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Psychedelics as an intervention for psychological, existential distress in terminally ill patients: A systematic review and network meta-analysis

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Mattia Marchi[1,2], Riccardo Farina[3], Karim Rachedi[1], Francesca Laonigro[1], Marija Franka Žuljević[4], Luca Pingani[1,2], Silvia Ferrari[1,2], Metten Somers[5], Marco P. M. Boks[5,6,7] and Gian M. Galeazzi[1,2]

Abstract

Background: The interest in psychedelics as a therapeutic intervention for existential distress of people with terminal illness grounds on their mechanism of action and effect on the spiritual/existential aspects accompanying end-of-life experiences.

Aims: This systematic review and network meta-analysis aimed at examining the efficacy and safety of psychedelic compounds for existential distress in terminally ill people.

Methods: PubMed, CINAHL, PsycINFO, EMBASE, and clinicaltrials.gov were searched for randomized controlled trials (RCTs) administering psychedelics for existential distress in people with terminal illnesses. Meta-analysis estimated the standardized mean difference (SMD) and odds ratio (OR), with corresponding 95% confidence intervals (95% CI), between treated and control groups in pairwise and network comparisons, using random-effects models. Post-treatment measures of depression and anxiety, as proxies of existential distress, and tolerability were the primary outcomes.

Results: Nine studies, involving 606 participants (362 treated with psychedelics: psilocybin, ketamine, 3,4-methylenedioxymethamphetamine, and lysergic acid diethylamide (LSD)) were included. The meta-analysis supported the efficacy of psychedelics on depression (SMD: –0.80 (95% CI: –0.98, –0.63)) and anxiety (SMD: –0.84 (95% CI: –1.20, –0.48)). Network meta-analysis identified psilocybin as the most effective compound for depression, and LSD for anxiety. However, head-to-head comparison between psychedelics did not reach statistical significance. The rates of treatment discontinuation and adverse events between psychedelics and controls were comparable.

Conclusions: Psychedelics, especially psilocybins and LSD, showed promising effects on depression and anxiety in people with terminal illnesses. Limitations include the small number of RCTs, methodological issues related to blinding, and the lack of direct comparisons between psychedelic compounds. Larger studies and comparative research are needed to consolidate these findings.

Keywords

Psychedelics, anxiety, depression, cancer, end-of-life care

Introduction

Psychedelics belong to the group of hallucinogens and are a group of compounds capable of inducing alterations in perception, mood, and various cognitive processes (Carhart-Harris, 2019). Conventional hallucinogenic, such as psilocybin, mescaline, and N, N-dimethyltryptamine (DMT), can be found in nature in plants, animals, or mushrooms and have been used by various native societies for a very long time, especially in ceremonial rites (Nichols et al., 2017). A transformative chapter in the history of psychedelics started with the discovery of lysergic acid diethylamide (LSD) in 1938 by the Swiss chemist Albert Hofmann (Sessa, 2018).

Although early research in the 1950s and 1960s explored the potential of psychedelics in psychotherapy (Pahnke et al., 1970), their recreational use during the counterculture movement led to widespread prohibition (Nutt et al., 2020). The Controlled Substances Act of 1970 classified many psychedelics as Schedule I drugs, impeding further scientific exploration (Bogenschutz and Johnson, 2016). This barrier was further compounded by the

[1]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
[2]Dipartimento ad Attività Integrata di Salute Mentale e Dipendenze Patologiche, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Emilia-Romagna, Italy
[3]Department of Mental Health and Drug Abuse, AUSL Modena, Modena, Italy
[4]Department of Medical Humanities, University of Split School of Medicine, Split, Splitsko-Dalmatinska, Croatia
[5]Department of Psychiatry, Brain Center University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands
[6]Department of Psychiatry, Amsterdam UMC, Amsterdam, The Netherlands
[7]Dimence Institute for Specialized Mental Health Care, Dimence Group, Deventer, The Netherlands

Corresponding author:
Gian M. Galeazzi, Dipartimento ad Attività Integrata di Salute Mentale e Dipendenze Patologiche, Azienda USL-IRCCS di Reggio Emilia, Via Giovanni Amendola 2, Reggio Emilia 42122, Italy.
Email: GianMaria.Galeazzi@ausl.re.it

lack of governmental funding for psychedelics research (Barnett et al., 2022).

The interest in the therapeutic potential of psychedelics re-emerged in the 21st century, driven by shifting societal attitudes and renewed scientific curiosity (Rivera-García and Cruz, 2023).

Psychedelics can be most concretely classified based on their pharmacology. Classical psychedelics, such as psilocybin, LSD, mescaline, and DMT, share agonist action at the serotonin 2A receptor subtype (5-HT2AR) (Carhart-Harris, 2019). Non-classical psychedelics like ketamine and 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy) act through other pathways, such as the antagonism on the N-Methyl-D-Aspartate Receptor (NMDAR) or monoamine modulation (Ley et al., 2023; Liechti and Holze, 2022; Marchi et al., 2022). Psychedelics then induce neurobiological changes in the central nervous system (CNS) encompassing heightened plasticity, increased brain entropy, and network disintegration and desegregation, which relate to profound modifications in consciousness and experience (Carhart-Harris and Goodwin, 2017). At the phenomenological level, this translates into changes in cognition, affect, and emotion, which may include hallucinations, mood elevation, an increase in emotional empathy, a heightened sense of introspection, and mystical-type experiences (Griffiths et al., 2011; Kometer et al., 2012; Liechti et al., 2017; Maclean et al., 2012; Schmid et al., 2015).

These psychedelic effects have drawn attention to their potential for treating a range of psychological conditions, including mood, anxiety, and addiction disorders (Chi and Gold, 2020; Gill et al., 2020; Giribaldi et al., 2021; Goel and Zilate, 2022; Marchi et al., 2022; Mitchell et al., 2021; Muttoni et al., 2019). The so-called "psychedelic experience," accompanied by preparation, dosing, psychological support, and integration is considered by most the supposed mechanism of action of the treatment (Carhart-Harris et al., 2018, 2021; Davis et al., 2021). In contrast, there is also a recent branch of research focusing on altering psychedelic treatments to remove the psychedelic experience, to putatively improve tolerability and deliverability (Husain et al., 2023; Lii et al., 2023; Rosenblat et al., 2023).

Recent research has also begun exploring the use of psychedelics in palliative care, particularly for alleviating existential distress in individuals with advanced, progressive, incurable diseases, or acute life-threatening conditions (Baker-Glenn et al., 2011; Schimmel et al., 2022). Existential distress encompasses a range of psychological and emotional challenges related to facing the end of life, including loss of meaning, death anxiety, and despair (Arrieta et al., 2013). From a psychopathological perspective, symptoms of depression, anxiety, and a desire to hasten death are common in patients experiencing existential distress (Mitchell et al., 2011).

While antidepressants and, to a lesser extent, benzodiazepines are used for depressed mood and anxiety in cancer patients, the evidence supporting their efficacy is limited and conflicting (Grassi et al., 2014; Ostuzzi et al., 2015; Walker et al., 2014). Antidepressants show delayed onset of clinical improvement, high relapse rates, and significant side effects which compromise treatment adherence, whereas benzodiazepines are generally only recommended for short-term use because of side effects and tolerance (Freedman, 2010; Gerhard et al., 2016; Li et al., 2012; Ostuzzi et al., 2015; Walker et al., 2014). Some existentially oriented psychotherapies have been developed to address these existential/spiritual issues; however, psychological approaches have shown only modest to moderate effects in alleviating emotional distress and improving quality of life (Breitbart et al., 2015; LeMay and Wilson, 2008; Spiegel, 2015). Consequently, there is a lack of pharmacotherapies or evidence-based combined pharmacological-psychosocial interventions for treating existential distress in cancer patients.

Given the molecular mechanism of action akin to antidepressants, and the impact on the spiritual and existential domains of psychological distress, the use of psychedelics to treat existential distress in terminally ill patients appears rational. Caregivers and healthcare practitioners in palliative and end-of-life settings have also expressed interest in psychedelic-assisted therapies for their patients, recognizing the potential benefits (Reynolds et al., 2022). Randomized controlled trials (RCTs) on this topic are increasingly available; however, the heterogeneity in the classification of these compounds and practical complexities, such as ensuring blinding, contribute to mixed trial results, and low-quality evidence (Schimmel et al., 2022).

In this systematic review and network meta-analysis, we aimed to assess the safety and efficacy of the treatment with psychedelics for existential distress in terminally ill people, and by comparing the different psychedelic compounds to identify which ones display a promising therapeutic profile.

Methods

This systematic review and meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Page et al., 2021). The protocol of this study was registered with PROSPERO (CRD42023467738).

Search strategy and selection criteria

We searched the PubMed (Medline), CINAHL, PsycINFO, EMBASE, and ClinicalTrials.gov databases until December 31st, 2023, using the strategy outlined in the Supplemental Table 1 of the Appendix. No restrictions regarding the language of publication or publication date were set. All RCTs (parallel group, crossover, or cluster) comparing psychedelics used as monotherapy or as add-on treatment via any route of administration to placebo or other active comparators in adults (aged 18 years or above) with life-threatening illness were eligible for the review. We consider life-threatening condition as any incurable or irreversible illness. We included trials of any of the following medications: classical psychedelics (whose mechanism of action involves serotonin), including psilocybin, LSD, mescaline, and DMT; non-classical psychedelics (with other mechanisms of action than serotonin), including ketamine and MDMA. We excluded qualitative studies, case reports, case series, and reviews, although the reference lists of the reviews have been screened to identify any potentially eligible studies that could have been missed during the literature search. We only included studies published in peer-reviewed journals, excluding conference abstracts and dissertations. If data from the same sample were published in multiple works, we performed deduplication by considering only the study that reported more exhaustive information. Sample overlap was ruled out through a careful check of the registration codes as well as the place and year(s) of sampling.

Outcomes

For our primary outcome, we considered efficacy, which we measured as the score on validated questionnaires on depression and anxiety, as proxies of existential distress. Where available, we also considered as secondary outcomes the pre-post treatment change in quality of life and death acceptance. Finally, we considered tolerability as the rate of dropouts due to any cause, dropouts due to adverse effects, overall side effects, and death, in the trial's arms. We assessed those outcomes available at the times closest to the median follow-up duration across the studies. Studies not reporting a quantitative estimation of at least one of these outcomes were excluded.

Data collection and extraction

All retrieved articles in the original search were screened independently by two review authors (M. M. and R. F.) for inclusion, first on the title, followed by the abstract. This initial screening was followed by the analysis of full texts to check compliance with inclusion/exclusion criteria: M. M. and R. F. independently screened full texts to identify studies for inclusion and recorded reasons for exclusion. All disagreements were explored until consensus was reached, and if consensus was not possible, another member of the team was consulted (G. M. G.). For each eligible trial, the review authors independently extracted the following information: (1) study characteristics (first author's last name, year of publication, country, study setting, eligibility criteria, number of participants randomized in each arm, number of participants with outcome assessment); (2) participant characteristics (age, sex, psychiatric diagnoses and stage of illness, symptoms severity at baseline, ongoing psychiatric treatment); (3) intervention details (comparator used, number of sessions, prescribed dosage and range, route of administration, co-interventions); (4) outcome measures of interest in each treatment arm (as post-treatment means and standard deviations (SDs) for continuous measures, and number of events for binary outcomes) and time of data collection. Extraction sheets for each study were cross-checked for consistency and any disagreement was resolved by discussion within the research group.

Statistical analysis

First, we did pairwise meta-analyses (psychedelics vs. controls) for our primary outcomes, namely depression and anxiety levels. Hedges' g standardized mean difference (SMD) for continuous outcomes, and pooled odds ratio (OR) for dichotomous outcomes, with 95% confidence intervals (95% CIs) were estimated using inverse variance models with random effects (DerSimonian and Laird, 1986). We used data from the intention-to-treat analyses in the included studies. The results were summarized using forest plots. Standard Q tests and the I^2 statistic (i.e. the percentage of variability in prevalence estimates attributable to heterogeneity rather than sampling error or chance, with values of $I^2 \geqslant 75\%$ indicating high heterogeneity) were used to assess between-study heterogeneity (Higgins and Thompson, 2002). When the meta-analysis included at least 10 studies (Sterne et al., 2011), we performed funnel plot analysis and the Egger test to test for publication bias. If analyses showed a significant risk of publication bias, we would use the trim and fill method to estimate the number of missing studies and the adjusted effect size (Duval and Tweedie, 2000; Sterne et al., 2008; Sutton et al., 2000; Terrin et al., 2003). Leave-one-out analysis and meta-regression were performed to examine sources of between-study heterogeneity. Meta-regression analysis was performed on a range of study-prespecified characteristics (i.e. age and sex of study participants, the country where the study was performed, level of depression or anxiety at the baseline, study design, and setting).

Next, we conducted random-effects network meta-analyses on both the primary and secondary outcomes to compare the efficacy and tolerability of different psychedelic compounds and comparators (Miladinovic et al., 2014; Salanti, 2012). We assumed that the amount of heterogeneity was the same for all treatment comparisons, and based the assessment of statistical heterogeneity in the entire network on the magnitude of the common τ^2 estimated from the network meta-analysis models (Jackson et al., 2014). We compared the magnitude of the heterogeneity variance with the empirical distribution (Rhodes et al., 2015; Turner et al., 2012). We used the loop-specific approach (Veroniki et al., 2013) and the design-by-treatment model (Higgins et al., 2012) to evaluate incoherence locally and globally, respectively. We established a hierarchy of competing interventions using surface under the cumulative ranking curve (SUCRA) and mean ranks (Salanti et al., 2011). We presented the results graphically using network graphs, forest plots, and rankograms.

The analyses were performed using *meta*, *metafor*, and *netmeta* packages in R (Balduzzi et al., 2019, 2023; R Core Team, 2024; Schwarzer, 2021). Statistical tests were 2-sided and used a significance threshold of $p < 0.05$.

Risk of bias assessment and the GRADE

Bias risk in the included studies was independently assessed by two review authors (R. F. and M. M.), using the Cochrane risk of bias tool (Higgins et al., 2011). Each item on the risk of bias assessment was scored as high, low, or unclear, and the GRADE tool was used to assess the certainty of evidence for each outcome (Schünemann et al., 2013). Further information is available in the Supplemental Appendix.

Statement of ethics

This systematic review is exempt from ethics approval because collected and synthesized data from previous studies in which ethical approval has already been obtained by the trial investigators at their respective local sites.

Results

Study characteristics

Figure 1 summarizes the paper selection process: from 248 records screened on title and abstract, 66 full texts were analyzed. Additionally, we found on clinicaltrials.gov current ongoing trials (thus, not included in this review): 11 on psilocybin and 1 on MDMA to treat depression, anxiety, or demoralization in people with cancer.

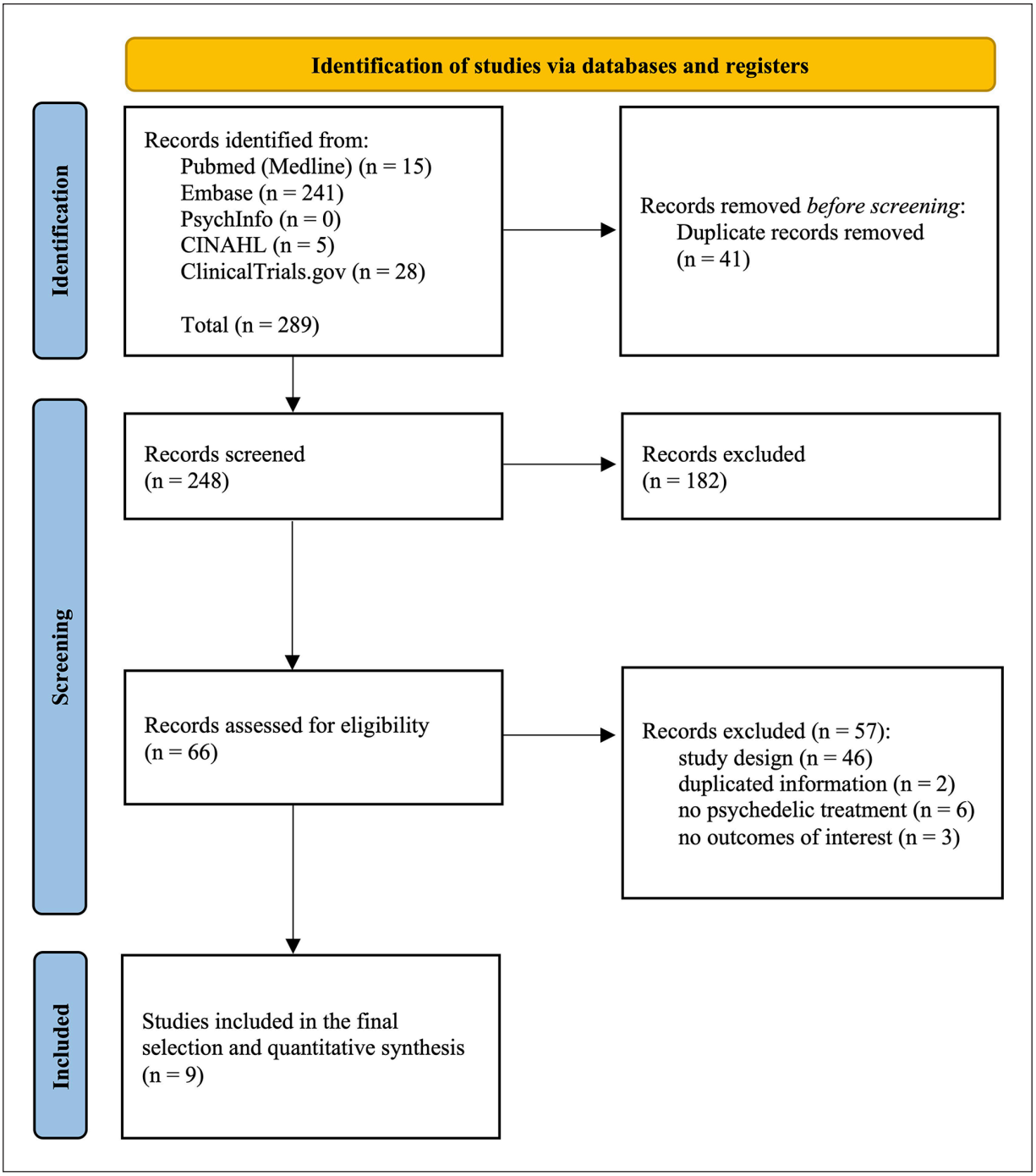

Figure 1. PRISMA flow diagram.
PRISMA: preferred reporting items for systematic reviews and meta-analyses.

The review process led to the selection of nine studies (Fan et al., 2017; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Holze et al., 2023; Liu et al., 2021; Ross et al., 2016; Wolfson et al., 2020; Xu et al., 2017), referring to nine different samples, corresponding to a total of 606 people (out of which 362 were treated with psychedelics and 244 were controls), which were included in the quantitative synthesis.

The trials were conducted in 3 countries: USA ($n=4$; 44%), China ($n=3$; 33%), and Switzerland ($n=2$; 22%). The overall percentage of females across the studies was 66%, mean age was 49.7 (SD = 5.2) years. The median duration of the trials was 28 days, ranging from 3 days to 6 months. All the studies involved participants with cancer, and three studies (33%) also involved people with other life-threatening conditions, such as amyotrophic lateral sclerosis (ALS), multiple sclerosis, or severe rheumatic conditions (such as vasculitis or connective disorders). The psychedelic treatment administered in the study were psilocybin ($n=3$; 33%), ketamine ($n=3$; 33%), LSD ($n=2$; 22%), and MDMA ($n=1$; 11%), used as monotherapy. The most common comparator was placebo ($n=6$; 67%), the remaining

trials used midazolam, LSD, and psilocybin both at a placebo-intended dose (each $n = 1$; 11%). The standardized mean score of depression and anxiety symptoms at the baseline, calculated as the mean of each sample mean score divided by its respective standard deviation, was 3.58 (SD = 2.12) and 5.82 (SD = 1.83), respectively. From a qualitative perspective, the modal value for depression was "moderate" and for anxiety "severe." The main characteristics of the studies included in the review are summarized in Table 1 (see also Supplemental Table 2 for details on the outcome measures considered in each study).

Pairwise meta-analyses of primary outcomes

The meta-analysis of the effect of psychedelics on depression included nine studies and yielded evidence supporting a large and significant effect of the treatment in reducing depressive symptoms (SMD: −0.80 (95% CI: −0.98, −0.63)), with no evidence of between-study heterogeneity (I^2: 0%; p-value: 0.734). The results are summarized in Figure 2.

The meta-analysis of the effect of the psychedelic treatment on anxiety symptoms was based on five studies and supported the efficacy of the treatment in reducing the anxiety symptoms, with a large effect (SMD: −0.84 (95% CI: −1.20, −0.48)), with evidence of negligible heterogeneity between the studies (I^2: 20%; p-value: 0.287). The results are summarized in Figure 3.

Although testing publication bias is suboptimal when using less than 10 studies, our investigation did not identify publication bias in either of the two analyses, as shown by Egger's test p-value > 0.05 and the funnel plots displayed in the Supplemental Figures 1 and 2.

The sensitivity analyses using the leave-one-out method, in which the meta-analyses of depression and anxiety are repeated after the exclusion of each study, showed no meaningful changes (i.e. <10%) in the effect size estimate and heterogeneity. This indicates that the results were not disproportionally influenced by any single study. The results of leave-one-out analyses are displayed in Supplemental Table 3.

The univariable meta-regression of the antidepressant and anxiolytic effects of psychedelic treatment were performed separately, on the following variables potentially acting as treatment effect modifiers: (1) mean age of participants, (2) mean percentage of females in the sample, (3) severity of symptoms of depression or anxiety at the baseline, (4) the country where the study was performed, (5) the study design (i.e. RCT vs. crossover RCT, and (6) the setting in which the treatment was delivered. The results of these analyses are presented in Table 2, and found that the estimate of the antidepressant effect of psychedelics was higher in crossover trials (unstandardized linear regression coefficients (B): −0.839 (95% CI: −1.14, −0.537)), conducted in China (B: −0.817 (95% CI: −1.03, −0.601)), and administering the psychedelic treatment in calm room (B: −1.01 (95% CI: −1.50, −0.52)). Regarding the anxiolytic effect, crossover RCT study design (B: −0.773 (95% CI: −1.18, −0.368)) conducted in Switzerland (−0.989 (95% CI: −1.77, −0.206)) provided higher estimates of the treatment effect.

Network meta-analyses of primary outcomes

We performed distinct network meta-analyses for depression and anxiety to explore the differential efficacy of individual

Table 1. Characteristics of the included studies.

Author, year (Trial ID)	Study design	Country	Diagnosis	Setting	Follow-up	*N* treatment/ *N* control	% Females	Mean age (SD) or range	Treatment	Control	*N* of sessions
Fan et al. (2017) (NR)	RCT	China	Cancer	Inpatient clinic	1 and 3 days	20/17	25	45.8 (14.4)	0.5 mg/kg racemic ketamine iv	0.05 mg/kg midazolam iv	One administration
Gasser et al. (2014) (NR)	RCT	Switzerland	Life-threatening illness (mostly cancer)	With psychological support	8 weeks	8/3	36	51.7 (9.1)	200 µg LSD po	20 µg LSD po	Two sessions 2 to 3 weeks apart
Griffiths et al. (2016) (NCT00465595)	Crossover RCT	USA	Life-threatening cancer	Aesthetic living-room-like environment	5 and 26 weeks	25/25	49	56.3 (1.4)	0.3–0.4 mg/kg psilocybin po	0.01–0.04 mg/kg psilocybin po	Two sessions 5 weeks apart
Grob et al. (2011) (NCT00302744)	Crossover RCT	USA	Life-threatening cancer (advanced stage)	Calm room within a medical center's unit	2 weeks	12/12	92	36–58	0.2 mg/kg psilocybin po	250 mg niacin po	Two sessions several weeks apart
Holze et al. (2023) (NCT03153579)	Crossover RCT	Switzerland	Life-threatening illness (mostly cancer)	With psychological support	2, 8, and 16 weeks	42/42	48	45 (12)	100 mg in 1 mL of solution with 96% ethanol po	1 mL 100% of ethanol po	Two sessions 6 weeks apart
Liu et al. (2021) (NR)	RCT	China	Cancer	Intra-operative administration	3 days; 1, 4, and 12 weeks	203/100	100	47.4 (9.4)	0.125 mg/kg racemic ketamine iv	saline solution iv	One administration
Ross et al. (2016) (NCT00957359)	Crossover RCT	USA	Life-threatening cancer	With psychological support	6 and 26 weeks	14/15	62	56.3 (12.9)	0.3 mg/kg psilocybin po	250 mg niacin po	One session
Wolfson et al. (2020) (NCT02427568)	RCT	USA	Life-threatening illness (mostly cancer)	Assisted psychotherapy	4 weeks	13/5	78	54.9 (7.9)	125 mg MDMA po	125 mg lactose po	Two sessions 2–4 weeks apart
Xu et al. (2017) (NR)	RCT	China	Cancer	Intra-operative administration	1 week	25/25	100	42.8 (6.7)	0.5 mg/kg racemic ketamine iv	saline solution iv	One administration

iv: intravenous route of administration; LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; N: number; NR: information not reported; po: "per os," namely oral route of administration; RCT: randomized controlled trial; SD: standard deviation; USA: United States of America.

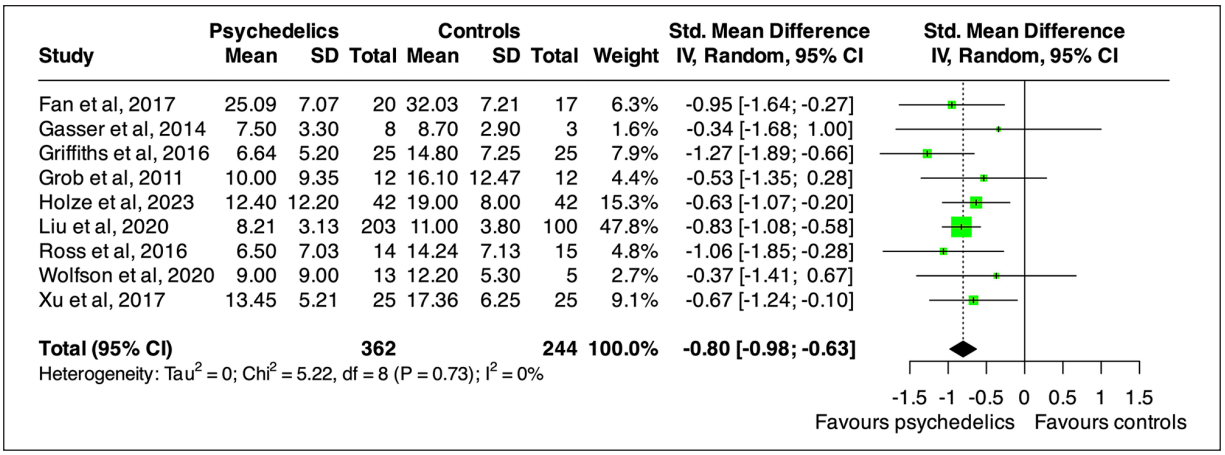

Figure 2. Forest plot of depression among psychedelic and control groups.
Note: The measures of depression across the studies were scaled as lower scores indicate lower depression.
IV: inverse variance; SD: standard deviation; 95% CI: 95% confidence interval.

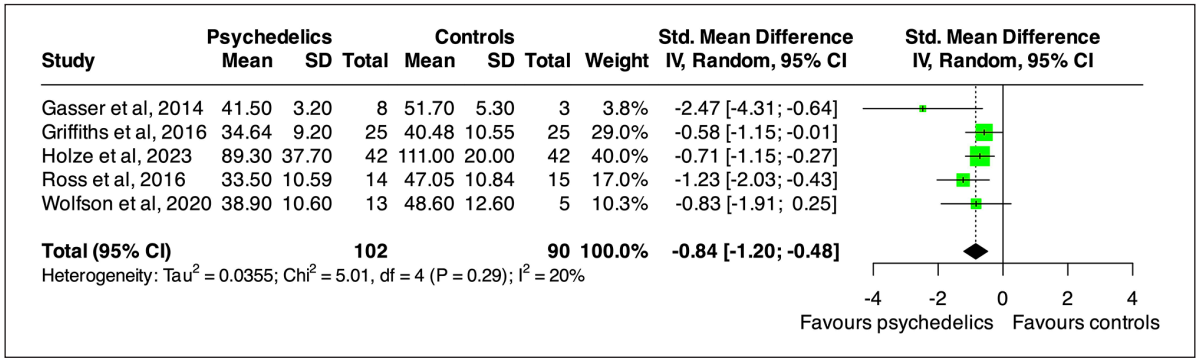

Figure 3. Forest plot of anxiety among psychedelic and control groups.
Note: The measures of anxiety across the studies were scaled as lower scores indicate lower anxiety.
IV: inverse variance; SD: standard deviation; 95% CI: 95% confidence interval.

Table 2. Univariable meta-regression results on antidepressant and anxiolytic effects of the treatment with psychedelics.

	Depression		Anxiety	
Variable(s)	*B* (95% CI)	*p*-value	*B* (95% CI)	*p*-value
Age	−0.029 (−0.074, 0.016)	0.203	−0.011 (−0.106, 0.085)	0.830
% Females[a]	0.001 (−0.005, 0.008)	0.714	0.002 (−0.037, 0.042)	0.908
Symptom severity at the baseline	−0.022 (−0.096, 0.050)	0.540	−0.17 (−0.594, 0.254)	0.432
Country				
USA	−0.116 (−0.559, 0.326)	0.607	0.141 (−0.857, 1.14)	0.782
China	−0.817 (−1.03, −0.601)	<0.001	NA	NA
Switzerland	0.211 (−0.258, 0.681)	0.378	−0.99 (−1.77, −0.206)	0.013
Study design				
RCT	0.052 (−0.315, 0.419)	0.782	−0.503 (−1.56, 0.557)	0.352
Crossover RCT	−0.839 (−1.14, −0.537)	<0.001	−0.77 (−1.18, −0.368)	<0.001
Setting				
Psychotherapy[b]	0.339 (−0.262, 0.939)	0.269	0.865 (−2.77, 4.50)	0.392
Calm room	−1.01 (−1.50, −0.52)	<0.001	−0.403 (−1.33, 0.520)	0.144
Inpatient clinic	0.056 (−0.787, 0.899)	0.897	NA	NA
Intra-operative	0.206 (−0.335, 0.746)	0.456	NA	NA

B: unstandardized linear regression coefficient; NA: information not available; RCT: randomized controlled trial; 95% CI: 95% confidence intervals.
[a]Sex assigned at birth.
[b]Psychedelic-assisted psychotherapy and psychedelic treatment with psychological support are collapsed in this category.

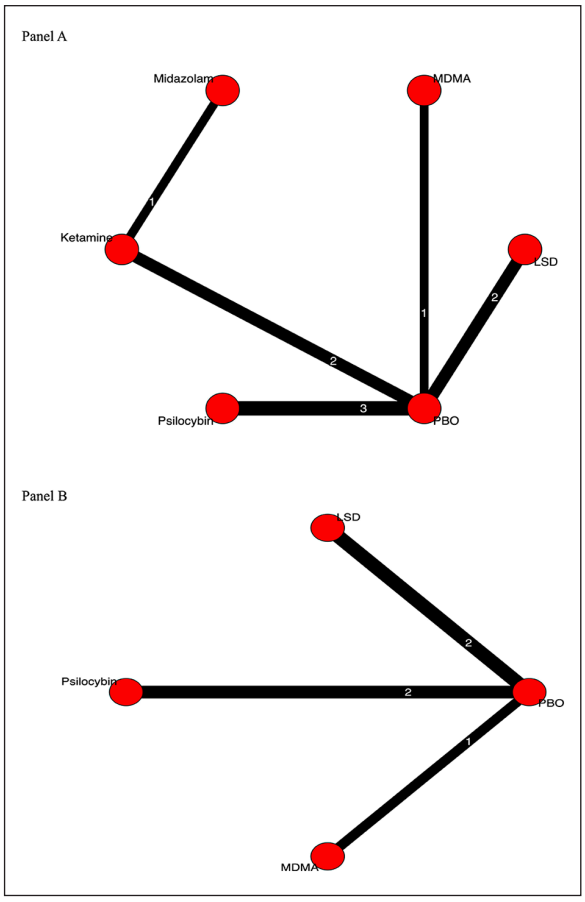

Figure 4. Network meta-analysis of eligible comparisons for the antidepressant effect (Panel A) and anxiolytic effect (Panel B).
Note: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (i.e. sample size).
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PBO: placebo.

psychedelic compounds for each condition. As can be seen in Figure 4, showing the network of eligible comparisons for the antidepressant and anxiolytic effects, all the psychedelic compounds had at least one placebo-controlled trial for the antidepressant effect, and ketamine was also compared to midazolam. For the anxiolytic effect, ketamine trials were not available. Notably, there were no trials comparing different psychedelics, therefore direct comparisons between psychedelics were not present in our network.

In terms of efficacy, ketamine, psilocybin, LSD, but not MDMA (and Midazolam) were more effective than placebo in reducing depressive symptoms. Psilocybin showed the largest antidepressant effect (SMD: −1.05 (95% CI: −1.46, −0.63)), followed by ketamine (SMD: −0.81 (95% CI: −1.03, −0.58)), and LSD (SMD: −0.61 (95% CI: −1.03, −0.20)). Concerning anxiety, only LSD showed a significant anxiolytic effect compared to placebo (SMD: −1.28 (95% CI: −2.44, −0.13)); while point estimates of the anxiolytic effect of psilocybin and MDMA favored these compounds, their CIs crossed the line of no effect, indicating that the advantage over placebo was not statistically significant (SMD: −0.90 (95% CI: −1.93, 0.13) and SMD: −0.87 (95% CI: −2.55, 0.81), for psilocybin and MDMA respectively). Interestingly, none of the psychedelic compounds outperformed the others in the head-to-head comparison (see Supplemental Figures 3 and 4 for all comparisons).

Since there were no closed loops in our networks, it was possible to assess within-design heterogeneity but not between-design inconsistency. Heterogeneity estimates ranged between I^2 0% for depression and 69% for anxiety. Figure 5 shows the network meta-analysis results for the effect of psychedelics compared to placebo on the primary outcomes.

Network meta-analyses of safety and tolerability

Across the trials, no death occurred, and discontinuation only appeared in one trial 1.8% of patients (1 out of 56) in both the treatment (psilocybin) and placebo arms due to adverse events. Given this limited number of events across the trials, it could be argued that the treatment with psychedelics was overall safe and well tolerated. In terms of the rates of treatment discontinuation due to any cause and the occurrence of any adverse effects, the network meta-analysis included three psychedelic compounds (i.e. LSD, MDMA, and psilocybin) for the first outcome, and ketamine in addition for the latter, all compared to placebo. The network graphs for these comparisons are displayed in Figure 6.

In the trials included in our network meta-analysis, only one case was reported where therapy was stopped due to anxiety accompanied by transient paranoid thoughts during psilocybin treatment (Griffiths et al., 2016); otherwise, no instances of severe adverse events were reported. Moreover, mild adverse events were transient and self-resolving at the end of psychedelic treatment. These included nausea and vomiting, psychological discomfort, and anxiety for psilocybin; thirst, jaw clenching, dry mouth, headache, and sweating immediately after administration of MDMA, and approximately 1 week after the administration fatigue, insomnia, and low mood (Wolfson et al., 2020). Nausea and dizziness were also reported in ketamine treatment (Liu et al., 2021; Xu et al., 2017). A transient increase in blood pressure has been reported for most psychedelics (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Holze et al., 2023; Ross et al., 2016).

The meta-analyses found no significant differences between the psychedelic compounds and placebo in terms of rates of treatment discontinuation for any cause and the occurrence of any adverse effects. The heterogeneity was I^2 0% for the analysis of the rate of treatment discontinuation, and 36% for the analysis of any adverse effects. The results are summarized in Figure 7 (see Supplemental Figures 5 and 6 for all comparisons).

We integrated analyses of efficacy and tolerability to perform head-to-head comparisons of antidepressant and anxiolytic effectiveness across the psychedelic compounds. These analyses found that psilocybin is the most effective and tolerated psychedelic for depression, although its superiority was statistically significant only in comparison to placebo and midazolam. Concerning the anxiolytic effect, LSD resulted superior to MDMA and psilocybin, but without evidence of statistical significance. The results are shown in Tables 3 and 4.

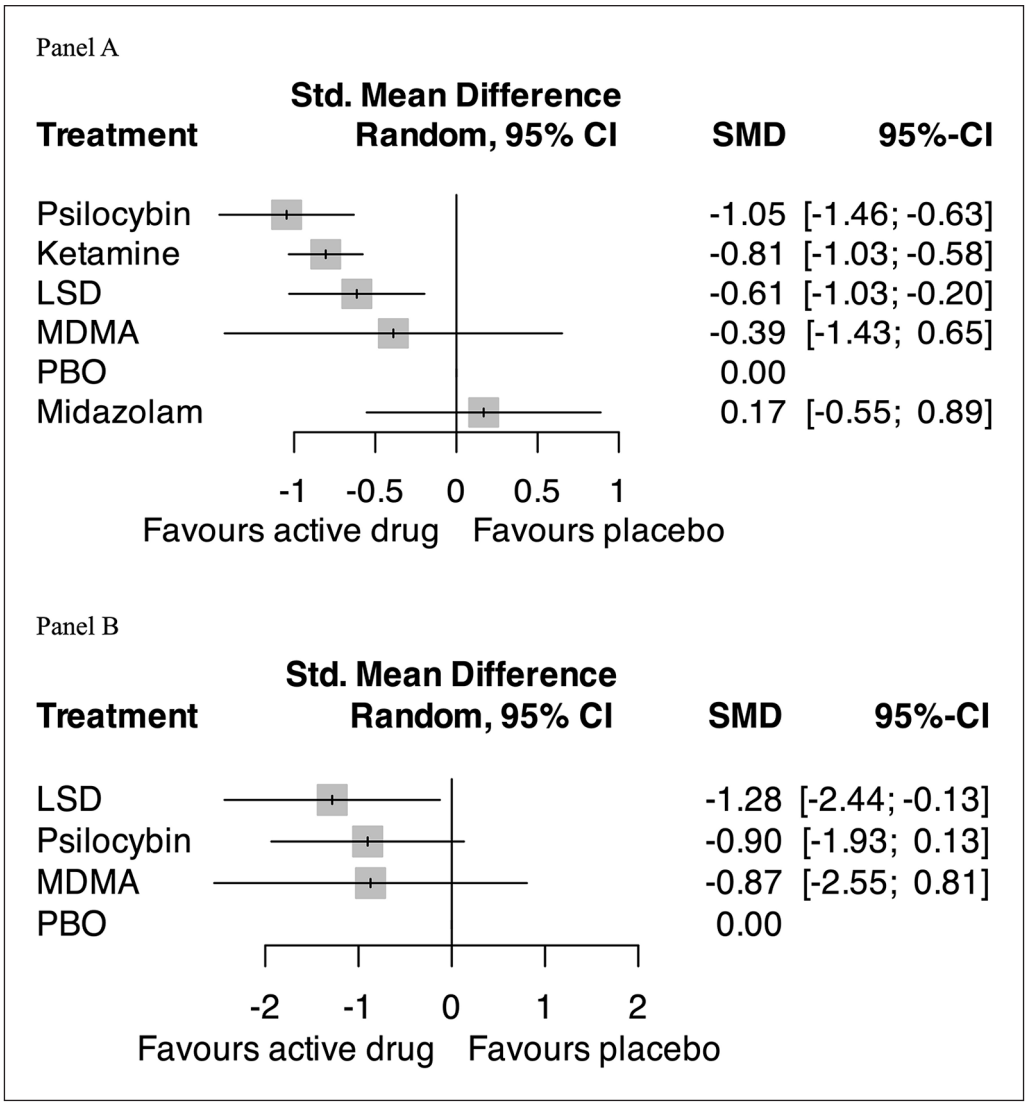

Figure 5. Forest plots of network meta-analysis of all trials for the antidepressant effect (Panel A) and anxiolytic effect (Panel B).
Note: The measures of depression and anxiety across the trials were scaled as lower scores indicate lower symptom severity. Active drugs were compared with placebo, which was the reference compound.
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PBO: placebo; SMD: standardized mean difference; 95% CI: 95% confidence interval.

Network meta-analyses of secondary outcomes

Our secondary outcomes analyses included network comparisons of death acceptance and quality of life across the treatment arms. As can be seen in Supplemental Figure 7, there were three placebo-controlled trials for death acceptance, two used psilocybin and one MDMA; and four placebo-controlled trials for quality of life, of which two used psilocybin, one LSD, and one MDMA. Notably, there were no trials comparing different psychedelics, therefore direct comparisons between psychedelics were not included in our network. Concerning death acceptance, neither psilocybin nor MDMA showed statistically significant efficacy compared to placebo; whereas, for the quality of life, psilocybin was the only treatment showing efficacy (SMD: 0.88 (95% CI: 0.29, 1.47)). Heterogeneity estimates ranged between I^2 41% for death acceptance and 35% for quality of life. Figure 8 shows the network meta-analysis results for the effect of psychedelics compared to placebo on the secondary outcomes (see also Supplemental Figures 8 and 9 for all comparisons).

Treatment hierarchy was evaluated for each outcome and based on 100 simulations. All the ranking of treatments based on cumulative probability plots and SUCRA are displayed in the Supplemental Table 4, and Supplemental Figures 10–15.

GRADE of the evidence

A detailed summary of the risk of bias in all 9 trials has been reported in the Supplemental Appendix (see Supplemental Figures 16 and 17), along with an assessment of the quality of the evidence (see Supplemental Table 5). In the GRADE system, the evidence from RCTs is initially set to high, there were

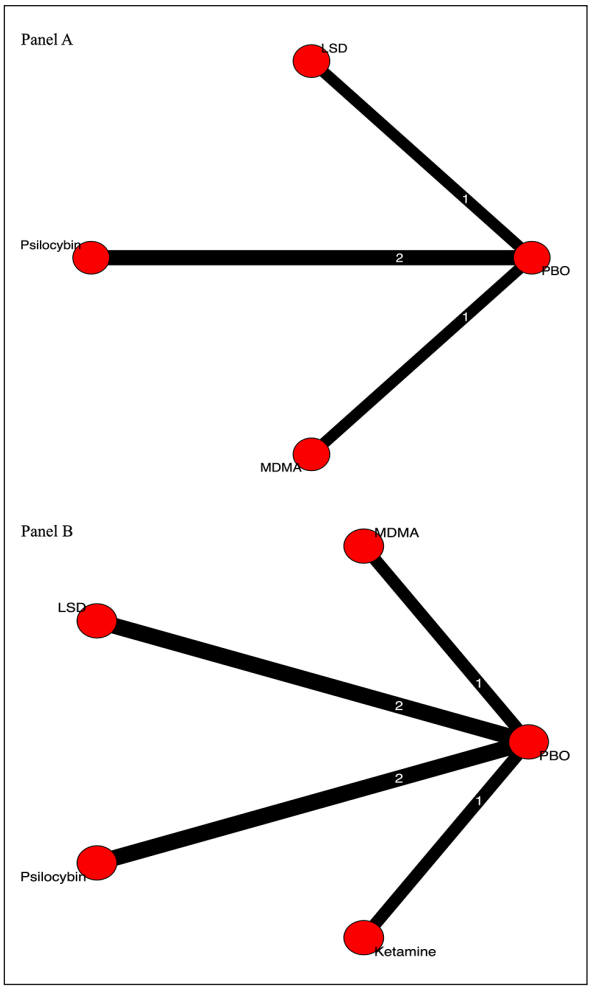

Figure 6. Network meta-analysis of eligible comparisons for the rate of treatment discontinuation due to any cause (Panel A) and the rate of any adverse effects (Panel B).
Note: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (i.e. sample size).
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PBO: placebo.

then criteria that can be used either to downgrade or upgrade (see further information in the Supplemental Appendix). The quality of the evidence was rated from moderate to low, predominantly due to threats related to blinding procedures and a limited number of trials contributing to the pooled estimates.

Discussion

This study set out to investigate the efficacy and safety of both classical and non-classical psychedelics for alleviating symptoms of depression and anxiety, as proxies of existential distress, in terminally ill patients and to identify the psychedelic compounds with more promising therapeutic profiles. Overall, our investigation found that psychedelics can be an effective and safe intervention in end-life care, although the estimates are based on a small number of trials available. Additionally, the difficulties in ensuring blinding procedures in many of the included trials inflate the risk of expectation bias. However, the therapeutic potential of psychedelics in end-life care echoes the findings of a previous systematic review (Schimmel et al., 2022), whose findings are complemented by our study which adds quantitative estimations of the efficacy of the treatment and head-to-head comparisons between different psychedelic compounds. In our network meta-analysis, we found that psilocybin—for depression and overall quality of life—and LSD—for anxiety—are the compounds associated with the largest clinical benefits, however, head-to-head comparison with other psychedelics did not reach statistical significance. These findings are limited also by the absence of research directly comparing different psychedelic compounds. Notwithstanding, the promising therapeutic profile of psilocybin and LSD aligns with current research investigating psilocybin for the treatment of major depressive disorder (MDD) (Giribaldi et al., 2021; Goodwin et al., 2022) and LSD for the treatment of anxiety, also associated with alcoholism (Fuentes et al., 2019; Inserra et al., 2023). In our analyses, LSD was also associated with significant improvements in depression, as well as psilocybin for anxiety, although this latter was without evidence of statistical significance. The comparable efficacy of psilocybin and LSD could have been expected, as their mechanism of action and subjective effects are closely comparable (dos Santos et al., 2016; Ley et al., 2023).

Among the other psychedelic compounds, only ketamine exhibited statistically significant improvement in depression compared to placebo, whereas MDMA was better than placebo but without evidence of statistical significance. Interestingly, ketamine has also been studied for MDD, particularly in treatment-resistant patients, showing efficacy in reducing depressive symptoms and suicidal ideation (An et al., 2021; Bahji et al., 2021; Witt et al., 2020). Instead, MDMA has been mainly studied to assist psychotherapy in the treatment of post-traumatic stress disorder (Mitchell et al., 2021) and there are no studies exploring its therapeutic potential for MDD or anxiety yet. It should be noted that the included trials employed only a single ketamine infusion. Evidence suggests that a standard course of three to six ketamine infusions is often necessary to achieve an acute antidepressant response in treatment-resistant patients (Phillips et al., 2019). Therefore, the effect of ketamine on depression in our study might be underestimated, although the trials involved patients without treatment-resistant depression.

Previous research suggested that the psychedelic experience, leading to changes in consciousness and perception up to the "ego-dissolution," is an important mediator of treatment response (Carhart-Harris, 2019). In contrast, the included studies that administered ketamine to anesthetized patients, thereby canceling out acute psychedelic and dissociative effects, also reported effects on depression, indicating that the psychedelic experience might not be necessarily needed for the effect of ketamine on depression (Liu et al., 2021; Xu et al., 2017). There is an ongoing debate about whether the enduring therapeutic effects of psychedelics are primarily driven by subjective effects—such as mystical-type experiences, psychological insights, and emotional breakthroughs—or by biological mechanisms, involving changes in neuroplasticity (Olson et al., 2021). Future trials should

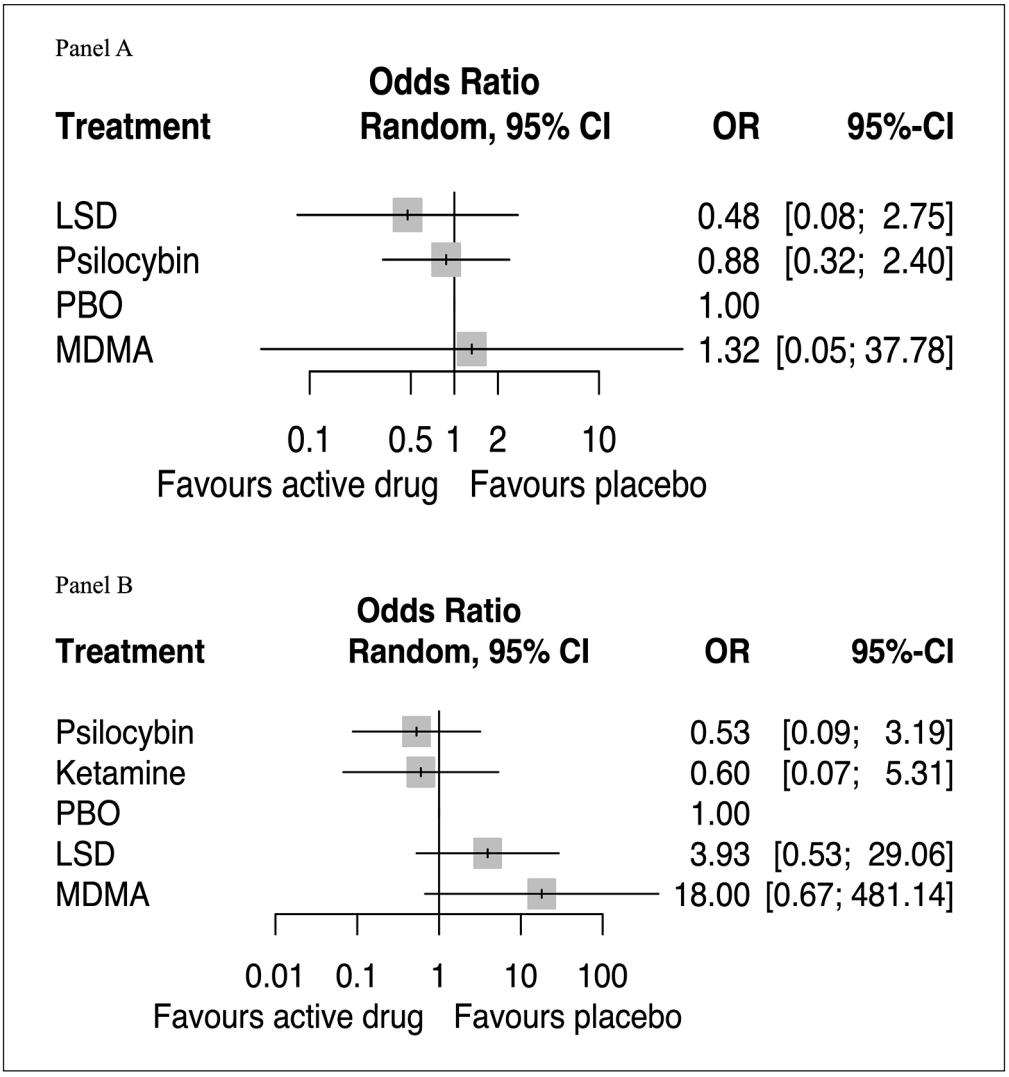

Figure 7. Forest plots of network meta-analysis of all trials for the rate of treatment discontinuation due to any cause (Panel A) and the rate of any adverse effect (Panel B).
Note: Active drugs were compared with placebo, which was the reference compound.
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PBO: placebo; OR: odds ratio; 95% CI: 95% confidence interval.

address the role of subjective patients' experience more thoroughly, as the psychedelic effects are usually either not assessed or regarded as unwanted "psychotic" side adverse effects in clinical trials (Grabski et al., 2020; Mathai et al., 2020).

In the same realm, the results of our meta-regression showed a larger antidepressant effect for psychedelic treatment administered in a calm room, confirming that set and setting are important factors for psychedelic treatment response (Hartogsohn, 2016). Surprisingly, and contrary to previous experience where psychedelics have been mainly used to facilitate psychotherapeutic interventions (Carhart-Harris and Goodwin, 2017; Mitchell et al., 2021; Pahnke et al., 1970), this was not replicated in our meta-regression. This could be related to confusion around the terms "psychedelic-assisted psychotherapy" and "psychedelic therapy with psychological support." Specifically, the latter mainly involves psychological support in preparation, dosing, and integration, while the first indicates the aforementioned in parallel to a non-directive psychotherapy trajectory (Goodwin et al., 2024). Among our study selection, only one study reported a description of the psychological intervention as intended psychedelic-assisted psychotherapy (Wolfson et al., 2020), whereas the others lacked details of the associated psychological intervention, or employed psychological support.

In the analysis of secondary outcomes, psilocybin was associated with the largest improvements in quality of life and albeit without statistical significance death acceptance. Despite the limited number of studies available (i.e. three for death acceptance and four for quality of life), these findings underscore an inherent aspect of the psychedelic experience, involving spirituality, empathy, introspection, and relaxation of high-level beliefs, which are particularly relevant to individuals facing terminal illnesses (Carhart-Harris, 2019). These domains could be better understood by future integration of these results with those from qualitative research exploring the psychedelic experience of

Table 3. Head-to-head comparisons for efficacy and tolerability of the five active drugs for the antidepressant effect.

Ketamine	0.15 (0.01, 2.95)	0.03 (0.01, 1.72)	0	1.13 (0.07, 19.1)
−0.19 (−1.48, 0.65)	LSD	0.22 (0.01, 10.2)	0	7.41 (0.50, 108.9)
−0.42 (−1.48, 0.65)	−0.23 (−1.34, 0.89)	MDMA	0	34.0 (0.80, 1434.5)
−0.97 (−1.66, −0.29)	−0.78 (−1.61, 0.05)	−0.56 (−1.82, 0.71)	Midazolam	0
0.24 (−0.23, 0.71)	0.43 (−0.15, 1.02)	0.66 (−0.46, 1.78)	1.21 (0.38, 2.04)	Psilocybin

Note: Drugs are reported in alphabetical order. The upper half of the table reports tolerability (i.e. the rates of adverse events), and the lower half of the table reports antidepressant efficacy. Data are SMDs with 95% CIs for efficacy and ORs with 95% CI for tolerability. These values compare the treatment specified in the column with the treatment specified in the row. For efficacy, SMDs lower than 0 favor the column-defining treatment (i.e. the first in alphabetical order). For acceptability, ORs lower than 1 favor the first drug in alphabetical order. To obtain SMDs for comparisons in the opposite direction, multiplication by −1 should be taken. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are underscored.
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; ORs: odds ratios; SMDs: standardized mean differences; 95% CIs: 95% confidence intervals.

Table 4. Head-to-head comparisons for efficacy and tolerability of the three active drugs for the anxiolytic effect.

LSD	0.22 (0.01, 10.2)	7.41 (0.50, 108.9)
−0.41 (−2.45, 1.62)	MDMA	34.0 (0.80, 1434.5)
−0.38 (−1.93, 1.17)	0.03 (−1.94, 2.00)	Psilocybin

Note: Drugs are reported in alphabetical order. The upper half of the table reports tolerability (i.e. the rates of adverse events), and the lower half of the table reports anxiolytic efficacy. Data are SMDs with 95% CIs for the efficacy and ORs with 95% CI for tolerability. These values compare the treatment specified in the column with the treatment specified in the row. For efficacy, SMDs lower than 0 favor the column-defining treatment (i.e. the first in alphabetical order). For acceptability, ORs lower than 1 favor the first drug in alphabetical order. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are underscored.
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; ORs: odds ratios; SMDs: standardized mean differences; 95% CIs: 95% confidence intervals.

terminally ill patients. Additionally, considering the potential traumatic value of witnessing the death of a loved one, it could be hypothesized that delivering psychedelic interventions to the closest relatives or to the caregiver could help alleviate their distress and improve reactions to bereavement in the longer term. So far, there are no published trials on this topic, but it is an intriguing avenue for future research.

In terms of safety, our investigation found a similar rate of dropouts and side effects for psychedelics and placebo, suggesting that psychedelic treatment was generally safe and well tolerated, in agreement with previous research (Schimmel et al., 2022; Schlag et al., 2022; White et al., 2023). Also, no case of dependence has been reported in the included trials. However, it can be argued that the occurrence of adverse events in controls (i.e. patients treated with placebo or placebo-intended doses of psychedelics) might have been influenced by the health state of the patients involved in the trials, who are fragile patients with life-threatening conditions, therefore limiting the generalizability of these findings.

According to the results of the current study, we can assert that the administration of psychedelic substances is generally safe, but should be tailored to fit the patient's needs, in relation to their specific condition. Current guidelines (Johnson et al., 2008) likely need updating to allow the safe administration of psychedelic therapy to cancer patients, who are currently excluded by guidelines that recommend administering psychedelic therapy to patients in good overall health. Additionally, current guidelines require that patients have no history of psychotic episodes, neurological disorders, or hypertension (Johnson et al., 2008). Hence, it is desirable to establish new inclusivity criteria that allow the safe utilization of psychedelic therapy also for patients with existential distress and explore approaches ensuring that the effects of psychedelic treatment do not exacerbate or trigger underlying conditions. Given the initial safety indications, it is desirable that investigations into therapeutic applications of psychedelics in end-life care will continue. Furthermore, future trials should focus on optimizing a "personalized" dose of psilocybin or LSD based on the specific needs and health condition of the patient.

Limitations

The results of this review should be interpreted considering its limitations. First, conducting blinded studies with psychedelic compounds poses significant challenges due to their pronounced psychoactive effects. As a result, both patients and evaluators may often correctly guess the treatment arm in many of the included studies. However, high rates of functional unblinding are not unique to psychedelics; as they have also been observed in trials of many psychiatric medications, including benzodiazepines, stimulants, older antidepressants, and antipsychotics (Başoğlu et al., 1997; Covey et al., 2010; Lin et al., 2022; Tajika et al., 2023). Overcoming this limitation is particularly challenging when evaluating psychedelics against placebo or molecules with mild psychoactive effects, such as benzodiazepines or microdose psychedelics. Therefore, future studies comparing different psychedelics at psychoactive dosages are essential to ensure blindness maintenance and enable direct comparisons between psychedelic compounds. Indeed, a second important limitation of our study is the lack of direct comparison data between psychedelics. This aspect particularly limited the performance of the network meta-analysis. Third, four of the nine studies were designed as crossover RCT and were identified as influencing the estimates of the antidepressant and anxiolytic effects favoring psychedelics. In particular, one of these trials unblinded participants after the crossover (Holze et al., 2023), increasing the risk of expectation bias. Also, bias due to the carryover effect (i.e. a continuation of the treatment effect in those transitioning from active agent to placebo without a sufficiently long wash-out period) cannot be ruled out. Fourth, the results of the network meta-analysis are limited by the small sample size due to the reduced number of studies in the literature and the

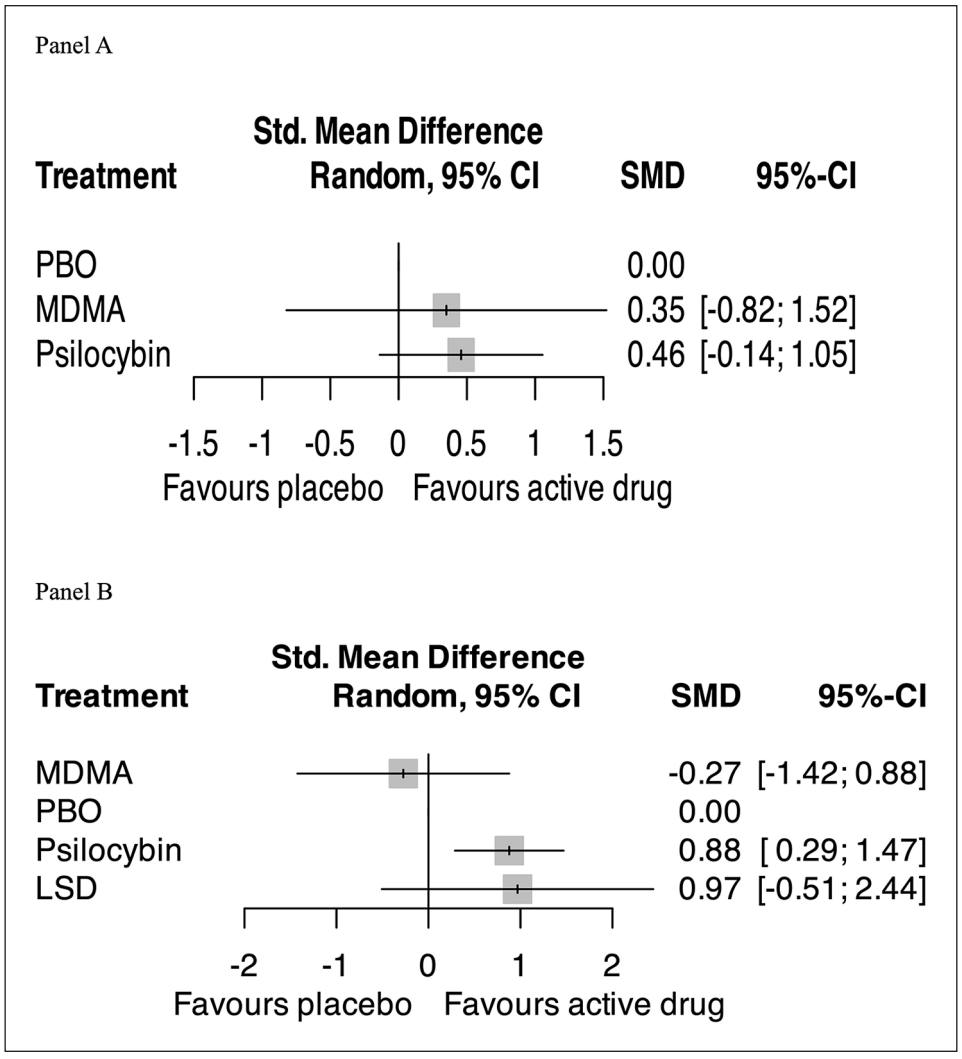

Figure 8. Forest plots of network meta-analysis of all trials for death acceptance (Panel A) and quality of life (Panel B).
Note: The measures of death acceptance and quality of life across the trials were scaled as higher scores indicate a better condition. Active drugs were compared with placebo, which was the reference compound.
LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PBO: placebo; SMD: standardized mean difference; 95% CI: 95% confidence interval.

limited number of participants in individual studies. This is reflected in the estimation of wide CIs, indicative of low statistical power and imprecision. The limited availability of experimental studies on psychedelics may be due to the difficulty in sourcing and experimenting with these compounds, which have long been and still are considered illicit substances in some parts of the world (Nutt et al., 2020). Additionally, it may also be considered as a result of reluctance in the scientific and clinical community regarding their use. Fifth, the included studies were conducted in only three countries: (1) China, (2) USA, (3) Switzerland. Although these reflect studies from three different continents, there are specificities in the compounds tested among the different countries, such as the exclusive use of LSD in Switzerland and ketamine in China. A wider dissemination of clinical trials could be an important objective for future research. Sixth, our search strategy targeted RCTs exclusively with psychedelics, limiting the possibility to perform indirect comparisons, within the network meta-analysis, with other interventions used for existential distress of terminally ill patients, such as "classic" antidepressants. Overall, in spite of the promising results of the studies presented, doubts remain about their generalizability. Therefore, it is advisable to conduct larger studies, ideally blinded and without crossover design, comparing different psychedelic compounds among themselves and with current treatments to better identify the role of psychedelics in alleviating existential distress in terminally ill patients.

Conclusions

In conclusion, our study suggests that psychedelics can be a valid treatment for anxiety and depression associated with life-threatening diseases, showing favorable efficacy and safety. Among the various psychedelic compounds investigated so far, psilocybin exhibited the most promising profile for depression and quality of life, and LSD for anxiety. However, the overall certainty of the evidence was low, mainly due to the limited number of trials

available and difficulties in ensuring effective blinding procedures with compounds having such marked psycho-somatic effects. Further studies with larger sample sizes and comparing different psychedelic compounds are needed to further improve understanding of the therapeutical effects and settle safety concerns, to ultimately inform on the role of psychedelic treatment in end-life care and enable its application in clinical settings.

Data availability statement

The codes for reproducing the datasets and the analyses can be accessed here: https://github.com/MattiaMarchi/Psychedelics-for-existential-distress-in-terminally-ill-people--network-meta-analysis

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ORCID iDs

Mattia Marchi https://orcid.org/0000-0003-2970-1276
Marija Franka Žuljević https://orcid.org/0000-0001-9805-7491
Gian M. Galeazzi https://orcid.org/0000-0003-2706-3362

Supplemental material

Supplemental material for this article is available online.

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