A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE ROLE OF PSYCHOLOGICAL SUPPORT IN TREATMENTS WITH PSILOCYBIN

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Resumo

Introdução: Após o ressurgimento da investigação da psilocibina, os ensaios clínicos têm apresentado resultados promissores relativamente ao efeito terapêutico deste composto nas perturbações relacionadas com a depressão. Embora tenha sido dada uma atenção considerável ao *set* e *setting*, nenhum estudo testou empiricamente o papel do apoio psicológico no aumento dos resultados clínicos positivos. **Objetivo:** O propósito deste estudo é realizar uma revisão sistemática e uma meta-análise para compreender se a psilocibina com intervenção psicológica é clinicamente eficaz e também avaliar como as variáveis da intervenção psicológica influenciam o efeito. **Métodos:** A estratégia de pesquisa e seleção foi concebida de acordo com as normas PRISMA. Foram utilizadas seis bases de dados e a lista final de artigos foi submetida a um processo de seleção independente do título, depois do resumo e, por fim, do texto integral. Foi concebido um modelo de extração de dados. A subsequente extração foi realizada por dois avaliadores independentes. **Resultados:** A revisão sistemática produziu um total de oito estudos no grupo dos estudos controlados randomizados e 10 estudos no grupo de ensaios clínicos. Ambas as meta-análises indicaram tamanhos de efeito significativos ($p<0.001$) e considerado grande. Para testar possíveis moderadores, foram efetuadas meta-regressões, mas não se obtiveram resultados significativos. Foram também efetuadas análises de subgrupos para explorar potenciais fontes de modificação do efeito. **Discussão:** Os tratamentos com psilocibina com apoio psicológico são clinicamente eficazes no tratamento de perturbações relacionadas com a depressão. O número de estudos foi insuficiente para fornecer resultados conclusivos sobre as variáveis da intervenção psicológica.

Palavras-chave: psicadélicos, revisão sistemática, meta-análise, apoio psicológico, psilocibina.

Abstract

Background: After the resurgence of psilocybin research, clinical trials have reported promising results regarding the therapeutic effect this compound has in depressive-related disorders. Although a considerable amount of attention has been given to the set and setting, no study has tested empirically if psychological support augments clinical results. **Objective:** The aim of this study is to conduct a systematic review and meta-analysis to understand if psilocybin with psychological intervention is clinically effective and to assess how variables within psychological intervention influence the effect. **Methods:** The search and selection strategy were designed following the PRISMA guidelines. Six different electronic library databases were searched and the final list of articles resulted from a process of independent review of title, then abstract and ultimately full text. A database template was designed and subsequent data extraction was conducted by two independent raters. **Results:** The systematic review yielded a total of eight studies in the randomized controlled trial group and 10 studies in the clinical trial group. Both meta-analyses indicated significant ($p<0.001$) and large effect sizes. To test for possible moderators, meta-regressions were performed but there were no significant results in both groups. Subgroup analyses were also conducted to explore potential sources of modification of treatment effect according to different subgroups. **Discussion:** Psilocybin treatments with psychological support are clinically effective in treating depression-related disorders. Overall, the number of studies was insufficient to provide conclusive findings on psychological intervention variables. Limitations and future research are discussed.

Keywords: psychedelics, systematic review, meta-analysis, psychological intervention, psilocybin.

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Literature Review

Literature review on the efficacy of clinical trials and subsequent contextualization of psychological support in psychedelic treatments

Bárbara de Sá Bessa

Introduction

Psychedelics are a class of psychoactive substances that change perception, mood and cognitive processes (Nichols, 2016). There are several types of psychedelics that can be classed according to different criteria. For instances, classic or serotonergic psychedelics are found in nature and are agonists or partial agonists of serotonin 5-$HT2_A$ receptors (e.g., psilocybin, Lysergic Acid Diethylamide (LSD), ayahuasca/Dimethyltryptamine (DMT) and mescaline) meaning that their primary pharmacological target in the brain is to activate the serotonin receptor and generate a biological response (Mendes et al., 2022). Non-classic or atypical psychedelics include substances such as 3,4-methylenedioxymethamphetamine (MDMA), ketamine and ibogaine which vary in their pharmacological mechanisms and principal binding target. For example, MDMA acts as a reuptake inhibitor and releaser of serotonin and dopamine, ketamine is a N-methyl-D-aspartate (NMDA) receptor agonist and ibogaine is a indole alkaloid with multiple targets (Mendes et al., 2022).

Even though there is a variety of psychedelic compounds with different mechanism of action and chemical structures, they all produce changes in the nervous system and thus create altered states of consciousness, often called trips. The psychedelic experience has been used in several contexts over hundreds if not thousands of years (Carhart-Harris & Goodwin, 2017). In certain parts of the globe, especially in indigenous cultures, psychedelics such as ayahuasca are associated with traditional and spiritual use. In western cultures, psychedelic use emerged intensely in mid of the 20th century in the context of research. Psychedelic research attracted investigations across several fields such as chemistry, neuropharmacology, cognitive neuroscience, anthropology, psychology, psychiatry among many others (Carhart-Harris, 2019).

In psychiatry, before the affluence of research in the mid-20th century, psychedelics became an appealing topic since it allowed researchers to model psychosis (Nichols & Walter, 2021). By having participants taking a psychedelic compound such as mescaline researchers can induce transient states that resemble certain aspects of psychosis (Maloney & Knauer, 1913). In turn, it is possible to understand the underlying neural and psychological mechanisms of psychotic symptoms. However, after Albert Hofmann ingested LSD for the first time, five years after being synthesized in 1938, Hofmann experienced its powerful effects which altered mood and cognition (Belouin & Henningfield, 2018). Psychedelic research expanded beyond modeling psychosis and started to be used for therapeutic purposes after Werner Stoll publishes

the first paper on psychological effects of LSD in humans in 1947 (Carhart-Harris & Goodwin, 2017).

During the upcoming years after Hofmann's breakthrough, research ensued and LSD showed great promise to treat various mental health disorders including depression (Savage, 1952), alcoholism (MacLean et al., 1961) and substance use disorders (Ludwig & Levine, 1965). The ability to produce powerful and occasionally enduring beneficial psychological effects led researchers to view LDS and other chemical related entities such as psilocybin and mescaline as potential breakthroughs in many areas of mental illness.

As psychedelic research was thriving, recreational use of these compounds was also growing. In the United States, the counterculture movement was characterized by a combination of political activism against the positions of the at the time government, a way of life and set of attitudes opposed to the prevailing social norm and the abundant recreational use of various psychedelic substances. All these factors together led governments to stigmatize the consumption of these substances and thus consider them a risk to society. This ultimately result in the placement of LSD and other psychedelic drugs into the most restrictively regulated drug schedule of the United States Controlled Substances Act (Schedule I) in 1970 (Belouin & Henningfield, 2018). Other international counterparts followed suit and psychedelic research suffered a halt. Therefore, human psychedelic research fell into a 25-year hiatus (Carhart-Harris & Goodwin, 2017).

It was until researchers from different parts of the globe began reviving human psychedelic research for therapeutic purpose that a new era of psychedelic research commenced. Consequently, the so-called second-wave of psychedelic research has originated several clinical trials using different substances for the treatment of various psychiatric disorders. Hence, this literature review aims to firstly report the effectiveness of published clinical trials to establish the value of psychedelics as new alternative treatment for psychiatric disorders. Secondly, the literature review will taper to introduce set and setting, an umbrella term present in clinical trials that describes the internal (set) and external (setting) factors of extra-pharmacological variables. Finally, psychological intervention in the context of psychedelic clinical trials, a component of set, will be addressed.

Effectiveness of Psychedelic Treatment

Depression

Treatment resistant depression. Treatment resistant depression (TRD) has been an important focus of psychedelic research in order to find alternative treatment offers for these patients. In 2018, a first open-label study attempted to investigate feasibility, safety, and efficacy of psilocybin in TRD, with authors reporting no major adverse effects, while depressive symptoms markedly reduced at 1 week, 3 months and 6 months after psilocybin (Carhart-Harris et al., 2018). More recently, a first phase 2 randomized clinical trial (RCT) tested the treatment effect of different dosages of psilocybin in TRD (25-mg group, 10-mg group, and 1-mg group) (Goodwin et al., 2022). In the highest dosage group, the rate of response was 37% and remission of 29% at 3 weeks but was not fully sustained at 12 weeks (response rate of 20%).

Previously, a smaller-scale randomized placebo-controlled trial aimed to test rapid antidepressant effects of ayahuasca for TRD (Palhano-Fontes et al., 2019). Patients were randomized to receive a single dose of either ayahuasca or placebo. Significant changes in depression severity with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale (HAM-D) were found when compared to placebo at all time-points. MADRS scores were significantly lower in the ayahuasca group compared with placebo at 1-day and 2-days, and at 7-days. Response rates were significantly higher in the ayahuasca group only at 7-days (64%) compared to the placebo group (27%) (Palhano-Fontes et al., 2019).

Major depressive disorder. Antidepressant effects of psychedelic substances have also been studied in the context of major depressive disorder (MDD) in the absence of treatment resistance. Davis and colleagues, in a randomized waiting list-controlled study, supported treatment efficacy and safety of psilocybin administration in patients diagnosed with MDD and found a remission rate larger than 50% (Davis et al., 2021). In the same year, Carhart-Harris and colleagues showed that two consecutive doses of psilocybin (10mg and 25mg) were as effective as daily escitalopram treatment, in a placebo-controlled RCT (Carhart-Harris et al., 2021). In 2023 another study showed positive results for 52 participants diagnosed with MDD. In this RCT, patients were randomized to receive either a single dose (0.215 mg/kg) of psilocybin or placebo in conjunction with psychological support (von Rotz et al., 2023). Half of the participants (54%) met the MADRS remission criteria in the psilocybin condition two weeks after the intervention.

Depression and anxiety related to life threatening illness. In 2011, a small cross-over placebo-controlled trial, in a cohort of 12 advanced-stage cancer patients, revealed trends towards reduction of depression and anxiety symptoms after psilocybin administration (Grob et al., 2011). Later on, two more robust double-blind cross-over trials, provided evidence of important antidepressant and anxiolytic effects of psilocybin in patients with cancer, when compared to active placebo (Griffiths et al., 2016; Ross et al., 2016). Importantly, the effects reported in these three studies were immediate and sustained after psilocybin. More recently, a phase 2, open-label study also in patients with cancer and major depressive disorder, but treated in a group setting with 3 to 4 patients, administered a fixed-dose of 25mg psilocybin to a total of 30 patients, while showing a robust reduction in MADRS scores from baseline to posttreatment of 19.1 points at week 8 (Agrawal et al., 2023). In this study, half of the patients showed full remission of depressive symptoms. Similar forms of depressive-like and existential suffering are also present among older long-term AIDS survivors. One study showed a reduction of symptoms of demoralization after the administration of psilocybin and group therapy in this population, and detected a clinically meaningful change in symptoms from baseline to 3-month follow-up (Anderson et al., 2020).

One clinical trial was completed to treat anxiety and psychological distress related to life-threatening illnesses using MDMA-assisted psychotherapy. Participants were randomized to receive either MDMA or placebo concomitantly with two 8 hours psychotherapy sessions. This study found meaningful positive changes in State-Trait Anxiety Inventory (STAI) Trait scores from baseline to one month after the second dosing session. The MDMA group had a greater mean reduction in STAI-Trait scores compared to the placebo group (Wolfson et al., 2020). The same trend occurred in secondary outcomes that measured depression (Montgomery-Åsberg Depression Rating Scale; Beck Depression Inventory), sleep quality (Pittsburgh Sleep Quality Index), and global functioning (Global Assessment of Functioning) where mean scores differences were always greater in the MDMA group. After a cross-over stage, nearly all outcomes improved, on average, from baseline to 6- and 12-month follow-up, with a statistically significant reduction within subjects (Wolfson et al., 2020).

Anxiety Disorders

Evidence on treatment of social anxiety disorders with psychedelic substances such as MDMA and Ayahuasca has also been published. In a phase 2 single-site double-blind, placebo-controlled pilot study 11 adults with autism spectrum disorder and severe social anxiety disorder (SAD) were randomized either to MDMA-assisted psychotherapy or inactive placebo plus

psychotherapy (Danforth et al., 2018). The Leibowitz Social Anxiety Scale (LSAS) was used as the primary outcome to measure change in SAD symptoms from baseline to primary endpoint (one month after last experimental session) and again at 6-months. Results indicate that the reduction in LSAS scores was significantly greater for the MDMA group than for the placebo group both at one month and 6-month follow-up compared to baseline (Danforth et al., 2018). Furthermore, LSAS means scores changed minimally from primary endpoint to follow-up for both groups, supporting durability of improvements for the MDMA group (Danforth et al., 2018).

In another study, proof-of-concept and placebo-controlled trial, the effects of ayahuasca were tested on 17 participants with social anxiety disorder (Dos Santos et al., 2021). Patients were randomized and all completed the experimental session and the 3 follow-up assessments (days 7, 14, and 21). Compared with placebo, the ayahuasca group had significantly improved self-perception of speech performance (Self-statements During Public speaking Scale) and increased somatic symptoms (Bodily Symptoms Scale) measured during acute ayahuasca effects.

In an earlier study, reduction of symptoms of anxiety were obtained with administration of LSD in patients with end-of life anxiety. This was a small double-blind, active placebo-controlled pilot study with 12 patients with anxiety associated to a life-threatening disease (Gasser et al., 2014). Participants were randomized to either received 200 μg/kg or 20 μg/kg of LSD (active placebo) in addition to 22 non-drug psychotherapy session. Administration of LSD was associated with significant State-Trait Anxiety Inventory (STAI) reductions in trait anxiety and state anxiety at the study endpoint, 2-months after the last dosing session (Gasser et al., 2014). STAI reduction were sustained for the 12-month follow-up completers after cross-over.

Post-traumatic Stress Disorder

Several clinical trials have been published with MDMA for treatment of symptoms of Post-Traumatic Stress Disorder (PTSD). In a large phase 3 trial for MDMA-assisted psychotherapy, 67% participants in the MDMA group, vs. 32% in the placebo control group, no longer met the diagnostic criteria for PTSD after treatment, with 33% of participants in the MDMA group, vs. 5% in the control group, achieving remission according to the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) 18 weeks after treatment (Mitchell et al., 2021). The effects of different doses of MDMA had been previously studied in a small RCT with 6 patients with chronic PTSD, where participants who received the highest dose (75mg)

showed the greatest reduction in mean PTSD symptom scores (-16) compared to the 50mg group (-9) and placebo group (-4.5) (Bouso et al., 2008). This was followed by a randomized and placebo-controlled pilot study in persons with chronic, treatment-resistant PTSD, demonstrating positive effects of MDMA-assisted psychotherapy. The rate of clinical response was 83% in the active group (125mg MDMA) versus 25% in the placebo group (lactose), two months after the second experimental session (Mithoefer et al., 2011). Long-term follow-up data for the 16 study completers described that CAPS scores did not differ significantly relative to the 2-month scores indicating sustained improvement in PTSD symptoms (Mithoefer et al., 2013). In another study, the effect of three MDMA (125mg) or active placebo (25mg) dosing sessions were tested in 12 participants with chronic, treatment-resistant PTSD. On average, CAPS scores assessed at baseline and three weeks after the last dosing session indicated 15.6 points reduction in the 125mg group compared to 3.2 points reduction in the 25mg group (Oehen et al., 2013). At an one-year follow-up, clinical response was observed in 4 out of 8 completers in the full-dose group with a reduction in PTSD symptom severity either from severe to mild or from severe to moderate (Oehen et al., 2013).

In the following step of the research plan for MDMA in the treatment of PTSD, two phase 2 randomized controlled trials assessed effects of two different dosages of MDMA relative to low doses of 30/40 mg MDMA (active control) and concomitant manualized psychotherapy. In both studies, changes in total score of the primary outcome measure showed that high-dose MDMA groups had the largest reduction in PTSD symptom relative to the comparator group one-month after treatment (Mithoefer et al., 2018; Ot'alora et al., 2018). Mithoefer and colleagues showed significant improvements in CAPS-IV total scores in groups treated with 125mg and 75mg MDMA when compared to 30mg MDMA (Mithoefer et al., 2018). Ot'alora and colleagues indicated greater mean changes on the same scale in the 125mg and 100mg groups compared to a 40mg group (Ot'alora et al., 2018). Follow-up data collected in both studies showed that 12 months after cross-over 67% (Mithoefer et al., 2018) and 76% (Ot'alora et al., 2018) of participants did not meet PTSD criteria, supporting durability of effects.

In a more recent small open-label trial, three participants benefited from MDMA-assisted psychotherapy, with authors reporting clinically significant improvement in CAPS-IV scores, namely with 32%, 65% and 89% reduction in each participant (Jardim et al., 2021). Also recently, a small open-label study also showed reduction of PTSD symptoms while testing the

effects of MDMA in couples undergoing cognitive-behavioural conjoint therapy (CBCT) (Wagner et al., 2021). Wagner and colleagues reported that for partners diagnosed with PTSD a significant and sustained improvement in PTSD scores was found, with a notable effect size at post-treatment, 3 and 6-months follow-up moments. Moreover, all but one PTSD patients entered sustained remission assessed with the Clinician-Administered PTSD Scale-5. Outcomes related to relationship satisfaction showed significant improvements for patients and partners (Wagner et al., 2021).

Substance Use Disorders

An initial preliminary observational study was conducted with 12 participants in Canada to observe changes among several psychological and behavioral factors related to substance use disorder 6 months after treatment with ayahuasca (Thomas et al., 2013). This small study found significant improvements in hopefulness, empowerment, mindfulness and quality of life. Similarly, self-reported alcohol, tobacco and cocaine use declined significantly, although cannabis and opiate use did not.

Ayahuasca is part of traditional south American medicines from the Amazon region and in this context the so-called Takiwasi treatment protocol has been studied for substance use disorders (O'Shaughnessy et al., 2021). This study found clinically positive and statistically significant changes in a group of 36 male inpatients across all repeatedly assessed psychological constructs, namely perceived stress, craving frequency, mental illness symptoms, spiritual well-being and emotional health. These changes appeared early in the treatment and were maintained over time. In this particular study, severity of the substance use disorder was measured only at intake, which limits understanding of the treatment effect for this pre-post-intervention design.

Another observational study using the Takiwasi treatment approach, while allowing psychotherapy, focused on changes in patient depression and anxiety scores throughout an inpatient SUD rehabilitation program, without reporting measures of SUD severity and in the absence of a control group (Giovannetti et al., 2020). The majority of the patients entered treatment with moderate to severe levels of depression (38%) and anxiety (61%) as measured by the BDI and Beck Anxiety Inventory (BAI), confirming comorbid psychiatric symptoms as a widespread characteristic of the sample. Mean BDI and BAI scores had a statistically significant reduction of approximately 50% between treatment entry and discharge. Upon treatment exit, 87% of patients reported to have mild or minimal depression levels, and 81% presented mild or minimal anxiety levels.

Finally, in another study involving traditional Amazonian medicine with ayahuasca for treatment of SUD, revealed a significant decrease, from before to approximately 1 year after treatment for substance use severity outcomes regarding drug use and alcohol use, as well as psychiatric status and social/familial relationships (Berlowitz et al., 2019). Also, emotional distress diminished significantly, as did substance craving. Quality of life of these 53 male patients increased significantly after treatment. These results provide indications for significantly improved SUD severity and comorbidities after Ayahuasca in a group of participants that were dependent on multiple substances, most prominently cannabis, alcohol, and cocaine (Berlowitz et al., 2019).

Opioid Use Disorder. Administration of Ibogaine was associated with the reduction of opioid withdrawal symptoms and drug use in patients with opioid use disorder (OUD) in several open-label studies conducted with limited times of observation after treatment. In one observational study, 30 subjects with opioid dependence diagnosed according to DSM-IV were evaluated with the Subjective Opioid Withdrawal Scale (SOWS) and Addiction Severity Index Composite (ASIC) scores after Ibogaine detoxification and follow-up outcomes at 1, 3, 6, 9, and 12 months (Brown & Alper, 2018). SOWS scores decreased from 31.0 pretreatment to 14.0 at 76.5 ± 30 hours post-treatment. At the 1-month post-treatment follow-up, 15 subjects (50%) reported no opioid use during the previous 30 days, with lower rates of 30-day abstinence at the 3 month and 12 month follow-up assessments (20% and 23% respectively) (Brown & Alper, 2018). Similarly, in a previous open-label study assessing long-term effects of ibogaine administration in patients with OUD, reduction in use of both other drugs and alcohol were reported by 21% of the total 14 participants at three and six months. At twelve months, from the total of 11 participants that remained in the study, 55% still reported reduced use of other drugs and 36% reduced use of alcohol. Furthermore, symptoms of depression decreased significantly over time with a significant reduction seen at 1-month post-treatment and continuing to the final 12-month assessment (Noller et al., 2018). In another study, a similar but larger sample of 50 individuals with OUD, that were assessed after a week-long ibogaine-assisted detoxification program, positive results were also found (Malcolm et al., 2018). Here, assessments were conducted only until 48h after treatment and showed that in this period of time 78% of patients did not exhibit objective clinical signs of opioid withdrawal, 79% reported only minimal cravings for opioids, and 68% reported subjective withdrawal symptoms in the mild range (Malcolm et al., 2018).

None of the previously described studies included a control group. There was only one randomized, double-blind, placebo-controlled study which evaluated the safety and tolerability of noribogaine, ibogaine's active metabolite, in patients with opioid dependence (Glue et al., 2016). This ascending single-dose study delivered 60, 120 or 180mg doses of noribogaine or matching placebo. Overall, noribogaine revealed a trend toward decreased total score in opioid withdrawal ratings in the 120mg dose group (Glue et al., 2016).

Alcohol Dependence Disorder. An initial open label proof-of-concept study tested safety and outcome of psilocybin in 10 participants suffering from alcohol-dependence treated with psilocybin administered orally in 1 or 2 supervised sessions, in addition to Motivational Enhancement Therapy (MET) (Bogenschutz et al., 2015). In this study, while indicators of abstinence did not change after initial 4 weeks of MET only, they increased significantly following psilocybin administration and this positive outcome was maintained at 36 weeks. In a later RCT, 95 participants with alcohol dependence according to DSM-IV were randomized to either psilocybin or diphenhydramine. Primary outcome was percentage of heavy drinking days during the 32-week double-blind period, which was significantly lower in the psilocybin group (9.7%) than in the diphenhydramine group (23.6%) (Bogenschutz et al., 2022).

Also, MDMA-assisted psychotherapy showed some positive impact on drinking behavior in an open-label study of safety and tolerability including 14 participants with AUD (Sessa et al., 2021). Drinking behavior was measured by units per week consumed one month before detoxification, at detoxification and 1, 2, 3, 6 and 9-months since detoxification. At 9-months post detoxification, the average units of alcohol consumption by participant was 18.7 units per week compared to 130.6 units per week before detoxification (Sessa et al., 2021).

Other conditions

In an open-label pilot-study of smoking cessation, 15 participants received two or three doses of psilocybin in the context of cognitive behavioral therapy (CBT) for smoking cessation. Twelve of 15 participants (80%) demonstrated abstinence, according to objectively quantifies biomarkers, at 6-month follow-up (Garcia-Romeu et al., 2015; Johnson et al., 2014, 2017).

One single small study (N = 9) was performed for treatment of Obsessive Compulsive Disorder (OCD) with up to 4 single-doses of psilocybin, ranging from low to high, separated by one week intervals (Moreno et al., 2006). All patients experienced a decrease of OCD symptoms according to YBOCS (23% to 100% reductions) and pre and post administration comparison for all doses was significant.

Set and Setting

There are aspects of the psychedelic experience that are a result of not only the effects of the drug but also the environment that the drug is being taken in. Set and setting are two overarching concepts that together represent one extra-pharmacological factor present in the psychedelic experience. Set refers to the mindset of participants meaning that the intentions, expectancy, and preparation that participants have regarding the experience can shape the experience itself. Setting denotes the physical, social and cultural environment in which the experience takes place (Hartogsohn, 2017).

The concept of set and setting surfaced within psychedelic research (Leary et al., 1963). Leary and colleagues were the first researchers to term background and situational variables as part of a broader concept in psychedelic research. They claimed that the set and setting is the most important determinant of the contents of psychedelic experiences (Hartogsohn, 2017). While acknowledging that this is a substantial assertation to claim, a better understanding of set and setting can prove useful to advancing current research in addition to reducing harms and fostering safer patterns of drug use (Hartogsohn, 2017). However, some authors have put forth that a component of set and setting, namely psychological support, can have a role on the clinical efficacy of psychedelic clinical trials (Carhart-Harris et al., 2018; Heifets & Olson, 2023; Leary et al., 1963) but get little empirical attention (Garel et al., 2023).

Psychological Intervention

Regarding set, psychedelic substances in most of the cases are administered with some form of psychological intervention in a tripartite model: preparation sessions, single or multiple drug dosing sessions and integration sessions after drug administration (Aday et al., 2022). Preparation sessions involve discussing intentions and expectations for the psilocybin experience, informing participants of likely psilocybin effects and building a therapeutic alliance with the facilitator (Horton et al., 2021). During dosing, the drug is administered to participants in a nondirective and supportive setting (Cavarra et al., 2022; Horton et al., 2021). Finally, during integration sessions participants implement and incorporate into one's life the key insights and awareness gained in the psychedelic experience (Bathje et al., 2022).

In conclusion, after the resurgence of psychedelic research, clinical trials have reported promising results regarding the therapeutic effect that different compounds have in various neuropsychiatric disorders. Even though there is a large amount of attention given towards the effects of the psychedelic substance, concepts such as set and setting emerged in research.

Therefore, more and more attention has been given to the structure and content of the psychological intervention component of psychedelic-assisted treatments.

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Empirical Article

A systematic review and meta-analysis on the role of psychological support in treatments with psilocybin

Bárbara de Sá Bessa

Introduction

The field of mental health faces challenges as current available treatments such as pharmacotherapies and psychotherapy are sometimes insufficient to treat the growing number of neuropsychiatric disorders. In addition, treatment resistance in psychiatric disorders affects 20-60% of patients supporting the need for new and effective treatments (Howes et al., 2022). It was estimated that 970 million people in the world suffer from a mental disorder of which 280 million have a depression-related disorder (Global Burden of Disease, 2019). The economic burden of depression is associated with the loss of tens of billions of dollars each year in the US alone where the largest component of this burden derives from lost work productivity (Wang et al., 2003). These numbers indicate a need for innovative treatments as not all individuals with depression do benefit from conventional treatments.

After the hiatus caused by governmental institutions in 1971, research on psychedelics for therapeutic purposes has made a resurgence in the past two decades. Typical and atypical psychedelics have taken significant steps to become alternative treatments for neuropsychiatric disorders. A typical psychedelic that has received much attention is psilocybin. In 2019, this classic psychedelic was considered by the United States Food and Drug Administration (FDA) as a breakthrough therapy for treatment-resistant depression (TRD) (eClinicalMedicine, 2023) since it has been revealing promising results (Carhart-Harris, Bolstridge, et al., 2018; Goodwin et al., 2022b). Other mood disorders such as major depression disorder (MDD) and depression related to a life-threatening illness were also treated with psilocybin in recent clinical trials which revealed encouraging results for depression (Agrawal et al., 2023b; Raison et al., 2023; von Rotz et al., 2023b).

The therapeutic mechanisms of psilocybin are still unknown. However, researchers have associated a high affinity that psilocybin has to the $5HT_{2A}$ serotonin receptor agonist actions. In turn, researchers established that psilocybin-induced effects are due to the $5HT_{2A}R$ activation (Nichols, 2016; Vollenweider et al., 1998). It is also claimed that psilocybin alters neural circuitry between areas such as the default mode network (DMN) and amygdala which may mediate antidepressant effects (Ling et al., 2022). For instance, the DMN is a network of brain regions during rest and self-referential thinking. Individuals with major depression disorder reveal increased or decreased DMN activity relative to controls (Chou et al., 2023). In general, psilocybin effects during dosing sessions and its mechanisms of action take the center stage

when explaining efficacy. However, they may not be the only variables present in psilocybin treatments.

Besides the dose of psilocybin and the number administration sessions, other extra-pharmacological factors commonly categorized as internal and external, such as 'set and setting', might influence clinical results but get little empirical attention (Garel et al., 2023). Regarding set, psilocybin is typically administered with some form of psychological intervention in a tripartite model: preparation sessions, single or multiple drug dosing sessions and integration sessions after drug administration (Aday et al., 2022). Preparation sessions involve discussing intentions and expectations for the psilocybin experience, informing participants of likely psilocybin effects and building a therapeutic alliance with the facilitator (Horton et al., 2021). During dosing, the drug is administered to participants in a nondirective and supportive setting (Cavarra et al., 2022; Horton et al., 2021). Finally, during integration sessions participants implement and incorporate into one's life the key insights and awareness gained in the psychedelic experience (Bathje et al., 2022).

Psychological interventions have different degrees of support. For instance, they vary in the total number of sessions and hours (Horton et al., 2021). They also differ in the structure and quality of support. There are psilocybin clinical trials that apply only psychological support (Carhart-Harris et al., 2018) others psilocybin-assisted psychotherapy (Ross et al., 2016b) or psilocybin-assisted therapy (A. Davis et al., 2021). The common understanding is that psychological support compared to psychotherapy is less specialized and qualified. However, it is not known if in terms of efficacy a less specialized and qualified support is as or more effective than a qualified one.

To date, there is no empirical evidence on the impact that different variables within psychological intervention with psilocybin have on treatments' outcomes. To address this important empirical gap, a systematic search of the literature and a meta-analysis will be performed to understand first understand if psilocybin treatment with psychological intervention is clinically effective and secondly, how different variables of psychological intervention play a role in the effect of psilocybin treatments. Such variables include the total hours of psychological intervention, the total number of sessions, the presence of absence of a manualized approach and the level of psychological intervention.

Methods

Protocol and registration

The systematic review protocol was registered by the principal researchers of the overarching project at the international prospective register of systematic reviews PRSPERO (CRD42022360058) and can be consulted online (https://www.crd.york.ac.uk/prospero/display record.php?RecordID=360058).

Search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were applied throughout the search (Moher et al., 2009). Search was performed on the following six different databases: PubMed, PsycINFO, Web-of-Science, EBSCOhost, EMBASE and Cochrane Library to include papers published up to November 2022. The search scope considered all studies registered in the selected databases, regardless of publication date, country of origin or methodology. Filters were applied by language and thus papers written in English, Portuguese, French, Spanish, Italian or German were considered. Additionally, studies using non-human models were filtered out.

The search strategy was in line with the search criteria registered on PROSPERO, including keywords identifying all different psychedelics (hallucinogen* or psychedelic*, LSD, Psilocybin, MDMA, ayahuasca, DPT, DMT, 5-MeO-DMT, mescaline, ibogaine) and psychiatric disorders (mental health disorder*, psychiatric disorder*, depression, major depressive disorder, major depression, treatment resistant disorder, dysthymia, affective disorder, adjustment disorder, anxiety, post-traumatic stress disorder, alcohol use disorder, substance use disorder, tobacco use disorder, obsessive compulsive disorder, autism, neuropsychological functioning, demoralization syndrome) which were to be included in the systematic review. However, each electronic database had a different structure and distinct rules. Therefore, syntax was adapted to fit each database (Appendix A).

Inclusion and exclusion criteria

Inclusion criteria were formulated according to the Participants, Intervention, Comparison, Outcome and Study design (PICOS) approach (Table 1). Exclusion criteria were studies that only included healthy participants, non-adult and non-human, non-original studies

data such as literature reviews, surveys or single-case and ecological studies. Conference proceedings, abstracts and thesis were also to be excluded.

Table 1

Participants, Intervention, Comparison, Outcomes and Study (PICOS) inclusion criteria utilized for the selection of articles.

Participants	All types of adult patients diagnosed with mental health disorder, classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), or any previous DSM edition, or its equivalent in the International Classification of Diseases (ICD).
Intervention	Single or multiple doses of a typical or atypical psychedelic substance such as Lysergic Acid Diethylamide (LSD), N,N-Dipropyltryptamine (DPT), Dimethyltryptamine (DMT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), mescaline, ibogaine at any dosage and in any route of administration.
Comparison	When available control or comparator group will be included. Such groups can be composed by: (1) patients who receive placebo or active placebo with and without psychological support; (2) patients on a waitlist with and without psychological support; (3) who received usual care (psychological support, anti-depressant).
Outcome	Clinical efficacy, i.e. reduce mental health disorder symptom severity and improve quality of life.
Study design	Randomized controlled trials evaluating the effect of psychedelic treatment in neuropsychiatric disorders. For a specific component of the analysis (meta-regression) we will also include non-controlled and/or open label trials, such as quasi-experimental study designs, case series and observational studies.

Study selection

After identification and duplicate removal, two researchers (BB and CS) reviewed the list of articles independently, selecting eligible articles according to PRISMA guidelines and PICOS criteria. Following identification, PRISMA guidelines are comprised of two stages: selection and eligibility.

The selection process was characterized by two moments. Firstly, each researcher reviewed the titles from the list of articles identified in the six databases. After the removal of

the excluded articles during the title selection, the same process was repeat only this time the abstract was used to include or exclude articles.

The eligibility process was characterized by downloading all articles and reading the full-text. Each researcher provided a reason when excluding an article. The reasons where coded from one two seven (non-human, non-original data, no treatment effect, no mental illness, single case, additional duplicate, same sample, respectively).

All steps taken during the selection and eligibility stages were comprised of consensus meetings where the two researchers resolved disagreements during the title, abstract and full-text review before advancing to the next point of the systematic review.

Data extraction

An excel database template was designed to define all different categories and subcategories of data to be extracted. All categories were sectioned into five different areas: identification, outcomes, follow-up, psychological intervention and adverse events.

Identification included categories such as paper identification, design of the study, type of psychedelic, study dropouts, number of participants, age, female percentage and diagnosis. Each category had other subcategories. For example, in study design data was extracted according to study type, intention-to-treat, study length, dosing session length, therapy length, primary endpoint, scale of primary endpoint, other scales and timepoint of follow-up.

For the outcome section, scales were organized by symptom (e.g., depression, anxiety, post-traumatic stress disorder). For example, all depressive scales were grouped in one sheet and all scales had three categories: primary outcome, active group and control group. The first category informed if the scale was used as primary outcome in the study. The latter categories had the same subcategories: baseline mean, standard deviation of the baseline mean, outcome mean, standard deviation of the outcome mean, mean difference between outcome and baseline means and standard deviation of the mean difference.

The follow-up section had the same layout as the outcome section. However, follow-ups were grouped by scale and each scale had ten different timepoints (e.g., weeks, months, years), meaning that each timepoints had baseline means, outcome means, mean differences and the associated standard deviations for each category.

The psychological intervention section comprised several categories. Firstly, there was a binary category to report if the study had psychological intervention (1) or not (0). Secondly, there were two major categories (e.g., psychological intervention and adjuvant psychological intervention) and each of them had the same subcategories assessing different components of the intervention (e.g., name, qualifications of the facilitator, training and manualized intervention). These subcategories were organized in binary categories, to assess if they were reported in the study, and in qualitative categories, to report the kind of designation/qualification/training included in the study. Psychological intervention was an intervention characterized by accompanying drug administration (e.g., pre-dosing, dosing and post-dosing) whereas adjuvant psychological intervention was created to represent in the data extraction all the additional psychological intervention that the study had. Facilitator adherence measures to the psychological intervention were also extracted. The number and total hours per session for preparatory sessions and integration sessions were extracted. Finally, there was a category that assessed the dosage of the compound in milligrams, the number of dosing sessions and the total of hours per dosing session.

The adverse events (AEs) section was defined by a body of systems and other type of AEs. There was in total 28 categories (e.g., cardiovascular, genito-urinary, motor, visual, gastrointestinal, respiratory, sexual, anxiety, depressed mood, euphoric mood, etc). There were also two other categories, one to report severe adverse events (SAE) and another to specify which SAE it was. Lastly, there was a category to specify the onset of the AEs. All of these 31 categories were grouped by timepoint and treatment arm (e.g., acute AE in the active group, acute AE in the control group; late AE in the active group, late AE in the control group; onset not specified in the active group, onset not specified in the control group).

Data extraction was also completed independently by two researchers (author of the dissertation and Brigite Wildenberg) based on information provided in the main article and supplementary materials. Consensus meetings were also partaken to ensure that data was collected accurately. If deemed adequate, the studies' authors were contacted to clarify or complete missing data in the publication.

Risk of bias assessment

Database bias was minimized by using six reference databases and by screening the reference lists from the chosen articles to include articles missed by our syntax as long as they

meet inclusion criteria. Regarding scope bias, it was minimized since the systematic review included publications in multiple languages. Source selection bias was further minimized by including all type of publications if they meet eligible criteria. To avoid risk of quality bias two researchers independently assessed the quality of each article included in the review reaching the final judgment by consensus.

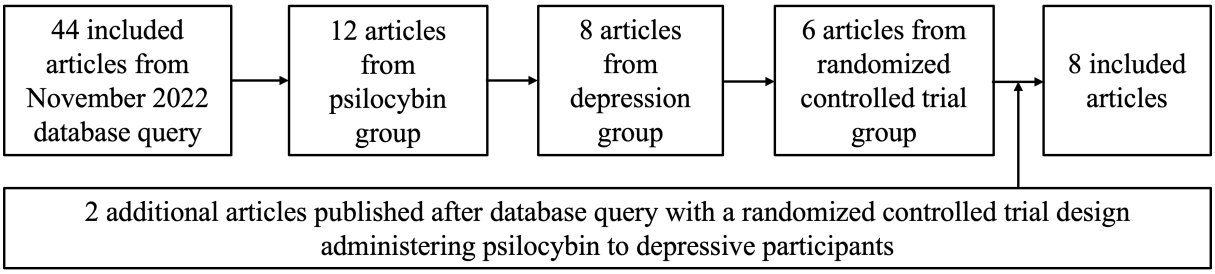
Psilocybin Treatment for Depression Groups: Selection Criteria

The systematic review described throughout the method section is part of a larger project, which was registered in PROSPERO. The current study included two different groups of clinical trials using psilocybin to treat depression-related disorders. Each group was analyzed using a distinct statistical method which is described in the statistical analysis section.

The first group included all randomized controlled trials studies where any dosage in any route of administration of psilocybin was administered to participants diagnosed with depression-related conditions (e.g., major depression disorder, treatment-resistant depression and depression related to a life-threatening illness). Therefore, the final articles for the randomized controlled trials group were selected from the included articles of the PRISMA flowchart in addition to two articles that met selection criteria and were published after the database query (Figure 1).

Figure 1

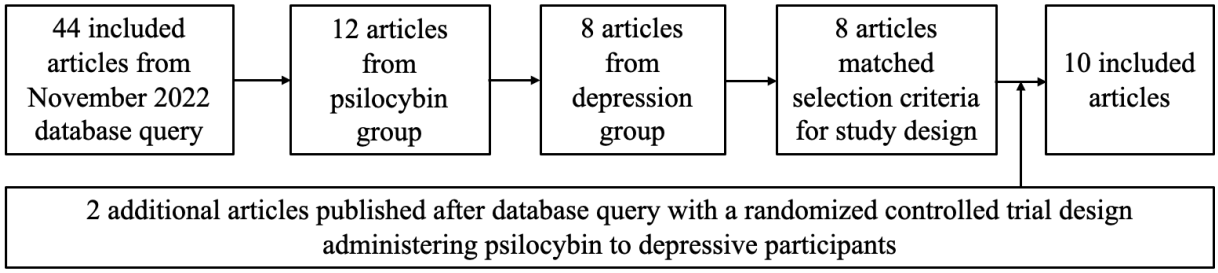
Article selection flowchart for randomized controlled trials group.



The second group included all clinical trials (e.g., RCTs, open-label trials) where any dosage in any route of administration of psilocybin was administered to participants diagnosed with depression-related conditions. Therefore, the final articles for the clinical trial group were selected from the included articles of the PRISMA flowchart in addition to two articles that met selection criteria and were published after the database query (Figure 2).

Figure 2

Article selection flowchart for clinical trials group.



Statistical analysis

In order to assess the main outcome, and considering the predicted high heterogeneity between studies, a random-effects meta-analyses was performed to compare how the presence or absence of psychological support contributes to clinical efficacy in psilocybin treatments in depressive participants of randomized controlled trials.

Between-group effect size

For the between-group effect sizes (ESs) standardized mean difference (SMD) or Cohen's d was computed using mean scores of the change in symptom severity between pre-treatment (pre) and post-treatment (post) for intervention (T) and control (C) conditions, along with the corresponding pooled standard deviation (SD_{pre}) and bias correction (c_p) according to the following formula (Morris, 2008):

$$d_{ppc2} = c_p \left[\frac{\left(M_{post,T} - M_{pre,T}\right) - \left(M_{post,C} - M_{pre,C}\right)}{SD_{pre}} \right]$$

where the pooled standard deviation and bias correction are defined as:

$$SD_{pre} = \sqrt{\frac{(n_T - 1)SD_{pre,T}^2 + (n_c - 1)SD_{pre,C}^2}{n_T + n_c - 2}}$$

$$c_p = 1 - \frac{3}{4(n_t + n_c - 2) - 1}$$

It is to note that the pooled standard deviation only applies the standard deviation of the pre-treatment of both treatment and control group. Morris compared three different formulas to calculate the effect size in a pretest-posttest-control group design. The results supported the second formula (d_{ppc2}) as the best choice (Morris, 2008). At the same time, the d_{ppc2} formula fitted the limitations of the data extraction since some studies did not provide in the article nor supplementary material the post-treatment standard deviations of the treatment and control group.

Regarding statistical dispersion, variance was calculated using the standard of error (SE) formula from Borenstein (Borenstein, 2009):

$$SE_{SMD} = \sqrt{\frac{n_T + n_C}{n_T n_C} + \frac{SMD^2}{2(n_T + n_C)}}$$

Within-group effect size

For the within-group ESs standardized mean difference (SMD) or Cohen's d the mean scores of the change in symptom severity between pre-treatment ($\bar{Y}_1$) and post-treatment ($\bar{Y}_2$) scores for the same intervention group were used according to the following formula (Borenstein, 2009):

$$d = \frac{\bar{Y}_{diff}}{S_{within}} = \frac{\bar{Y}_1 - \bar{Y}_2}{S_{within}}$$

where the within-groups standard deviation (S_{within}) is defined as:

$$S_{within} = \frac{S_{diff}}{\sqrt{2(1-r)}}$$

and the standard deviation of the difference scores (S_{diff}) is defined as:

$$S_{diff} = \sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$$

where S_1 is the standard deviation of $\bar{Y}_1$ and S_2 is the standard deviation of $\bar{Y}_2$. In both formulas (S_{within} and S_{diff}) the correlation between pre-scores and post-scores (r) was used and it was assumed to be 0.5 (Borenstein, 2009).

Regarding statistical dispersion, variance was calculated using the standard of error (SE) formula from Borenstein (Borenstein, 2009):

$$SE_d = \sqrt{V_d}$$

where the variance of the effect size (V_d) is defined as:

$$V_d = \left(\frac{1}{n} + \frac{d^2}{2n}\right) 2(1 - r)$$

A univariate meta-regression and subgroup analysis were also conducted for both statistical methods. Statistical heterogeneity was evaluated using the I^2 test (>35% for heterogeneity). Since high heterogeneity is expected, a random-effect model was used when conducting meta-analysis for each outcome either for between and within-group effect sizes. Publication bias will be evaluated using funnel plot and Eggers' test. The software Statistical Package for the Social Sciences (SPSS) was used.

Results

Descriptive results of the literature review

The initial literature search resulted in 13597 articles. After title, abstract and full-text review 44 eligible articles were included (Figure 3). In addition, the selection of clinical trials with psilocybin in patients with depression resulted in 10 articles (Figure 1 and 2), published between 2011 and 2023, which were included in this systematic review (see Table 2 for full details on each study).

Figure 3

PRISMA Flowchart

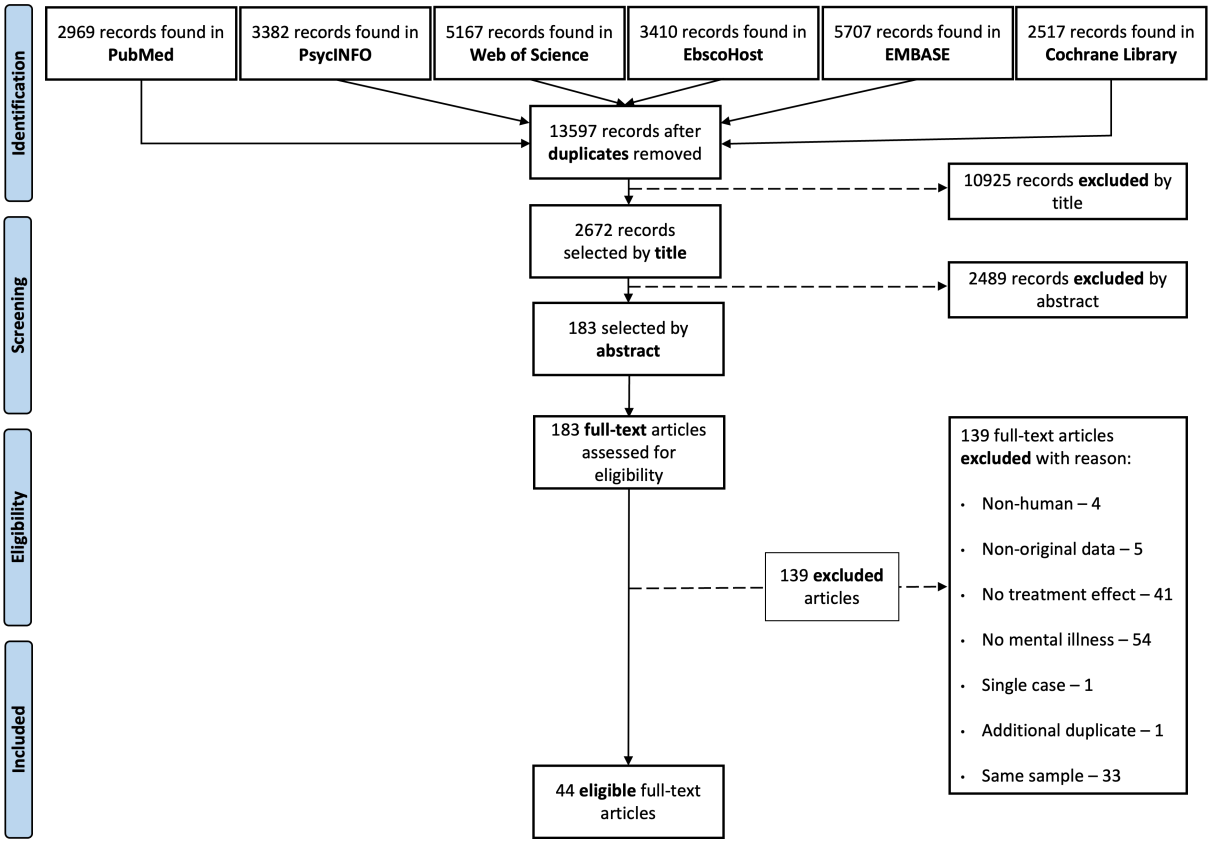


Table 2

Descriptive summary of included studies for both groups (N = 10).

Study	Indication	Primary Outcome	N[a]	Study Design	Drug Dose	Dosing Sessions[b]	Control Group	Primary Endpoint	Outcome[d]
Raison et al. 2023	MDD	MADRS	104 (psilocybin n=51; niacin n=53)	RCT	25mg	1	Niacin	43-days after baseline	MADRS week 6 (range 0-60): -19.1 (psilocybin) -6.8 (placebo)
von Rotz et al. 2023	MDD	BDI, MADRS	52 (psilocybin n=26; placebo n=26)	Double-blind, RCT	0.215 mg/kg	1	Inert placebo	14-days after dosing session	BDI week 2 (range 0-63): -13.2 (psilocybin) -5.2 (placebo)
Goodwin et al. 2022	TRD	MADRS	233 (psilocybin 25mg n=79; psilocybin 10mg n=75; psilocybin 1mg n=79)	Double-blind, parallel-group, randomized trial	25 or 10mg	1	Low-dose psilocybin (1mg)	3-week after baseline	MADRS week 3 (range 0-60): -12.0 (25 mg) -7.9(10 mg) and -5.4 (1 mg)
Carhart-Harris et al. 2021	MDD	QIDS-SR-16	59 (psilocybin 25mg n=30; psilocybin 1mg n=29)	Double-blind, RCT	25mg + 6-week placebo	2	Low-dose psilocybin (1mg) + 6-week escitalopram	6-week after dosing session 1	QIDS-SR-16 week 6 (range 0-27): -8 (psilocybin) -6 (escitalopram)
Davis et al. 2021	MDD	GRID-HAMD	24 (immediate treatment n=13; delayed treatment n=11)	Randomized, waiting list-controlled trial	20-30mg/70kg	2	Waiting list	8-week after baseline	GRID-HAMD week 8: -14.4 (immediate treatment) 1 (delayed treatment)
Griffiths et al. 2016	CAD	GRID-HAMD, HAM-A	51 (high-dose 1st n=25; low-dose 1st n=26)	Double-blind, RCT with cross-over	22 or 30mg/70kg	1	Low-dose psilocybin (1 or 3mg/70 kg)	5-week after dosing session	GRID-HAMD 5 weeks: -16.3 (High-Dose-1st) -15.8 (Low-Dose-1st)
Ross et al. 2016	CAD	BDI, HADS, STAI	26 (psilocybin 1st n=12; niacin 1st n=14)	Double-blind, RCT with cross-over	0.3mg /kg	1	Niacin	7-week after dosing session[c]	BDI week 2 (range 0-63): -7.9 (psilocybin 1st) -3.9 (niacin 1st)
Grob et al. 2011	CAD	BDI, POMS, STAI	12 (psilocybin n=6; niacin n=6)	Double-blind, RCT (within-subject)	0.2mg /kg	1	Niacin	2-weeks after dosing session	BDI week 2 (range 0-63): -6.1 (psilocybin 1st) -1.2 (placebo 1st)
Anderson et al. 2020	Demoralization	DS-II	18	Open-label trial	0.3-0.36 mg/kg	1	NA	6-week after baseline	DS-II week 6 (range 0-32): -6.7
Carhart-Harris et al. 2018	TRD	QIDS-SR-16	19	Open-label trial	10 and 25mg	2	NA	5-week after dosing session 2	QIDS-SR-16 week 5 (range 0-27): -9.2

Note. MDD: Major Depressive Disorder; TRD: Treatment Resistant Depression; CAD: Cancer-related Anxiety and/or Depression; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self Report; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; STAI: State-Trait Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; RCT: Randomized Controlled Trial; NA: Not Applicable.

[a] sample size at primary endpoint; [b] number of dosing sessions before crossover; [c] last timepoint before cross-over selected as primary endpoint is not reported, [d] mean differences of pre-post scores between treatment and control group

Demographics

Regarding demographic information, sex and age were extracted. From the 10 included studies women percentage ranged from 0-92% and the mean was 50.1. The mean age across studies varied from 37-59 and the mean was 46 (see Table 3 for a descriptive summary of the two variables).

Table 3

Demographics of included studies for both groups.

Study	% Women	Mean Age
Raison et al. 2023	50	41.1
von Rotz et al. 2023	63	36.8
Goodwin et al. 2022	52	39.8
Carhart-Harris et al. 2021	34	41.2
Davis et al. 2021	67	39.8
Anderson et al. 2020	0	59.2
Carhart-Harris et al. 2018	32	44.1
Griffiths et al. 2016	49	56.3
Ross et al. 2016	62	56.3
Grob et al. 2011	92	Not reported

Psychological Intervention

All of the included studies indicated the use of a psychological intervention (n = 10). Ten of the nine studies reported a name (see Table 4) with the exception for Grob et al. 2011 as the article did not provide any type of designation for the psychological support described in

the study. All studies except for Anderson et al. 2020 used one psychological intervention that accompanied psilocybin treatment. Anderson et al. 2020 used two types of psychological intervention, psilocybin-assisted group therapy and individual psychotherapy. The latter was considered an adjuvant treatment. Consequently, it was the study with the larger number of sessions (11) and total number of hours (15.5). In terms of the studies reporting the application of a therapy manual to conduct the psychological intervention, either mentioned in the main article or in the supplementary materials, 60% of the included studies did not report using a manualized approach (see table 4). Overall, the number of total of sessions (mean ± SD = 6.1 ± 2.5; range = 11-3) and total hours (mean ± SD = 11.3 ± 3.5; range = 15.5-5) did not disperse much from the mean.

All of the included studies reported the number of pre- and post-dosing of the psychological intervention. Concerning the report of hours per session, 40% of the included studies in the systematic review did not report the time provided in pre- and/or post-dosing sessions.

Table 4

Descriptive summary of psychological intervention variables.

Study	Psychological Intervention	Manualized intervention reported	Total sessions[a]	Total hours[a]
Raison et al. 2023	Psychological Support	Yes	4	12
von Rotz et al. 2023	Psychological Counselling	No	5	5
Goodwin et al. 2022	Psychological Support	Yes	5	NA
Carhart-Harris et al. 2021	Psychological Support	No	9	NA
Davis et al. 2021	Supportive Psychotherapy	No	7	11
Anderson et al. 2020	Psilocybin-assisted group therapy + Individual Psychotherapy	Yes	8 + 3	12 + 3.5
Carhart-Harris et al. 2018	Psychological Support	No	4	NA
Griffiths et al. 2016	Psychological Support	No	7	12.5
Ross et al. 2016	Medication-assisted Psychotherapy	Yes	6	12
Grob et al. 2011	No description	No	3	NA

Note. NA: Not Available [a] pre-dosing sessions and post-dosing sessions

Regarding the structure of the psychological interventions, all studies followed a three stages model: pre-dosing sessions, dosing sessions and post-dosing sessions (see Table 5). Pre-dosing sessions included at least one session (N=10, 100%). Pre-dosing sessions varied among studies in total number of sessions (mean ± SD = 2.1 ± 0.9; range = 1-3) and total hours (mean ± SD = 5.6 ± 2.6; range = 2-8). Post-dosing sessions included at least three sessions (N = 10, 100%). Dosing sessions only ranged between one or two. Three studies administered psilocybin twice whereas the rest (N = 7) administered psilocybin once. Typically, psilocybin sessions took about 6 to 8 hours. Pre-dosing sessions varied among studies in total number of sessions (mean ± SD = 3.5 ± 2.2; range = 3-8) and total hours (mean ± SD = 4.1 ± 1.3; range = 3-6).

Table 5

Descriptive summary of psychological intervention variables (continuation).

Study	Pre-dosing session		Dosing session		Post-dosing session	
	Sessions	Hours	Sessions	Hours	Sessions	Hours
Raison et al. 2023	1	8	1	7	3	4
von Rotz et al. 2023	2	2	1	6	3	3
Goodwin et al. 2022	3	NA	1	6	2	NA
Carhart-Harris et al. 2021	1	3	2	6	8	NA
Davis et al. 2021	2	8	2	8	5	3
Anderson et al. 2020	4 + 1	1.5 + 1.5	1	6	4 + 1	1.5 + 2
Carhart-Harris et al. 2018	1	4	2	NA	3	NA
Griffiths et al. 2016	3[b]	7.9	1[c]	7	4	4.6
Ross et al. 2016	3	6	1	8	3	6
Grob et al. 2011	3	NA	1[c]	6	0	NA

Note. [b] mean of number of sessions [c]number of dosing sessions before crossover

As for the qualification and training of the session facilitators, most of the studies reported varying amounts of credentials ranging from psychologists, psychotherapist, psychiatrists, social workers, nurses, physicians with varying levels such as bachelor, master's or doctorate degrees (see Table 6).

Reported training was also extracted. There were less studies reporting training for the facilitators guiding pre-dosing, dosing and post-dosing sessions. Half of the studies provided some degree of training (N = 5). Nevertheless, the mode of reporting was heterogeneous. Some studies provided training details by reporting the instructor's name (Griffiths et al., 2016) and others the mode delivery (Anderson et al., 2020; Goodwin et al., 2022). Raison et al. 2023 did

not provide any details, from the description it is only known that training occurred. On the other hand, Ross et al. 2016 provided a specific approach of training (NYU Psychedelic Psychotherapy Training Program).

Table 6

Descriptive summary of psychological intervention variables (continuation).

Study	Reported qualifications of facilitators	Reported training of facilitators
Raison et al. 2023	"Doctoral-level psychologists or physicians with MDD treatment experience and co-facilitators held a minimum of a bachelor's degree in a mental health–related field"	"All facilitators completed study-specific training prior to engaging with participants"
von Rotz et al. 2023	"Physician or psychologist"	-
Goodwin et al. 2022	"Psychologists with at least master's-level qualifications, psychiatrists, master's-level practitioners, nurses, diploma-level cognitive behavioral therapists, or doctorate-level mental health specialists"	"Online learning platform, in-person training, clinical training, and ongoing individual mentoring and webinars"
Carhart-Harris et al. 2021	"Psychologists, psychotherapists and psychiatrists"	-
Davis et al. 2021	"Bachelor's, master's, doctorate, and medical degrees in social work, psychology and psychiatry"	-
Anderson et al. 2020	"Psychiatrists, psychologists, social workers, chaplains and an internist"	"Half-day in-service training in the model using role plays"
Carhart-Harris et al. 2018	"Psychiatrist"	-
Griffiths et al. 2016	"From college graduate to PhD"	"Study staff originally trained by William Richards PhD"
Ross et al. 2016	"6 psychiatrists; 2 psychologists; 4 oncology social workers; 1 oncology nurse; and 2 master's level counselors"	"NYU Psychedelic Psychotherapy Training Program"
Grob et al. 2011	-	-

Adherence evaluation to the psychological intervention and the reporting of the results were assessed during extraction. No article reported adherence measures to the psychological intervention in psilocybin-assisted treatments.

Quantitative Results

A meta-analysis was performed to assess if psilocybin treatment with psychological intervention was clinically effective. Moreover, meta-regressions and subgroup analyses were also performed to understand to which extend different aspects of psychological intervention impact the treatment effect size. Such variables included the level of expertise of a given psychological intervention, i.e. if the psychological intervention followed a manual or not and the total number of sessions and hours and psilocybin dosage was also examined to analyze its influence on the effect size.

The number of studies of each group (randomized controlled trials using a between-group effect size and clinical trials including open-label trials using a within-group effect size) assumed an increase of one trial since Goodwin et al. 2022 had two active groups that received treatment. Therefore, the number of studies for the RCT group is nine and the clinical trial group is 11.

Psilocybin Randomized Controlled Trials in Depressed Patients Group

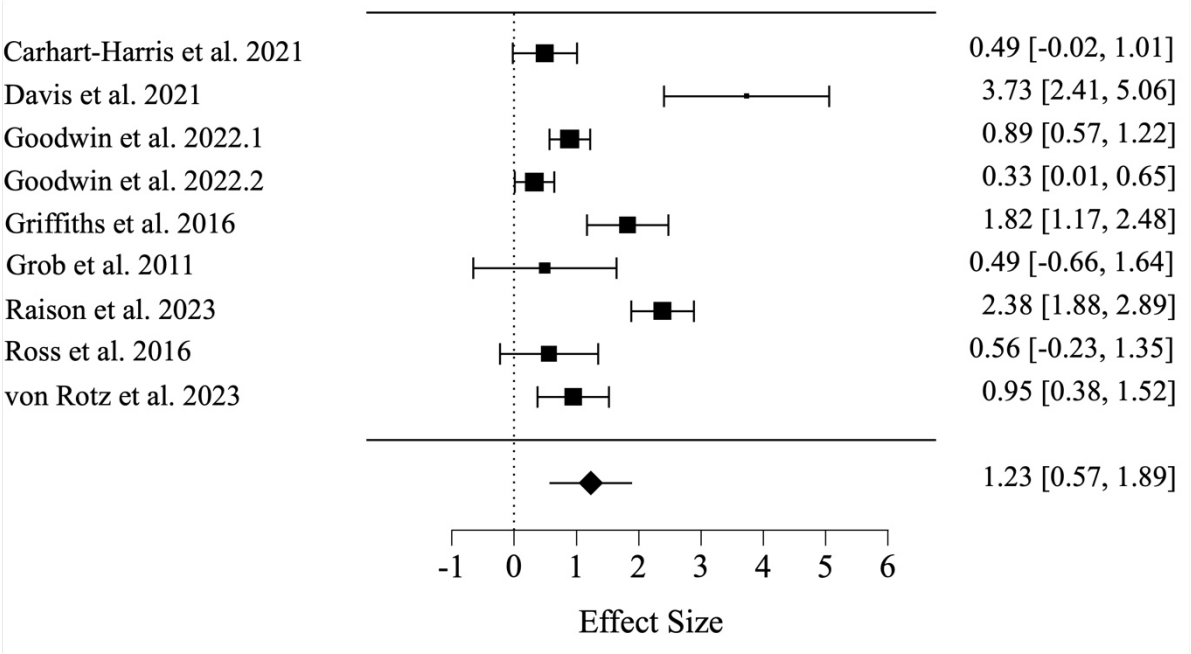
Between-group meta-analysis. In this meta-analysis, the clinical efficacy of psilocybin treatments with psychological support was examined in nine treatment groups of eight randomized controlled trials published between 2011 and 2023. The analysis included a total of 561 participants.

The overall effect size, as measured by the mean difference in psilocybin treatment group and the control group, was 1.23 (SE = 0.34, 95% CI 0.57 to 1.89, $p < 0.001$), indicating a statistically significant and clinically meaningful reduction in symptom severity favoring psilocybin treatments with psychological support to treatment control.

The effect was large (>0.8). The forest plot (Figure 4) indicates how the effect sizes of each clinical trial are distributed along with the confidence intervals. The overall effect size which corresponds to the diamond shape symbol is also represented in the forest plot.

Figure 4

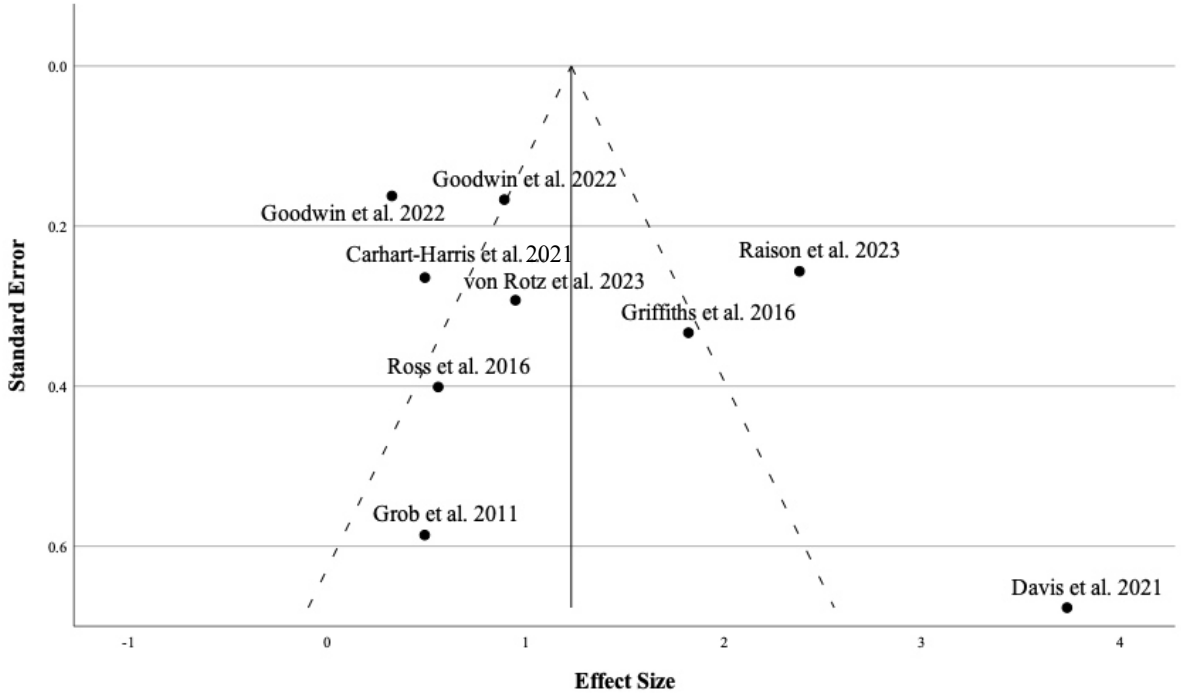
Forest plot for between-group meta-analysis.



Substantial heterogeneity was observed among the included studies (I^2 = 92%), suggesting variability in the effect sizes across trials. Publication bias was assessed using funnel plot (Figure 5) and Egger's regression test, which did not indicate significant bias (p = 0.73). However, there is some asymmetry in the funnel plot. For example, Davis et al. 2021 (N = 24) showcases a substantial larger effect size compared to the other studies with greater sample sizes which can indicate a small study effect.

Figure 5

Funnel plot for between-group meta-analysis.



Meta-regression. Meta-regressions were run to assess if the effect size would increase or decrease depending on the moderator. None of the continuous variables indicated a significant influence on the effect size (Table 7).

Table 7

Meta-regression on the effect of psychological intervention and dosage variables on the effect size.

Type	Estimate	Standard Error	95% CI		p-value
Total number of sessions	-0.538	0.503	-1.830	0.754	0.333
Total number of hours	0.465	0.233	-0.537	1.467	0.184
Dosage in milligrams	0.029	0.133	-0.314	0.916	0.838

Subgroup analysis. As displayed in Table 8, four sub-analyses were conducted for psychological intervention variables and one sub-analyses for dosage.

There was a significant effect of a manualized intervention in psilocybin treatments with psychological intervention, where the presence and the absence of a manual significantly

influenced the effect size. For instance, a manualized intervention decreased the overall effect size whereas the lack of a manual augmented the effect size.

Regarding the level of the psychological intervention, only psychological support, in comparison with psychotherapy, yield a significant impact on the effect size.

There were also significant effects in psilocybin treatments with psychological intervention when the number of sessions of the psychological intervention was between 5-6 or 7-9.

There was also a significant effect regarding the number of hours of the psychological intervention when the intervention was provided in greater or equal to 12 hours.

Finally, both groups of dosage of psilocybin influenced the effect size. A higher dose (≥25 mg) augmented the effect size whereas a smaller dose (<25 mg) diminished the overall effect size.

Table 8

Subgroup analyses on the effect of psychological intervention and dosage variables on the effect size.

Subgroup	Type	N	Effect Size	95% CI		p-value
Manualized Intervention	Yes	4	1.043	0.134	1.952	0.025*
	No	5	1.427	0.345	2.510	0.010*
Level of Psychological Intervention	Psychological Support	7	1.062	0.481	1.643	<0.001*
	Psychotherapy	2	2.100	-1.008	5.207	0.185
Total number of sessions	3-4	2	1.511	-0.336	3.358	0.109
	5-6	4	0.671	0.329	1.013	<0.001*
	7-9	3	1.932	0.144	3.721	0.034*
Total number of hours	<12	2	2.274	-0.449	4.998	0.102
	≥12	3	1.623	0.582	2.664	0.002*
Dosage in milligrams	<25	4	0.544	0.183	0.904	0.003*
	≥25	5	1.772	0.731	2.813	<0.001*

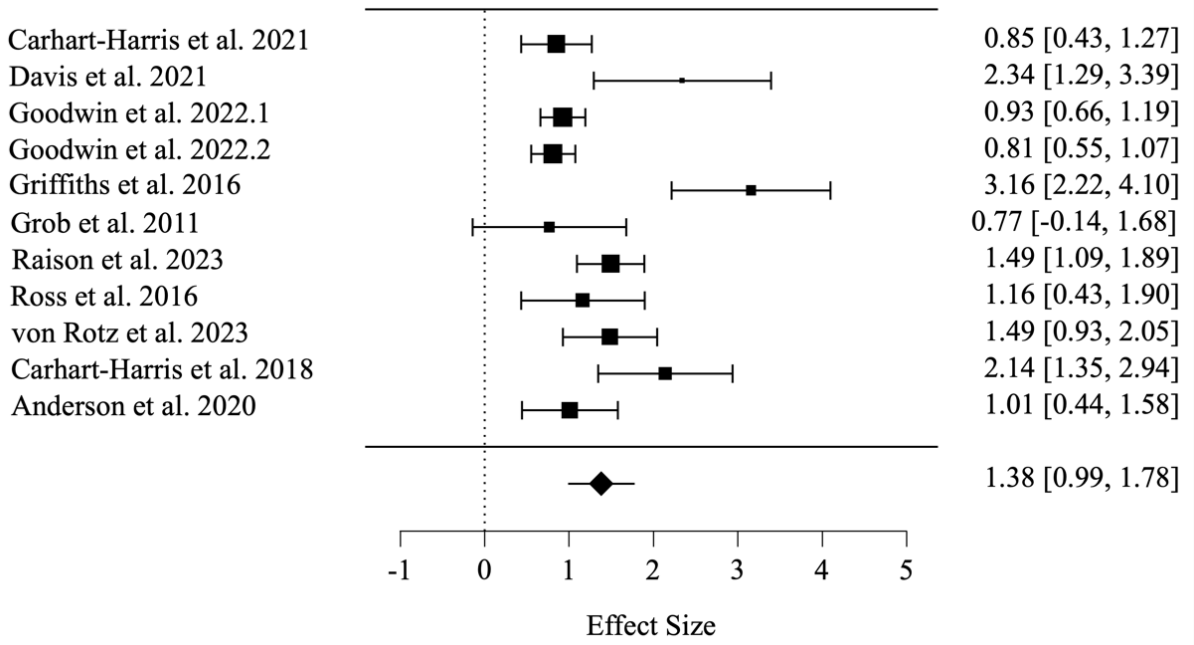
Note. *Significant p-value.

Psilocybin Clinical Trials in Depressed Patients Group

Within-group meta-analysis. In this meta-analysis, the clinical efficacy of psilocybin treatments with psychological support was examined in 11 treatment groups of 10 clinical trials published between 2011 and 2023. The analysis included a total of 598 participants. The overall effect size, as measured by the mean difference of the pre-treatment and post-treatment symptom severity mean scores, was 1.38 (SE = 0.20, 95% CI 0.99 to 1.78, $p < 0.001$), indicating a statistically significant and clinically meaningful reduction in symptom severity favoring psilocybin treatments with psychological support. The effect was also large (>0.8).

Figure 6

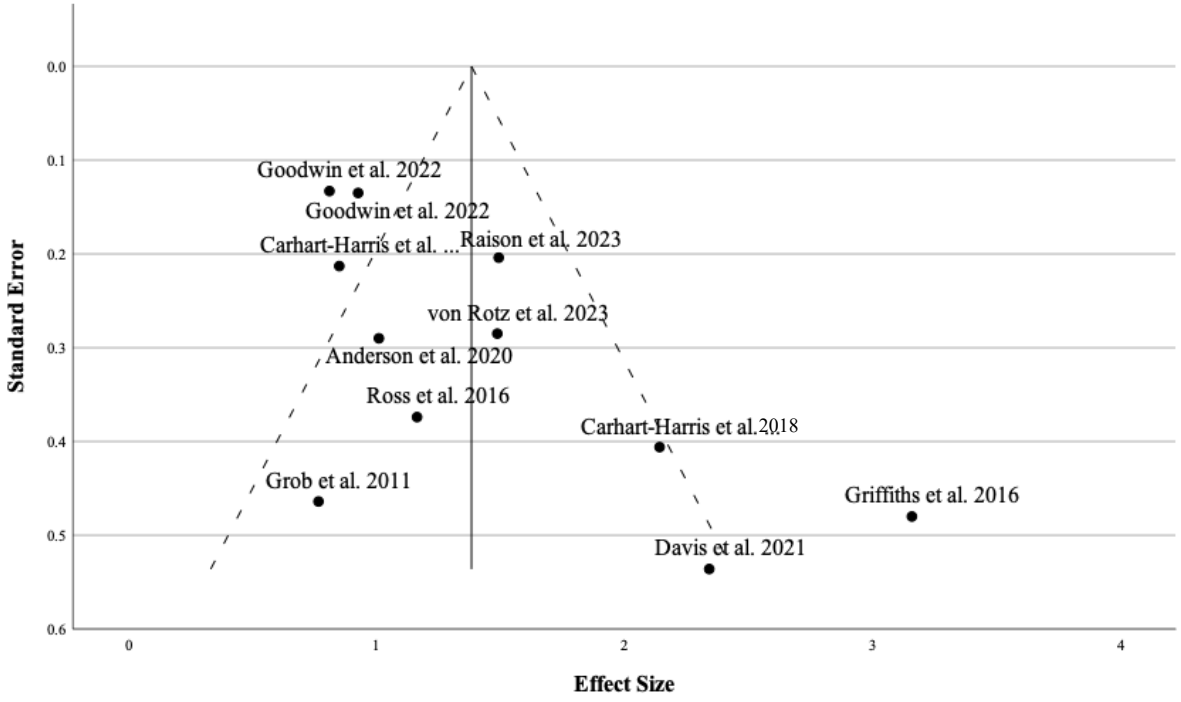
Forest plot for within-group meta-analysis.



Substantial heterogeneity was observed among the included studies (I^2 = 86%), suggesting variability in the effect sizes across trials. Publication bias was assessed using funnel plot (Figure 7) and Egger's regression test, which did not indicate significant bias (p = 0.23). Moreover, there is little asymmetry in the funnel plot. For example, Griffiths et al. 2016 (N = 51) showcases a considerable larger effect size compared to the other studies with greater sample sizes which can also indicate a small study effect.

Figure 7

Funnel plot for within-group meta-analysis.



Meta-regression. Meta-regressions were run to assess if the effect size would increase or decrease depending on the moderator. None of the continuous variables indicated a significant influence on the effect size (Table 9).

Table 9

Meta-regression on the effect of psychological intervention and dosage variables on the effect size.

Type	Estimate	Standard Error	95% CI		p-value
Total number of sessions	0.162	0.160	-0.530	0.853	0.420
Total number of hours	-0.355	0.186	-1.155	0.445	0.196
Dosage in milligrams	0.327	0.142	-0.282	0.936	0.147

Subgroup analysis. As displayed in Table 10, four sub-analyses were conducted for psychological intervention variables and one sub-analyses for dosage.

There were significant effects in all subgroups, meaning that all groups impacted the overall effect size in a significant manner.

In this within-group analysis, a manualized intervention also decreased the overall effect size whereas the lack of a manual enlarged the effect size.

Regarding the level of the psychological intervention, psychological support did not change substantially the effect size (1.384 to 1.387) whereas psychotherapy slightly increased the effect (1.384 to 1.396).

There were also significant effects in psilocybin treatments with psychological intervention when the number of sessions of the psychological intervention was between 6 and 8 which greatly increased the overall effect size compared to the other intervals (3-5 and 9-11) which decreased the effect size.

There was also a significant effect regarding the number of hours of the psychological intervention, both factors increased the effect size.

In this analysis, a higher dose (≥25 mg) also augmented the effect size whereas a smaller dose (<25 mg) diminished the overall effect size.

Table 10

Subgroup analyses on the effect of psychological intervention and dosage variables on the effect size.

Subgroup	Type	N	Effect Size	95% CI		p-value
Manualized Intervention	Yes	5	1.045	0.782	1.309	<0.001*
	No	6	1.741	1.013	2.469	<0.001*
Level of Psychological Intervention	Psychological Support	8	1.387	0.879	1.896	<0.001*
	Psychotherapy	3	1.396	0.684	2.108	<0.001*
Total number of sessions	3-5	5	1.224	0.849	1.599	<0.001*
	6-8	4	2.188	1.014	3.362	<0.001*
	9-11	2	0.907	0.571	1.243	<0.001*
Total number of hours	<12	2	1.794	0.991	2.596	<0.001*
	≥12	4	1.653	0.765	2.542	<0.001*
Dosage in milligrams	<25	5	1.186	0.806	1.566	<0.001*
	≥25	6	1.663	0.837	2.489	<0.001*

Note. *Significant p-value.

Discussion

The role of extra-pharmacological factors such as psychological intervention on the clinical efficacy of psychedelic clinical trials is widely discussed in the literature (Carhart-Harris, Roseman, et al., 2018; Heifets & Olson, 2023; Leary et al., 1963). In this systematic review, all psilocybin studies had a concomitant psychological intervention to treat patients with depression. Therefore, it was unfeasible to compare clinical efficacy in psilocybin treatment with and without psychological intervention. For this reason, the aim of this study was to understand if various variables of psychological interventions may impact the overall effect in studies that provide psilocybin-assisted treatments.

The current study found a large effect size in both between- and within-groups meta-analysis which shows that psilocybin treatments with psychological intervention are clinically effective in treating patients with depression. However, it is possible that due to a small number of studies, variables of psychological intervention such as total number of sessions and total number of hours did not yield significance when assessing their moderating effect in meta-regressions. In addition, dosage also did not show significance as a possible moderator for the overall effect size. In the subgroup analysis for the between-group meta-analysis, there was discrepancy regarding significance among groups.

A manualized intervention contributed to a lower overall effect size and a non-manualized intervention showed a higher effect size which suggests that the presence of a rigid and structured intervention can have an unwanted influence on treatment. Evidence has shown that a manualized treatment is not empirically supported as more effective than non-manualized treatment (Truijens et al., 2019). Therefore, psychological intervention could have a negative influence on outcome due to an undesirable application of the manual. The patients might see the support of the facilitator as non-genuine due to an overly structured, step-by-step use of the manual. This in turn can create a less authentic therapeutic alliance. However, there is a stereotype that treatments manuals are overly rigid and they are to replace therapist skills, creativity, and judgement (Addis & Cardemil, 2006). This is why it is important to understand how facilitators are adhering to the treatment manual. However, none of the studies applied treatment adherence assessment which might also show some limitations regarding this finding.

Regarding the level of psychological intervention, only psychological support, in contrast with psychotherapy, yield a significant impact on the effect size. This outcome could be due to the number of trials being uneven as there was seven studies using psychological support in comparison with two using psychotherapy. However, this significant effect might

suggest that a less specialized intervention is ideal for this type of treatment. Even though there is little research on specialized versus non-specialized interventions, a meta-analysis comparing Cognitive Behavioral Therapy (a specialized psychological intervention) with non-specialized therapy for alleviating positive symptoms in schizophrenia indicated that there were no clinically significant differences between the two interventions in reducing symptoms (Kennedy & Xyrichis, 2017). This might open a discussion about what might be more effective for this innovative intervention with psychedelic substances such as psilocybin. Moreover, psychological support requires less specific training compared to psychotherapy which in turn offers the opportunity for professionals of different areas such as psychiatry, nursing and social work provide this type of non-specialized treatment. However, there are studies that provide a manualized psychological support hence there is still a degree of training and guidance.

With the results of this study there might be a suggestion that the number of sessions which are more adequate for treatments with psilocybin are 5-6 or 7-9 as these two groups were significant. Regarding the total number of hours, it seems that psychological interventions which are equal or greater to 12 hours significantly contribute to the effect size. Most research on the ideal number of sessions and/or hours is assessed for psychotherapy as a stand-alone treatment and not for psychological interventions in the context of psychedelic treatments. For example, a meta-regression analysis assessed how many sessions are optimal and what best intensity of psychotherapy is needed to treat depression and results were inconclusive as more research is needed to establish the robustness of these findings (Cuijpers et al., 2013).

In the context of psychedelic treatments, a recent systematic review investigated the optimal number of sessions in substance-assisted psychotherapy, specifically in serotonergic psychedelics, but only assessed the number of administration sessions. However, there was still no conclusive evidence regarding the number of optimal administration sessions for specific substances and disorders (Thal et al., 2023). Nonetheless, Thal and colleagues did not provide regard to the total number of sessions or hours that occur before and after the administration of psychedelics. This showcases the lack of importance that researchers give to psychological intervention components in psychedelic research. Even though the results of the current study are preliminary and need to be considered with caution, it is an encouraging step for future research to develop more empirical evidence about this component and assess their results in light of the current ones.

The amount of dosing in milligrams was also assessed to understand if higher dosages significantly impacted the effect size in comparison with lower dosages. There is an indication

that a dose that is equal or greater to 25 milligrams positively influences the overall effect size whereas a lower dose decreases it which suggest that antidepressive effect of psilocybin is greater when higher does are administered. This result is supported by previous literature on the dose effect of psilocybin treatments in patients with depression (Li et al., 2022). However, a more recent meta-analysis concluded that there are different optimal doses for different population with depression-related disorders (Perez et al., 2023). Nevertheless, the study specified that higher values were more optimal for treatment-resistant depression groups.

In the subgroup analysis for the within-group meta-analysis section, all variables contributed to the effect size which suggests a possible saturation in efficacy by the pharmacological substance and not the psychological variables assessed in the current study. This saturation effect suggests that the variables at play are not distinctive characteristics for the effect. It may be assumed that regardless of the type and amount of psychological intervention, it might be the substance itself that produces change irrespective of the amount of dosage.

Overall, psychological intervention was heterogeneous across studies. The total number of sessions and hours did not overlap in any of the included studies which denotes the lack of protocolized approaches for all clinical trials. Training is similarly heterogeneous as well. In order to understand the impact of the psychological intervention this variable needs to be as exactly described and controlled for as the amount of the tested substance in milligrams. As there is a variety of protocols and models of psychological support across psilocybin clinical trials, researchers should collaborate to overcome this weakness as heterogeneity might not beneficiate systematically assessment of results across trials.

Limitations and Future Research

The presented results must be interpreted with caution as only a small number of studies could be identified according to selection criteria of the current study, thus conclusions remain preliminary. Moreover, subgroup analyses are entirely observational in their nature and are not based on randomized comparisons hence their findings should not be presented as definitive conclusions (Higgins et al., 2019). Therefore, the findings of the current study should be accepted with reservation and be further examined in future research.

Potential links between the total number of sessions/hours and therapeutic outcomes should also be assessed in future research. However, before exploring these specific components of psychological intervention, a pilot study testing if treatment with psychedelic

substances is clinically more effective with or without a psychological intervention should be completed. Perhaps there are other psychedelic compounds that offer the chance to conduct such study since psilocybin treatments clinical trials are all accompanied with a psychological intervention. More clinical trials of psychedelic treatment for therapeutic purposes should design studies with a therapy control group to assess the role of psychological support in psychedelic treatments as implemented by Grabski and colleagues in a double-blind phase 2 ketamine clinical trial for adults with alcohol-use disorder (Grabski et al., 2022). Studies should also consider measuring adherence to the protocol to address the role of non-manualized approaches in larger meta-analysis and in psychotherapy research to be sure that the psychological intervention that is being implemented in a certain study is similar.

Despite the mentioned limitations, the results of this systematic review and meta-analysis offer complex insights about psychological interventions that are present in treatment with psilocybin. Overall, not only could researchers propose to compare psychedelic interventions with and without psychological support but also researchers should attempt to reach a more homogeneous psychological intervention across psilocybin clinical trials in order to facilitate its testing.

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