applied for all patients presenting different core psychiatric disorder than depression, and

that would be eligible to psilocybin-assisted psychotherapy for their comorbid depression. As mentioned, lower dose than 25 mg/70 kg should even be considered – with for instance a first threshold at the ED50% for secondary depression (ED95 of 9 mg/70 kg) – in most disorders where anxiety of psychotic symptoms might occur (e.g.; anxiety disorders; schizoaffective disorders (Arnovitz et al., 2022); bipolar depression (Gard et al., 2021); autism spectrum disorders (Markopoulos et al., 2022); borderline personality (NCT05399498). Although some clinical trials including patients with borderline personality have started, several years might be needed before such population of patients could benefit of the proper optimal dose of psilocybin (MacCallum et al., 2022).

Finally, it is important to acknowledge that other confounding parameters, such as age and the novelty of the psychedelic experience, might interact with the ED95. For instance, the mean age of patients with secondary depression is higher than that of the primary depression subgroup, which could reasonably impact the near maximum dose (39.2 and 56.2 years). Additionally, Li and colleagues, in their meta-analysis, reported that the first or unique dose of psilocybin received was generally more impactful in decreasing depressive symptoms compared to subsequent doses (Li et al., 2022). Hallucinogens-naïve patients may potentially exhibit a more significant response to psilocybin due to the novelty of the psychedelic experience (Haijen et al., 2018). However, in most studies, there was limited to no information available on the lifetime use of hallucinogens among the participants.

4.2. Real-world clinical relevance of results

Our dose-response meta-analysis suggests that the optimal dose of psilocybin significantly varies among patients with resistant depression, those with MDD, and individuals with anxiety disorders. In most cases, the results indicate a very large effect size for the standardized mean difference (1.62 for primary depression and 1.0 for secondary depression). In Li and colleagues' meta-analysis, the effect size observed for psilocybin is also very large but presents a bit more uncertainty (2.19 for primary depression and 1.0 for secondary depressed patients) (Li et al., 2022). In both analyses, the results are much more important that the one communally accepted for conventional antidepressants effect size on depression (0.3) (Cipriani et al., 2018b). Indeed, while neurobiological mechanisms play a crucial role, it is essential to acknowledge that part of the very large effect size observed in our dose-response meta-analysis could also be attributed to factors such as the intensity of the psychedelic experience induced by relevant doses of psilocybin and the supportive psychotherapeutic setting (Yaden and Griffiths, 2021). To note, only a quarter of included patients had previously experimented with at least one psychedelic trip, and in most cases many decades before the trials. Although we here focus on single or two sessions of psychedelic-assisted psychotherapy, only Carhart-Harris and colleagues have compared psilocybin with daily escitalopram treatment and found no significant difference in depression score (Carhart-Harris et al., 2021). This fMRI study supports a specific antidepressant effect of psilocybin combined with psychotherapy from escitalopram, possibly by modulating neuroplasticity. In a recent analysis of the fMRI data of this study, Daws and colleagues propose that 5-HT2A receptor-rich higher-order functional networks became more functionally interconnected and flexible after psilocybin treatment – which is not the case with escitalopram – suggesting a specific antidepressant mechanism for psilocybin therapy, the global increases in brain network integration (Daws et al., 2022).

4.3. Dose response association of the occurrence of adverse events

Our results are consistent with good tolerability of psilocybin, with no serious adverse physical or psychological reactions (MacCallum et al., 2022). For overall physical discomfort and elevation of blood pressure, we encountered a significant dose-association with an increasing curve. Most common adverse events were transient, mild to moderate headache and nausea, and we found a significant dose-association with mostly ascending curve, suggesting that highest doses are most likely to generate most side effects. Of importance, the definition of psychological discomfort and 'long-lasting psychotic symptoms' varied across included trials which limit the interpretation of both curves.

For psychological discomfort, all panic reactions reported occurred during the psychedelic trips (potentially associated to the anxious ego dissolution phenomena, or increased disorganization), and were easily handled with immediate psychological support with no requirement of specific medication. These common adverse events during psychedelics trips mostly occur at the highest dose but were not consistently reported in all clinical trials. For instance, in Von Rotz and colleague trials (dose of 15 mg), there were no report of such reactions. On the opposite, in the Davis and colleague trial where the Challenging Experience Questionnaire is used (Barrett et al., 2016), many patients experimented episode of anxiety (26% and 15% for high 30 mg, and low doses 20 mg, respectively), and 2% of patients experimented transient episodes of paranoid ideation (Supplementary Table S4). Long-lasting possible psychotic reactions that last the day following the psilocybin trial, were only described in the Carhart-Harris and colleague trial (illusions, abnormal dreams) (Carhart-Harris et al., 2021). Although these adverse events are rare and dose-dependent, these inconsistent definitions and measures limit our conclusions.

4.4. Limitations

This current meta-analysis has several limitations that contribute to the considerable heterogeneity found in the results. First, although most studies were of good quality, the total number of patients included with primary depression is adequate for dose-response models ($>$300 inclusions), but not for secondary depression, which limits the strength of our findings. Studies with negative results might also not have been published, which could affect the accuracy of the dose-response model. Moreover, while these robust findings allow us to extract a dose-response curve for efficacy, there is often significant heterogeneity in the depres-

sive syndromes included in clinical trials (Østergaard et al., 2011).

Secondly, for the studies including patients with secondary depression, whose pathophysiology is distinct from that of MDD and present a different drug response, considerable heterogeneity is found. These studies encompass various levels of depressive symptoms, such as acute stress disorder, generalized anxiety disorder, adjustment disorder with anxiety and depressed mood, and dysthymic disorder, due to cancer. We were not able to isolate each diagnosis, making it difficult to address psilocybin efficacy in each diagnosis separately. Furthermore, acute depression was not addressed, limiting extrapolation to such population. Additional double-blind RCTs are warranted to examine the efficacy of psilocybin in treatment-resistant depression, as only one study focused on this population (Goodwin et al., 2022). Although we gathered 7 studies, the long-lasting (>1 months) antidepressant effect of psychedelics is also still a matter of debate. Furthermore, only one study compared psilocybin-assisted psychotherapy to antidepressants, and no comparison to other add-on psychotherapy is available. Long-term safety has also not been studied. Nevertheless, one RCT with 12-months follow-up (Gukasyan et al., 2022) found that the antidepressant effects of two psilocybin doses (total of 50 mg/70 kg) on patients with MDD were sustained during a 12 month follow up. However, the current main questions debated is whether classical placebo are adequate agents for blinding of psychedelics agents (Butler et al., 2022; Nayak et al., 2023), and whether the generalization of results to all populations is coherent (Michaels et al., 2018).

4.5. Consideration for future studies

Despite the mentioned limitations, our results offer innovative insights into approaching the optimal psilocybin dose for treating MDD. However, important aspects of psychedelic-assisted therapy need further consideration. The absence of concrete psychedelic-assisted psychotherapy, as most studies only provided psychological support, and the use of intensity scales to quantify the subjective psychedelic effects of the trip (e.g., the five-dimensional altered states of consciousness) are questionable. Future studies should aim to report factors that may significantly impact the intensity of psychedelic sessions, such as safety and screening, set, setting, therapeutic relationship, open or closed eyes, expectations, and preparation.

In the current studies, the dose-response curves are limited to the total dose administered in each trial for patients with depression. More studies are needed to identify the most effective dosing pattern in terms of efficacy and risk. In particular, future studies should examine the influence of non-pharmacological factors (e.g., subjective aspects of the psychedelic experience) that could mediate the effect of the clinical response (Preller and Vollenweider, 2018).

5. Conclusions

Our findings suggest a dose-response relationship for the use of psilocybin combined with psychotherapeutic support in treating primary depression, with a curve that reaches a plateau. The optimal therapeutic dose, beyond which no further therapeutic gain is observed, depends on the specific patient population and potential confounding factors like age and previous psychedelic experience. In the short term and in clinical settings, psilocybin demonstrates a reasonable safety profile with transient and mostly benign adverse events. This dose-response curve for the efficacy of psilocybin will aid in designing future clinical trials, particularly for populations with treatment-resistant depression and other co-morbid diagnoses related to depression.

Availability of the code and other materials

The code used for analysis is available via open access at the following link: https://cran.r-project.org/web/packages/dosresmeta/index.html

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Author contributions

NP and FL screened papers and extracted data. NP and Mis ran analyses and wrote the first draft of the paper. MS and MiS designed the study, provided supervision, ran analyses, and critically revised the paper. All authors contributed equally to the final version of this paper.

Conflict of interest

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Supplementary materials

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